Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead, Berkshire
SL6 4AY
United Kingdom

PROTOCOL NUMBER: 257MS201

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A 2-Part, Multicenter, Randomized, Blinded, Active-Controlled Phase 2 Study to Sequentially Evaluate the Safety and Efficacy of BIIB091 Monotherapy and BIIB091 Combination Therapy With Diroximel Fumarate in Participants With Relapsing Forms of Multiple Sclerosis

EU TRIAL NUMBER: 2022-502552-31-00

IND NUMBER: 143053

DATE: 09 December 2022
Version 2.0
FINAL
Supersedes previous Version 1.0 dated 30 September 2022

SPONSOR INFORMATION

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead, Berkshire
SL6 4AY
United Kingdom

Biogen Australia PTY Ltd.
Suite 1, Level 4
2 Banfield Rd,
Macquarie Park, NSW 2113
Australia

For urgent medical issues in which the study Medical Director should be contacted, please refer to the Study Contact List for complete contact information.

The Sponsor may transfer any or all of its study-related responsibilities to a contract research organization and other third parties; however, the Sponsor retains overall accountability for these activities.

SPONSOR SIGNATURE PAGE

Protocol 257MS201 Version 2.0 was approved by:

Thomas Jerome Hanna, MB BCh BAO, MRCS, MFPM, Executive Medical Director Multiple Sclerosis Clinical Development Biogen	Date (*DD MMM YYYY*)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. KEY STUDY ELEMENTS

1.1. Synopsis

Protocol Title:	A 2-Part, Multicenter, Randomized, Blinded, Active-Controlled Phase 2 Study to Sequentially Evaluate the Safety and Efficacy of BIIB091 Monotherapy and BIIB091 Combination Therapy With Diroximel Fumarate in Participants With Relapsing Forms of Multiple Sclerosis	
Protocol Number:	257MS201	
EU Trial Number	2022-502552-31-00	
Version Number:	2.0	
Name of Study Treatment:	Research Name:	BIIB091
	Generic Name:	Not applicable
	Trade Names:	Not applicable
Study Phase:	2	
Study Indication:	Relapsing forms of multiple sclerosis (MS)	
Study Rationale:	BIIB091 is an orally active, potent, selective, reversible (noncovalent), and peripherally restricted small-molecule inhibitor of Bruton's tyrosine kinase (BTK), a tyrosine-protein kinase that is a key signaling node immediately downstream of B cell receptor (BCR) and Fc receptor (FcR) engagement. The Sponsor is developing BIIB091 for the treatment of MS. Diroximel fumarate (DRF) is an aminoethyl ester of monomethyl fumarate (MMF) that undergoes presystemic hydrolysis through esterases to produce the active metabolite, MMF. DRF (BIIB098) was developed as a delayed-release, gastro-resistant oral treatment for relapsing MS (RMS) under the trade name Vumerity [VUMERITY® USPI 2022; Vumerity™ SmPC 2022]. The combination of the inhibition of B-cell and myeloid-cell activation with BIIB091 and the modulation of the proinflammatory properties of T cells and myeloid cells with DRF could have an additive or synergistic effect and result in transformative efficacy in suppressing central nervous system (CNS) inflammation. In addition, this combination therapy is expected to have minimal overlapping adverse effects based on	

clinical monotherapy data and nonclinical data from the 90-day combination toxicology study. The combination therapy also has minimal potential for drug-drug pharmacokinetic (PK) interactions.

To characterize the clinical safety and efficacy profile of BIIB091 monotherapy in MS patients prior to assessment of BIIB091 and DRF combination therapy, this adaptive study design consists of 2 sequential parts. Part 1 of this study will evaluate the safety and efficacy of 2 dose levels of BIIB091 monotherapy compared to the standard-dose DRF (462 mg twice daily [BID]). Part 2 of this study will evaluate the safety and efficacy of the selected BIIB091 dose in combination with either the standard dose (462 mg BID) or a lower dose (350 mg BID) of DRF, and both combination therapies will be compared to the standard-dose DRF.

Rationale for Dose and Schedule Selection:

Dose Recommendation

In both Part 1 and Part 2, BIIB091 will be dosed with the immediate-release (IR) tablet formulation BID via oral administration after regular meals (within 30 to 60 minutes after meals) for a total of 48 weeks. BIIB091 should not be taken in the fasted state. In Part 1, BIIB091 350 mg BID and 250 mg BID will be used as the high dose and low dose, respectively. In Part 2, the BIIB091 dose will be selected based on benefit-risk evaluation of Part 1 data.

DRF will be supplied as capsules consisting of enteric-coated, pH-sensitive DRF minitablets. In both Part 1 and Part 2, participants treated with the standard-dose DRF will take the starting dose of 231 mg BID for the first 7 days and then 462 mg BID thereafter. In Part 2, participants receiving the BIIB091 and low-dose DRF combination therapy will take DRF 231 mg BID for the first 7 days and then 350 mg BID thereafter.

Rationale for targeting a high level of BTK inhibition with BIIB091

The Phase 2 clinical trial of tolebrutinib (a covalent, irreversible BTK inhibitor) showed that only the highest dose (60 mg once daily [QD]) significantly reduced T1 gadolinium-enhancing (GdE) lesions at 12 weeks in participants with RMS [Reich 2021]. In a Phase 1 trial, the 60-mg QD dose demonstrated approximately 93% of mean target occupancy in the periphery [Owens 2022]. Similarly, a Phase 2 study of evobrutinib (another

covalent, irreversible BTK inhibitor) showed that the largest and most sustained reduction in annualized relapse rate (ARR) was achieved at the highest dose of 75 mg BID, when over 95% of BTK target occupancy was achieved in the periphery in about 98% of treated patients [Montalban 2019]. These data suggest that a high level of BTK inhibition in the periphery is required to achieve sufficient efficacy in reducing disease activity in MS.

Rationale for BIIB091 Doses

It is hypothesized that as a noncovalent inhibitor of BTK, BIIB091 treatment will provide clinical benefit in patients with MS as a group mainly through selectively and reversibly targeting BTK-related functions in B cells. Examination of the cluster of differentiation (CD)69 expression level on B cells after ex vivo BCR-mediated activation allows for the assessment of the inhibitory effect of circulating BIIB091 [Bame 2021]. In the multiple ascending dose (MAD) part of the first-in-human Phase 1 Study 257HV101, administration of 150 mg BID or 300 mg BID of BIIB091 for 14 days demonstrated > 90% mean inhibition of CD69 expression, which was maintained from Day 2 through Day 14 dosing intervals. Serum levels of BIIB091 at trough concentration (C_{trough}) appeared to be associated with the magnitude of CD69 inhibition and PK/pharmacodynamic (PD) modeling predicted an observed curve-fit EC90 corresponding to approximately 221 ng/mL. Therefore, a C_{trough} of 221 ng/mL had been set as the lower limit of exposure to maintain a high degree of CD69 inhibition.

Analysis of the clinical data from the Study 257HV101 indicated that QT prolongation is an identified risk with BIIB091. The QT prolongation was dose dependent (observed only at higher exposure levels) and was driven primarily by maximum concentration (C_{max}). Based on the concentration-QT interval corrected for heart rate (QTc) analysis in the single ascending dose (SAD) part of the study, for which the model provided the best fit at high concentrations, a mean placebo-corrected change-from-baseline Fridericia corrected QT interval (ΔΔQTcF) [i.e., placebo-corrected ΔQTcF] exceeding 15 ms can be avoided by keeping the C_{max} under approximately 4018 ng/mL. Therefore, a mean C_{max} of less than 4018 ng/mL had been set as the upper limit of exposure based on concentration-QTc analysis.

Part 1B data from the Phase 1 formulation PK study, Study 257HV105, demonstrated that the administration of the BIIB091 IR tablet formulation at 250 mg twice on Day 1 (12 hours apart)

in the fasted state and at 350 mg twice on Day 1 (12 hours apart) under the fed state resulted in a mean C_{max} < 4018 ng/mL and a mean C_{trough} > 221 ng/mL. In addition, simulated data at steady state from the population PK (popPK) model based on Study 257HV101 and Part 1B of Study 257HV105 supported a dose range of 200 to 350 mg with BID dosing based on achieving the above thresholds. The BIIB091 350 mg dose, when administered as a single dose and in a 2-dose regimen in Part 1B of Study 257HV105, was well tolerated and may potentially achieve > 90% of CD69 inhibition in B cells in > 90% of treated participants at steady state.

Study 257HV105 Part 3 evaluated the PK, PD, and safety of a 7-day treatment with BIIB091 IR 250 mg BID under the fed state in 10 evaluable participants. Based on available data from the 10 participants, the BIIB091 250 mg BID dose showed a favorable safety and tolerability profile. The mean C_{max} and concentration at dosing time plus dosing interval (C_{tau}) were 2500 ng/mL and 407 ng/mL on Day 7 (steady state), respectively. Mean C_{tau} at steady state was above 221 ng/mL in 9 of these 10 treated participants.

To elucidate the exposure-response relationship, 2 BIIB091 doses were selected for Part 1 of this Phase 2 study. The proposed BIIB091 high dose (350 mg BID) and low dose (250 mg BID) were selected to target a high level of BTK inhibition (represented by > 90% CD69 inhibition) in > 90% and 80% to 90% of participants, respectively. Both doses are expected to have favorable safety and tolerability profiles. Data from Part 1 of the Phase 2 study will be used to select the BIIB091 dose with the optimal benefit-risk profile for Part 2. The selected BIIB091 dose for Part 2 could be different from the Part 1 doses (e.g., 300 mg BID).

Rationale for DRF Doses

The standard dose of DRF in the Phase 2 study will follow the approved DRF dose regimen.

In the context of BIIB091 and DRF combination therapy, it is hypothesized that a lower dose of DRF could potentially reduce some of the possible side effects associated with combination therapy while maintaining a high level of efficacy. Di-ester fumarate therapy mainly modulates T-cell immunity. Given inhibition of B-cell-mediated antigen presentation to T cells following BIIB091 treatment, the degree of direct T-cell

immunomodulation required to achieve maximal efficacy within MS patients may be reduced. This could potentially allow for a lower than standard dose of DRF when dosed in combination with BIIB091.

DRF is an aminoethyl ester of MMF that undergoes presystemic hydrolysis through esterases to produce MMF. MMF is also the active metabolite of the approved drug product DMF (dimethyl fumarate; Tecfidera). Both DRF and DMF produce their therapeutic effects primarily by the active metabolite MMF. PK assessment has demonstrated the exposure of MMF after oral administration of 462 mg DRF and 240 mg DMF in adults is bioequivalent.

Studies C-1900, 109MS301, and 109MS302 have demonstrated that DMF 240 mg BID (480 mg daily) and 240 mg 3 times daily (TID) [720 mg daily] doses had comparable levels of efficacy, whereas the 120 mg TID dose (360 mg daily, i.e., 75% of the approved dose) demonstrated a reduction in the number of T1 GdE lesions from Baseline, although not statistically significant. Therefore, the lower dose of DRF is selected at 350 mg BID, corresponding to approximately 75% of the standard DRF daily dose.

Study Objectives and Endpoints

Part 1

Primary Objective	Primary Endpoint
To investigate the safety and tolerability of BIIB091 monotherapy in participants with RMS	• Incidence of adverse events (AEs) from the date of study treatment and incidence of serious AEs (SAEs) from the date of signing of informed consent form (ICF) through the Follow-Up Visit

Secondary Objectives	Secondary Endpoints
To evaluate the effects of BIIB091 monotherapy on the magnetic resonance imaging (MRI) measures of active CNS inflammation	• Cumulative number of new T1 GdE lesions at Weeks 8, 12, and 16 • Cumulative number of new or enlarging T2 hyperintense lesions at Weeks 8, 12, and 16 • Cumulative volume of new or enlarging T2 hyperintense lesions at Weeks 8, 12, and 16
To evaluate the effect of BIIB091 monotherapy on QTc and other electrocardiogram (ECG) parameters	• QT interval corrected for heart rate using Fridericia's formula (QTcF), RR, PR, QRS, and QT intervals, and heart rate • Incidence of ECG abnormalities as assessed by 12-lead ECG measurements

Part 2

Primary Objective	Primary Endpoint
To evaluate the effects of BIIB091 combination therapy with DRF compared with the DRF monotherapy arm, on the key MRI measure of active CNS inflammation	• Cumulative number of new T1 GdE lesions at Weeks 8, 12, and 16

Secondary Objectives	Secondary Endpoints
To evaluate the effects of BIIB091 combination therapy with DRF compared with the DRF monotherapy arm on additional MRI measures of active CNS inflammation	• Cumulative number of new or enlarging T2 hyperintense lesions at Weeks 8, 12, and 16 • Cumulative volume of new or enlarging T2 hyperintense lesions at Weeks 8, 12, and 16
To investigate the safety and tolerability of BIIB091 combination therapy with DRF in participants with RMS	• Incidence of AEs from the date of study treatment and incidence of SAEs from the date of signing of ICF through the Follow-Up Visit

To evaluate the effect of BIIB091 combination therapy with DRF on QTc and other ECG parameters	• QTcF, RR, PR, QRS, and QT intervals and heart rate • Incidence of ECG abnormalities as assessed by 12-lead ECG measurements

Exploratory objectives and endpoints (Part 1 and Part 2) are listed in Section 4.

Study Design:

This is a 2-part, multicenter, randomized, blinded, active-controlled Phase 2 study to sequentially evaluate the safety and efficacy of BIIB091 monotherapy and BIIB091 combination therapy with DRF in participants with RMS.

The study will be conducted in 2 parts. Both Part 1 and Part 2 each include a 4-week screening period, a 16-week double-blind active-controlled treatment period, a 32-week blinded active-controlled treatment period, and a 2-week post-treatment safety follow-up period. Participants with absolute lymphocyte count (ALC) < lower limit of normal (LLN) at the 2-week safety Follow-Up Visit will return in 2 weeks for retesting and confirmation, and follow-up will be extended for those participants at intervals of every 8 weeks to monitor their lymphocyte counts until their ALC > LLN, or for a period up to 6 months, or until they commence another disease-modifying therapy, whichever occurs first.

In Part 1, participants with active RMS will be randomized to 3 treatment groups: high-dose BIIB091 monotherapy (350 mg BID), low-dose BIIB091 monotherapy (250 mg BID), and DRF monotherapy at standard dose (462 mg BID). An analysis of the Part 1 primary, secondary, and selected exploratory endpoints will be performed after all participants complete the 16-week visit. An independent data monitoring committee (IDMC) will review the safety and lab data from the Part 1 Week 16 analysis to recommend whether Part 2 should be initiated (see Section 12.8 and Section 14.3.2 for details). In the event of unfavorable safety findings, the IDMC could recommend pausing or stopping a cohort or the study or a modification to the study design. Details regarding the IDMC review of data will be provided in the IDMC charter. Selected Sponsor team members will be unblinded to participate in the primary analysis of Part 1 data at Week 16, to determine whether to proceed to Part 2 based on the overall benefit-risk profile and to select the BIIB091 dose to be used in Part 2.

In Part 2, participants with RMS will be randomized to 3 treatment groups: the selected BIIB091 dose in combination with standard dose (462 mg BID) of DRF, the selected BIIB091 dose in combination with lower dose (350 mg BID) of DRF, and DRF monotherapy at standard dose (462 mg BID). The primary analysis comparing the BIIB091/DRF combination therapy to DRF monotherapy will be performed after all participants complete the Week 16 visit in Part 2.

Final analysis of the 48-week data from Part 1 and Part 2 will allow for the assessment of longer-term safety and efficacy of BIIB091 monotherapy and BIIB091 combination therapy with DRF. For maintenance of blinding, members of the study management team who are not involved in the Week 16 data review (in Part 1 and Part 2) and the study sites will remain blinded for the entire duration of the study (Section 7.4). Details on how the study blind is maintained will be provided in a separate unblinding plan.

For both Part 1 and Part 2, participants will visit the study site for safety, MRI, and clinical efficacy assessments at Day -28 to Day 1 (MRI assessments should be completed at least 7 calendar days and no more than 14 calendar days prior to Baseline [Day 1]), and Weeks 4, 8, 12, 16, 24, and 48. Additional specific safety assessments will be performed at Weeks 1, 2, 6, 36, and 50. The primary efficacy endpoint in Part 2 will be the cumulative number of new T1 GdE lesions at Weeks 8, 12, and 16 (Section 4).

During Part1 or Part 2 of the study, if an MS relapse is suspected, the participant should return to the study site for an unscheduled visit and be evaluated within 72 hours of the onset of the event to determine if a relapse has occurred. Treatment of an acute relapse event may proceed at the discretion of the treating neurologist only after the examining neurologist has completed their examination. The treatment for relapse in this study is intravenous methylprednisolone (IVMP) ≤ 1000 mg/day for up to a maximum of 5 days with or without an oral prednisone taper (up to 15 days). Any changes to this treatment should first be discussed with the Study Medical Director or designee. If the start of a treatment for a relapse with high-dose corticosteroids falls within 7 days of the next scheduled visit, every attempt should be made to obtain the MRI before administration of the first dose of high-dose corticosteroids. If outside the visit window, visit should be recorded as unscheduled. The MRI at an

unscheduled visit prior to steroid treatment must be ≥ 21 days after the prior MRI. However, if an MRI at an unscheduled visit is < 21 days after a prior MRI, then the use of gadolinium (Gd)-based contrast agents/media should be strongly avoided, unless determined by the Investigator to be clinically indicated. In this scenario, the next regularly scheduled MRI should also be obtained.

Study Location: Approximately 80 sites globally are planned.

Study Population: This study will be conducted in participants who meet the following criteria:

- Aged 18 through 55 years old, inclusive, at the time of informed consent
- Time since MS symptom onset < 20 years
- Diagnosed with MS per the 2010 or 2017 McDonald's criteria [Polman 2011; Thompson 2018]
- Must have Expanded Disability Status Scale (EDSS) score of 0 through 5.0 at Screening
- Must have at least 1 of the following occurring prior to Baseline (Day 1):
  - ≥ 2 clinical relapses in the last 24 months (but not within 30 days prior to Baseline [Day 1]) with at least 1 relapse during the last 12 months prior to randomization
  - ≥ 1 clinical relapse within the past 24 months (but not within 30 days prior to Baseline [Day 1]) and ≥ 1 new brain MRI lesion (Gd-positive and/or new or enlarging T2 hyperintense lesion) within the past 12 months prior to randomization. The baseline MRI could be used to satisfy this criterion (local MRI readings are allowed). For new or enlarging T2 hyperintense lesions, the

reference scan cannot be > 12 months prior to randomization

– ≥ 1 GdE lesion on brain MRI within 6 months prior to randomization

Detailed criteria are described in Section 6.

Number of Planned Participants: Approximately 275 participants will be randomized.

Treatment Groups: Participants will be randomized into treatment groups. The randomization will be stratified by intensive PK cohort (Yes/No) and region (Eastern Europe vs. Other). For stratification, Eastern Europe will include participants from countries such as Poland and the Czech Republic.

Part 1:

BIIB091 monotherapy

- high dose (350 mg) BID (N = 50)
- low dose (250 mg) BID (N = 50)

DRF monotherapy

- standard dose (462 mg) BID (N = 25)

Part 2:

BIIB091 and DRF combination therapy

- BIIB091 selected dose with DRF standard dose (462 mg) BID (N = 50)
- BIIB091 selected dose with DRF low dose (350 mg) BID (N = 50)

DRF monotherapy

- standard dose (462 mg) BID (N = 50)

See Section 3.1.2 for details.

Placebo tablets and placebo capsules (matching the appearance of BII091 tablets and DRF capsules, respectively) will be

	administered to maintain blinding of the treatment group assignments by disguising both the type of study drug and dose level administered (see Section 7.3 for details).
Sample Size Determination:	The planned sample size is 275 participants. Accounting for a 12% dropout rate, 275 participants are planned to be enrolled in the study. Of these, 125 participants will be randomized in Part 1 and 150 will be randomized in Part 2. In Part 2, a sample size of 50 participants per group (44 evaluable) was designed to detect an 80% reduction from the mean number (standard deviation) of 1.2 (3) cumulative new T1 GdE lesions over MRI scans at Weeks 8, 12, and 16 in the standard dose of DRF monotherapy with approximately 90% power and a 10% Type 1 error rate. A sample size of 50 participants (44 evaluable) per treatment group will allow for an 80% or greater probability of observing at least 1 occurrence of an AE with an event rate of 3.6%. In Part 1, intensive PK will be collected in up to 25 participants (approximately 10 participants in each BIIB091 group and approximately 5 participants in the DRF group). In Part 2, intensive PK will be collected in up to 30 participants (approximately 10 participants in each group).
Visit Schedule:	Participants will have up to 12 scheduled visits during the study. Study assessments conducted at each visit are listed in the Schedule of Activities (Table 1). Participants in Part 1 of the study cannot participate in Part 2 of the study. Visit days are calculated with respect to Day 1 (the date of first dose).
Duration of Study Participation:	The study duration for participants in either Part 1 or Part 2 will be approximately 54 weeks and includes the following: • 4-week screening period • 16-week double-blind, active-controlled treatment period • 32-week blinded, active-controlled treatment period

- 2-week post-treatment safety follow-up period

Diagnostic and Monitoring Procedures:	MRIs and PD biomarkers will be collected but not used for study diagnostic and monitoring purposes. MRIs may be used by the treating physician or other non-study site staff for patient treatment purposes.Konectom is not intended for or being developed as a standalone or adjunctive diagnostic device. Konectom does not provide any recommendations or conclusions related to diagnosis or treatment.
Benefit-Risk Analysis:	BIIB091 is hypothesized to provide clinical benefits in patients with MS as a group mainly through selectively and reversibly targeting BTK-related functions in B cells and myeloid cells. QTc prolongation is an identified risk for BIIB091 (see the BIIB091 Investigator's Brochure [IB] for details). This Phase 2 study will continue to follow risk mitigation measures for QT/QTc prolongation, which will include intensive 12-lead triplicate ECGs during the first month of dosing in all participants. Additional risk mitigations for the QT/QTc prolongation will be reflected in the inclusion and exclusion criteria, discontinuation criteria, and when applicable, study stopping criteria. Furthermore, based on its mode of action (MOA), there is a theoretical increased risk of infections. General risk mitigation for infections will also be implemented. Coronavirus disease 2019 (COVID-19)-specific risk mitigations will also be implemented in accordance with the Sponsor's monitoring and prevention control measures for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and will be amended based on emerging local, regional, and national guidance. Additionally, as hemorrhage and bleeding have been described as class side effects for earlier generation BTK inhibitors [von Hundelshausen and Siess 2021], the monitoring for potential BIIB091 effects on platelet function will be implemented in this study. DRF, under the trade name Vumerity®, has been approved by the United States (US) Food and Drug Administration (FDA) for the treatment of adults with RMS and in the European Union (EU) for the treatment of relapsing-remitting MS (RRMS) [VUMERITY® USPI 2022; Vumerity™ SmPC 2022], and subsequently approved in several countries. In participants with RRMS, DRF demonstrated safety and tolerability in 2 global Phase 3 studies (see the DRF IB for details). Risk mitigation for DRF in this study will include monitoring for ALC, leucocyte counts, liver function, and opportunistic and other infections.

Additional risk mitigations specific for DRF will be reflected in the inclusion and exclusion criteria, discontinuation criteria, and when applicable, study stopping criteria.

The combination therapy of BIIB091 and DRF is expected to provide a convenient oral option with an expected transformative efficacy and a favorable safety and tolerability profile. Although BIIB091 has a risk of QTc prolongation, a QTcF study of DRF did not show a clinically meaningful effect on QTc interval and no compounding effect is expected for the combination. Lymphopenia may be observed with DRF, mostly impacting CD4 and CD8 T cells with an initial decline and stabilization by approximately 24 weeks. While BIIB091 exerts its effects on B cells, it is not a B-cell-depleting agent and therefore, BIIB091 is not expected to cause additive lymphopenia. Additionally, DRF may cause elevation in hepatic transaminases as anticipated from the DMF data where the active metabolite is the same as DRF (most were $\leq 3 \times$ upper limit of normal in clinical studies, and these abnormalities resolve upon DMF discontinuation). To date, BIIB091 has no evidence of increased risk of elevation in liver enzymes based on the limited available clinical data, but acknowledging that other BTK inhibitors in late phases of development have reported hepatic events, a more conservative approach is applied here. The monitoring plan for liver enzymes is detailed in Section 8.1.

There is a theoretical risk for increased infections with the combination treatment despite having a minimally overlapping MOA. Enhanced risk mitigations for infections will be implemented in this study with close monitoring of ALC, leukocyte count, immunoglobulin (Ig) levels, and more stringent inclusion and exclusion criteria and discontinuation criteria.

As with many clinical studies, there is some burden for participants. This clinical study includes 12 scheduled study visits, up to 14 blood sample collections, 8 scheduled MRI tests, physical discomfort from participation, and time spent on completing assessment questionnaires. Despite that, participants in this study are expected to benefit from intensive monitoring and management of their disease. Moreover, all participants will be receiving a form of active drug (either BIIB091, DRF, or both) that is expected to have a positive impact on their disease.

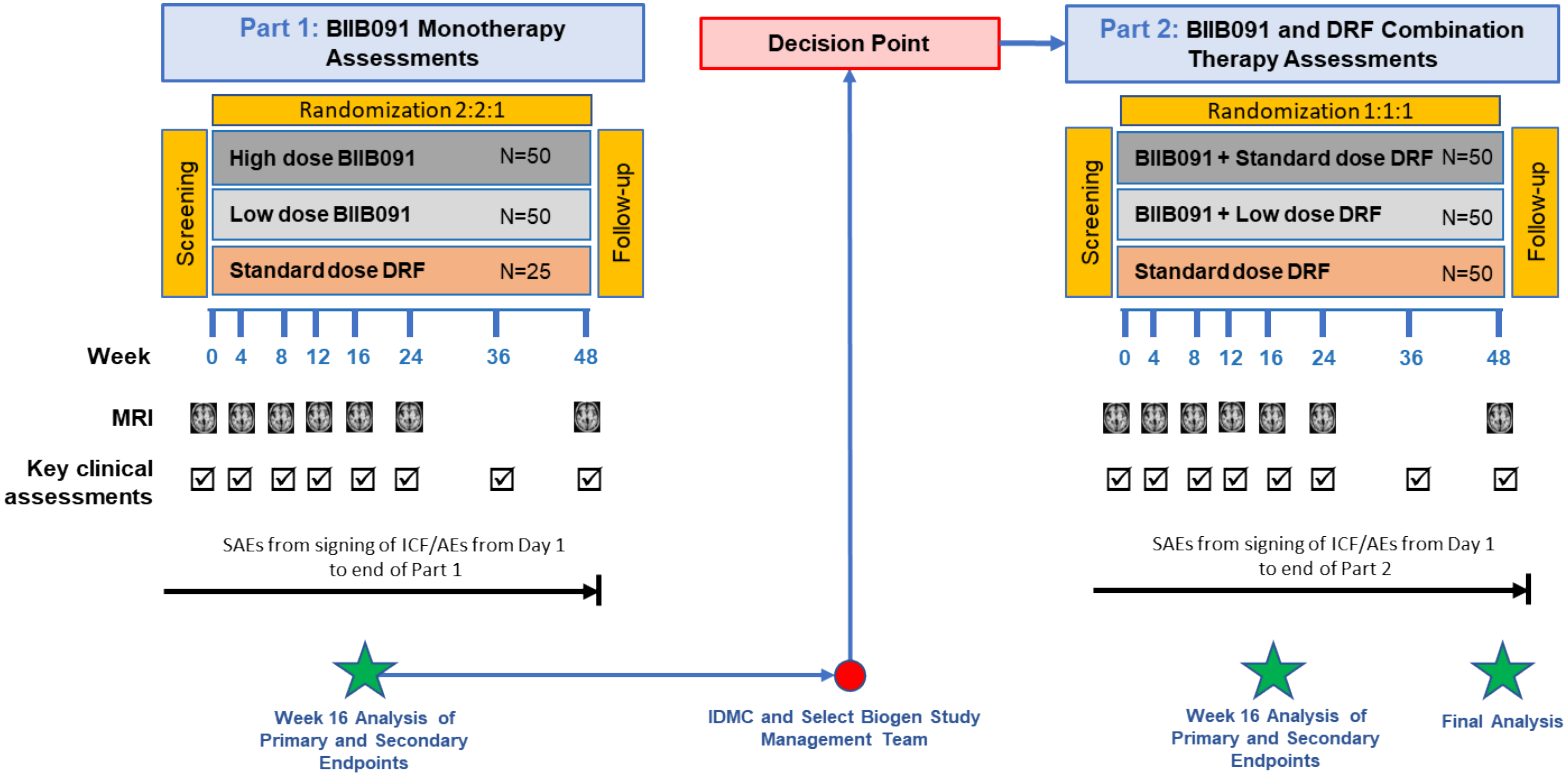
For treatment with either BIIB091 or DRF or the combination, an IDMC will review the clinical data and make recommendations regarding the study conduct (Section 14.3.2).

Considering the minimally overlapping MOA, toxicology combination therapy data, outlined risk mitigation strategies, and the need for a highly efficacious oral therapies in MS, testing the combination of BIIB091 with DRF in this Phase 2 study would provide a favorable benefit-risk profile.

1.2. Study Design Schematic

A schematic of the study design is shown in Figure 1.

Figure 1: 257MS201 Study Design



Note: BIIB091 formulation dose for Part 2 to be determined following Part 1 (Week 16) Analysis.

1.3. Schedule of Activities

Study assessments conducted at each visit are listed in Table 1.

Table 1: Schedule of Activities for Part 1 and Part 2

Tests and Assessments	Screening Visit	Baseline Visit[1]	Randomized, Double-Blind Treatment Period[2]							Randomized, Blinded Treatment Period[3]			Unscheduled Visit[4]	ET[5]	Blinded Post-Treatment Safety Follow-Up Visit
Week	**(Within 4 Weeks of Baseline)**	**Day 1**	**Week 1 ± 2 Days**	**Week 2 ± 2 Days**	**Week 4 ± 3 Days**	**Week 6 ± 3 Days**	**Week 8 ± 3 Days**	**Week 12 ± 3 Days**	**Week 16 ± 3 Days**	**Week 24 ± 5 Days**	**Week 36 ± 5 Days**	**Week 48 ± 5 Days**			**Week 50 ± 5 Days**
Eligibility Assessments[6]															
ICF (Main)	X														
Optional ICF for Future Scientific Research	X														
Optional ICF for Genetic Research	X														
Eligibility Criteria[7]	X	X													
Medical History and Prior MS Treatment	X	X													
HIV Testing[8]	X														
FSH[9]	X														
Serum Pregnancy Test[10]	X	X										X			
Hepatitis B (Total HBcAb, HBsAg, and Anti-HBsAg), Hepatitis C, and TB Screen (QuantiFERON)	X														
SARS-CoV-2 Test[11]	X	X													
Randomization		X													

Tests and Assessments	**Screening Visit**	**Baseline Visit**[1]	**Randomized, Double-Blind Treatment Period**[2]							**Randomized, Blinded Treatment Period**[3]			**Unscheduled Visit**[4]	**ET**[5]	**Blinded Post-Treatment Safety Follow-Up Visit**
Week	**(Within 4 Weeks of Baseline)**	**Day 1**	**Week 1 ± 2 Days**	**Week 2 ± 2 Days**	**Week 4 ± 3 Days**	**Week 6 ± 3 Days**	**Week 8 ± 3 Days**	**Week 12 ± 3 Days**	**Week 16 ± 3 Days**	**Week 24 ± 5 Days**	**Week 36 ± 5 Days**	**Week 48 ± 5 Days**			**Week 50 ± 5 Days**
Safety Assessments															
Physical Examination	X	X[12]						X		X	X	X	X	X	X
Vital Signs[13]	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Triplicate 12-Lead ECG[14]	X	X[12]	X	X	X		X	X	X	X	X	X	X	X	X
Hematology[15], Coagulation, and Blood Chemistry	X	X[12]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[10]			X	X	X		X	X	X	X	X			X	X
Urinalysis	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Anti-Tetanus, Anti-Pneumococcal, and Anti-Influenza Antibody Titers[16]		X										X		X	
Total Ig, IgG (including subtypes), IgM, IgA, and IgE	X	X		X	X		X	X	X	X	X	X		X	
C-SSRS[17]	X				X		X		X	X	X	X		X	
PK/PD Assessments[18]															
Plasma for BIIB091 PK and DRF PK[19]		X	X	X	X		X	X	X	X	X	X	X	X	X
Serum for Exploratory Biomarkers	X	X			X		X	X	X	X	X	X	X	X	X
DNA Sample (optional)[20]		X													
TBNK	X	X			X		X		X			X		X	
Whole Blood for Immune Cell Subset Analysis	X	X			X		X		X			X		X	X

Tests and Assessments	**Screening Visit**	**Baseline Visit**[1]	**Randomized, Double-Blind Treatment Period**[2]							**Randomized, Blinded Treatment Period**[3]			**Unscheduled Visit**[4]	**ET**[5]	**Blinded Post-Treatment Safety Follow-Up Visit**
Week	**(Within 4 Weeks of Baseline)**	**Day 1**	**Week 1 ± 2 Days**	**Week 2 ± 2 Days**	**Week 4 ± 3 Days**	**Week 6 ± 3 Days**	**Week 8 ± 3 Days**	**Week 12 ± 3 Days**	**Week 16 ± 3 Days**	**Week 24 ± 5 Days**	**Week 36 ± 5 Days**	**Week 48 ± 5 Days**			**Week 50 ± 5 Days**
Whole Blood for CD69 Assessment	X	X			X		X		X			X		X	X
Whole Blood for Myeloid Assessment	X	X			X		X		X			X		X	X
Efficacy Assessments															
PRO Questionnaires[21]		X						X	X	X	X	X		X	
Brain MRI With and Without Gd[22]	X				X		X	X	X	X		X	X[4, 22]	X[23]	
EDSS	X[24]	X[12]			X		X	X	X	X	X	X	X	X	
T25FW, 9HPT-D, and 9HPT-ND[25]	X	X			X		X	X	X	X	X	X		X	
SDMT and LCLA		X					X	X	X	X	X	X		X	
In-Clinic Konectom Administration[26]		X			X		X	X	X	X	X	X		X	
At-Home Use of Konectom[27]			----------Use of smartphone application----------												
MS Signs and Symptoms	X	X			X		X	X	X	X	X	X	X	X	
Relapse Assessment[4]													X		
Drug Administration															
BIIB091 and Matching Placebo[28]		----------BIIB091 monotherapy (Part 1) and BIIB091/DRF combination therapy (Part 2)----------													
DRF and Matching Placebo[28]		----------DRF monotherapy (Part 1 and Part 2) and BIIB091/DRF combination therapy (Part 2)----------													
Completion of Patient Diary		--Study medication to be recorded in the Patient Diary (for doses administered at study visits and at home)--													

Tests and Assessments	**Screening Visit**	**Baseline Visit**[1]	**Randomized, Double-Blind Treatment Period**[2]							**Randomized, Blinded Treatment Period**[3]			**Unscheduled Visit**[4]	**ET**[5]	**Blinded Post-Treatment Safety Follow-Up Visit**
Week	**(Within 4 Weeks of Baseline)**	**Day 1**	**Week 1 ± 2 Days**	**Week 2 ± 2 Days**	**Week 4 ± 3 Days**	**Week 6 ± 3 Days**	**Week 8 ± 3 Days**	**Week 12 ± 3 Days**	**Week 16 ± 3 Days**	**Week 24 ± 5 Days**	**Week 36 ± 5 Days**	**Week 48 ± 5 Days**			**Week 50 ± 5 Days**
Clinical Drug Supplies															
BIIB091 and Matching Placebo		X			X		X	X	X	X	X				
DRF and Matching Placebo		X			X		X	X	X	X	X				
Review Previous Patient Diary and Dispense New Patient Diary		X			X		X	X	X	X	X	X			
Monitoring															
Concomitant Therapy/Procedures	---------- Concomitant therapy monitoring from signing of ICF through EOS ----------														
AE Recording		----------AE monitoring from the first dose of treatment through EOS----------													
SAE Recording	----------SAE monitoring from signing of ICF through EOS----------														
ADE/UADE Recording	----------ADE/UADE monitoring from signing of ICF through EOS----------														

[1] The Baseline Visit assessments can be split over 2 consecutive days and must be completed prior to the administration of the first dose on Day 1.

[2] The Part 1 and Part 2 treatment periods are double blinded up to the Week 16 Visit.

[3] After Week 16, the participants, the sites, and the study management team members who are not involved in the Week 16 data analysis, will continue to be blinded through Week 48.

[4] Unscheduled visits are to be determined at the discretion of the treating neurologist if no relapse is suspected. Participants are to return to the study site for a separate relapse assessment evaluation (see Section 5.3) to be performed within 72 hours of the onset of any new or worsening neurologic symptom(s). Participants in the Czech Republic must begin treatment for an acute relapse within 5 days of symptom onset, even if the MRI scan has not yet been performed. EDSS should only be assessed at an unscheduled visit if relapse is suspected. Hematology, blood chemistry, and urinalysis will be performed only at the discretion of the treating physician if infection or metabolic disturbance is suspected to be contributing to the unscheduled visit. See footnote 22 for MRI at unscheduled visit for relapse.

[5] Participants who discontinue study treatment early are encouraged to remain in the study and continue protocol-required tests and assessments through the EOS and Follow-Up Visits and would not complete an ET Visit. Participants who withdraw from the study should complete the ET Visit at the time of withdrawal and are also encouraged to complete the blinded post-treatment Follow-Up Visit unless withdrawal is due to death or withdrawal of consent.

[6] Tests and assessments must be completed prior to dispensing study treatment to participants. It is not required that all screening tests and assessments be completed during a single visit.

[7] All inclusion/exclusion criteria should be assessed at the Screening Visit and confirmed prior to the first dose of study treatment.

[8] HIV testing will be performed at the Screening Visit unless prohibited by local regulations.

[9] For women suspected not to be of childbearing potential. Results must be known prior to enrollment.

[10] For WOCBP. Results must be known prior to enrollment.

[11] SARS-CoV-2 PCR test must be performed at the Screening Visit and repeated if the Screening Visit occurs > 2 weeks prior to Baseline (Day 1). Further testing during the study is permitted at the discretion of the Investigator. Testing may be conducted by the central laboratory selected by the Sponsor or locally (Appendix 1).

[12] If the test performed at the Screening Visit is within 7 days of Baseline (Day 1), the assessment does not need to be repeated at Baseline (Day 1).

[13] Participants will have their body temperature, pulse rate, respiratory rate, and diastolic and systolic blood pressure measured. Participants must remain in the same sitting position for 5 minutes prior to having their pulse rate and blood pressure taken.

[14] ECG should be recorded after the participant has been supine for at least 5 minutes. Triplicate ECGs will be recorded at the 2- and 5-hour intensive PK sampling timepoints (Week 4 Visit).

[15] Participants with ALC < LLN at the 2-week safety Follow-Up Visit will return in 2 weeks for retesting and confirmation, and follow-up will be extended for those participants at intervals of 8 weeks to monitor their lymphocyte counts until their ALC > LLN, or for a period up to 6 months, or until they commence another disease-modifying therapy, whichever occurs first. Laboratory safety assessments will be conducted at the central laboratory. The platelet function test may be conducted at the central laboratory or local laboratory, as applicable. All sites are required to conduct the platelet function test if they have the capability to perform it on site or at an external laboratory.

[16] These tests are only for participants who will have received pneumococcal or tetanus vaccine within 5 years or influenza vaccine within 1 year of study participation.

[17] The Baseline screening C-SSRS version will be used at Screening, and the Since Last Visit C-SSRS version will be used for subsequent visits.

[18] Samples for all PK/PD assessments will need to be collected before study treatment administration on the day of the visit unless otherwise noted.

[19] Intensive PK sampling in a subset of participants (see Section 12.9) will be conducted at Week 4 Visit. The PK sampling timepoints for BIIB091, MMF, and HES are -15 minutes (predose) and 1, 2, 3, 4, and 5 hours (postdose; relative to time 0 [the first dose administered]) on that day (see Table 2).

[20] Where local regulations and ethics committee approval allows, an optional blood DNA sample will be collected for unspecified future exploratory genetic research. Participants who opt for this one-time optional DNA sample collection will be required to sign an optional Genetic Research ICF.

[21] PRO questionnaires (i.e., PROMIS-29 profile and FSMC) must be completed under the supervision of the primary treating nurse or study coordinator during clinical visits before objective test performance is tested. Refer to the Study Reference Guide for additional instructions.

[22] MRI assessments should be completed at least 7 calendar days and no more than 14 calendar days prior to Baseline (Day 1) before dosing; subsequent scans will be performed on Weeks 4 (± 3 days), 8 (± 3 days), 12 (± 3 days), 16 (± 3 days), 24 (± 5 days), and 48 (± 5 days). IV corticosteroid treatment and oral corticosteroid treatment must be discontinued 4 weeks prior to and during the Screening period. Brain MRI scans will be performed according to a standardized imaging protocol before and after the administration of single-dose Gd. If the start of a treatment for a relapse with high-dose corticosteroids falls within 7 days of the next scheduled visit, every attempt should be made to obtain the MRI before administration of the first dose of high-dose corticosteroids. If outside the visit window, visit should be recorded as unscheduled. The MRI at an unscheduled visit prior to steroid treatment must be ≥ 21 days after the prior MRI. However, if an MRI at an unscheduled visit is < 21 days after a prior MRI, then the use of Gd should be strongly avoided, unless determined by the Investigator to be clinically indicated. In this scenario, the next regularly scheduled MRI should also be obtained.

[23] MRI at ET Visit will only be performed if an MRI was not performed within 3 weeks prior to termination.

[24]The Screening EDSS will be considered when determining participant eligibility.

[25]Participants should perform 2 separate practice tests for T25FW, 9HPT-D, and 9HPT-ND at their Screening Visit, separated by at least 5 minutes. These data will be recorded. Following the 2 practice tests, participants should complete each test again, separated by at least 5 minutes; the latter data will be recorded as a result of the Screening Visit. If the tests performed at Screening are within 7 days of Baseline (Day 1), they do not need to be repeated at Baseline (Day 1). Only the official test scores are entered into EDC.

[26]For in-clinic Konectom assessments, the 6MWT and MSIS-29 v2 assessments only need to be at Baseline (Day 1) and Weeks 8, 16, 24, 36, and 48.

[27]At-home tests will be requested daily for the first-week post-Baseline (Day 1) and weekly for the remainder of the trial. At-home tests will not be requested for weeks with in-clinic Konectom administration.

[28]For all participants in the study, the time and date of the first dose of treatment must be recorded by site staff in the eCRF. For participants in the intensive PK subset, the time and date of the dose during the Week 4 visit must be recorded by site staff in the eCRF.

Table 2: Schedule of Sample Collection for Intensive PK Sampling in a Subset of Participants at Week 4 Visit for Part 1 and Part 2

	PK Sample Collection Schedule (relative to the first BID [morning] dose)
Predose	-15 minutes
Postdose	1 hour
	2 hours
	3 hours
	4 hours
	5 hours

2. LIST OF ABBREVIATIONS

ΔQTcF	change-from-baseline Fridericia corrected QT interval
ΔΔQTcF	placebo-corrected change-from-baseline Fridericia corrected QT interval
6MWT	6-Minute Walk Test
9HPT	9-Hole Peg Test
9HPT-D	9-Hole Peg Test in the dominant hand
9HPT-ND	9-Hole Peg Test in the nondominant hand
ADE	adverse device event
AE	adverse event
AESI	adverse events of special interest
AI	artificial intelligence
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
aPTT	activated partial thromboplastin time
ARR	annualized relapse rate
AST	aspartate aminotransferase
BCR	B cell receptor
BID	twice daily
BLNK	B-cell linker
bpm	beats per minute
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
CD	cluster of differentiation
CE	Conformité Européenne
CIS	clinically isolated syndrome
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPST	cognitive processing speed test
C-QT	concentration-QT
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{tau}	concentration at dosing time plus dosing interval
C_{trough}	trough concentration
CYP3A4	cytochrome P450 3A4
DC	dendritic cell

DDI	drug-drug interaction
DHA	Directions for Handling and Administration
DMF	dimethyl fumarate
DNA	deoxyribonucleic acid
D	dominant
DRF	diroximel fumarate
EC_{90}	90% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
eGFR	estimated glomerular filtration rate
ELISPOT	enzyme-linked immunospot assay
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ET	early termination
EU	European Union
FAS	Full Analysis Set
FcR	Fc receptor
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FSMC	Fatigue Scale for Motor and Cognitive Function
GA	glatiramer acetate
GC	germinal center
GCP	Good Clinical Practice
Gd	gadolinium
GdE	gadolinium-enhancing
GI	gastrointestinal
GLP	Good Laboratory Practice
HBc	hepatitis B core
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
HES	2-hydroxyethyl succinimide
HIV	human immunodeficiency virus
HPMC	hydroxypropyl methylcellulose
IB	Investigator's Brochure
IC	immune complex
IC_{50}	half-maximal inhibitory concentration
ICE	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation

IDMC	independent data monitoring committee
IFN	interferon
Ig	immunoglobulin
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IR	immediate release
IRB	Institutional Review Board
IRT	interactive response technology
ISO	International Organization for Standardization
ITAM	immunoreceptor tyrosine-based activation motif
IV	intravenous
IVIg	intravenous immunoglobulin
IVMP	intravenous methylprednisolone
JCV	John Cunningham Virus
LCLA	Low-Contrast Letter Acuity
LDL	low-density lipoprotein
LLN	lower limit of normal
macro	macrophage
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMF	monomethyl fumarate
MOA	mechanism of action
mono	monocyte
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSIS-29 v2	29-Item Multiple Sclerosis Impact Scale version 2
ND	nondominant
Nf-κB	nuclear factor-kappa B
NfL	neurofilament
NIST	National Institute of Standards and Technology
Nrf2	nuclear factor (erythroid derived 2) like 2
NSR	nonsignificant risk
OATP1B1	organic anion transporting polypeptide 1B
ODRS	overall disability response score
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PFA	platelet function analyzer
PI	Principal Investigator
PK	pharmacokinetic(s)
PLCγ2	phospholipase C gamma 2

PML	progressive multifocal leukoencephalopathy
PMS	progressive multiple sclerosis
popPK	population pharmacokinetics
PPMS	primary progressive multiple sclerosis
PR	PR interval of the ECG
PRL	paramagnetic rim-positive lesion/phase rim lesion
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	prothrombin time
QD	once daily
QRS	QRS interval of the ECG
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RMS	relapsing multiple sclerosis
RNA	ribonucleic acid
ROS	reactive oxygen species
RR	RR interval of the ECG
RMS	relapsing multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBT	Static Balance Test
SD	standard deviation
SDMT	symbol digit modalities test
SEL	slowly expanding/evolving lesion
SmPC	Summary of Product Characteristics
SPMS	secondary progressive multiple sclerosis
SUSAR	suspected unexpected serious adverse reaction
T25FW	timed 25-Foot Walk
TB	tuberculosis
TBNK	T cell, B cell, NK cell
TEAE	treatment-emergent adverse events
TEC	tyrosine kinase expressed in hepatocellular carcinoma
Th1	T helper 1 cells
Th2	T helper 2 cells
Th17	T helper 17 cells
TID	3 times daily
TQT	thorough QT
TSH	thyroid-stimulating hormone
UADE	unanticipated adverse device event
ULN	upper limit of normal
US	United States

USPI	United States Prescribing Information
UTT	U-Turn Test
WBC	white blood cell
WOCBP	women of childbearing potential

3. INTRODUCTION

3.1. Study Rationale

Currently, there are multiple approved treatments for RMS. However, there remains a significant unmet need in safety, tolerability, convenience, and efficacy of current therapies for MS (see Section 3.2.1 and Section 3.2.2).

BIIB091 is an orally administered, potent, selective, noncovalent (reversible), and peripherally restricted small-molecule inhibitor of BTK, a tyrosine-protein kinase that is a key signaling node immediately downstream of the BCR and FcR engagement. Because it is a reversible inhibitor of BTK, BIIB091 may couple robust efficacy in quieting circulating inflammatory cells with the ability to restore immune functions rapidly after discontinuation when vaccination or management of AEs is needed. The population for this study includes adult participants with RMS.

Unlike irreversible BTK inhibitors that are reliant on BTK half-life to sustain target occupancy over a dosing interval, based on current nonclinical data, the main and desired pharmacologic activity of BIIB091 is expected to depend primarily on and correlate with circulating levels of the compound. The half-life of BIIB091 in humans is relatively short (based on data from the first-in-human Study 257HV101 and Study 257HV105 Part 1B, median $t_{½}$ ranged from 6 to 16 hours across all dose levels), with QD or more frequent dosing required to maintain inhibition of BTK function and subsequent inhibition of B-cell activation, as measured by upregulation of surface expression of CD69. CD69 was chosen as a biomarker of B-cell activation because the upregulation of the CD69 membrane protein is BTK-dependent and correlates with the induction of other proteins upon BCR-mediated B-cell activation. It is expected that inhibition of BTK will also result in inhibition of FcR-mediated myeloid-cell activation, which can be assessed in basophils by surface expression of CD63.

DRF (BIIB098) was developed as a delayed-release, gastro-resistant oral treatment for RMS. DRF, under the trade name Vumerity®, has been approved by the US FDA for the treatment of adults with RMS and in the EU for the treatment of RRMS [VUMERITY® USPI 2022; Vumerity™ SmPC 2022]. DRF is an aminoethyl ester of MMF. In the GI tract, DRF undergoes rapid and complete presystemic hydrolysis through esterases to produce MMF. DRF produces its therapeutic effects primarily by the active metabolite MMF [Werdenberg 2003]. MMF is further metabolized through the tricarboxylic acid cycle, with the exhalation of carbon dioxide as the primary route of elimination, accounting for approximately 60% of the dose. In participants with RRMS, DRF demonstrated safety and tolerability in 2 completed global Phase 3 studies: Study ALK8700-A301 (EVOLVE-MS-1) and Study ALK8700-A302 (EVOLVE-MS-2). In both studies, DRF at a dose of 231 mg BID for 1 week followed by 462 mg BID for 96 weeks (in EVOLVE-MS-1) and at a dose of 462 mg BID for 4 weeks (in EVOLVE-MS-2) had an acceptable safety profile and was well tolerated (see the DRF IB).

The combination of the inhibition of B-cell and myeloid-cell activation with BIIB091 and the modulation of the proinflammatory properties of T cells and myeloid cells with DRF could have an additive or synergistic effect and result in transformative efficacy in minimizing the

underlying inflammation that drives cumulative disability. In addition, this combination therapy is expected to have minimal overlapping adverse effects based on clinical monotherapy data and nonclinical data from the 90-day combination toxicology study. The combination therapy is also expected to have minimal potential for drug-drug PK interactions.

To characterize the clinical safety and efficacy profile of BIIB091 monotherapy in patients with MS prior to assessment of BIIB091 and DRF combination therapy, this adaptive study design consists of 2 sequential parts. Part 1 of this study will evaluate the safety and efficacy of 2 dose levels of BIIB091 monotherapy compared to the standard-dose DRF. Part 2 of this study will evaluate the safety and efficacy of the selected BIIB091 dose in combination with either the standard dose (462 mg BID) or a lower dose (350 mg BID) of DRF, and both combination therapies will be compared to the standard-dose DRF (Figure 1).

3.1.1. Rationale for Study Population

The overall objective of this study is to evaluate the potential efficacy and safety of BIIB091 alone and in combination with DRF in participants with relapsing forms of MS between the ages of 18 and 55 years. People with relapsing forms of MS make up the majority of MS patients. The specific population for this study is representative of the demographics of relapsing forms of MS by clinical and imaging criteria, as well as by age. Based on the study's inclusion and exclusion criteria, it is anticipated none or only a few participants would be incapable of giving informed consent and this study excludes minors.

Clinical data demonstrating the benefit of inhibition of the BTK pathway in patients with RMS are starting to emerge in the literature. Results from a recent Phase 2 clinical trial of the covalent (irreversible) BTK inhibitor evobrutinib in RMS demonstrated significantly fewer T1 GdE lesions during Weeks 12 through Weeks 24 in the evobrutinib 75 mg QD group compared to placebo [Montalban 2019]. Additionally, a Phase 2 clinical trial of the covalent (irreversible) BTK inhibitor tolebrutinib (SAR442168) in patients with RMS demonstrated a significant reduction in the number of new T1 GdE and new or enlarging T2 hyperintense lesions at 12 weeks in the tolebrutinib 60 mg QD group compared to placebo [Reich 2021].

3.1.2. Rationale for Dosing Regimen

3.1.2.1. Rationale for BIIB091 Doses

The Phase 2 clinical trial of tolebrutinib (a covalent, irreversible BTK inhibitor) showed that only the highest dose (60 mg QD) significantly reduced T1 GdE lesions at 12 weeks in participants with RMS [Reich 2021]. In a Phase 1 trial, the 60 mg QD dose demonstrated approximately 93% of mean target occupancy in the periphery [Owens 2022]. Similarly, a Phase 2 study of evobrutinib (another covalent, irreversible BTK inhibitor) showed that the largest and most sustained reduction in ARR was achieved at the highest dose of 75 mg BID when over 95% of BTK target occupancy was achieved in the periphery in about 98% of treated patients [Montalban 2019]. These data suggest that a high level of BTK inhibition in the periphery is required to achieve sufficient efficacy in reducing disease activity in MS.

As a noncovalent inhibitor of BTK, it is hypothesized that BIIB091 treatment will provide clinical benefit in patients with MS as a group mainly through selectively and reversibly targeting BTK-related functions in B cells. Examination of the CD69 expression level on B cells after ex vivo BCR-mediated activation allows for the assessment of the inhibitory effect of circulating BIIB091 [Bame 2021]. In the MAD part of the first-in-human Phase 1 Study 257HV101, administration of 150 mg BID or 300 mg BID of BIIB091 for 14 days demonstrated > 90% mean inhibition of CD69 expression, which was maintained from Day 2 through Day 14 dosing intervals. Serum levels of BIIB091 at C_{trough} appeared to be associated with the extent of CD69 inhibition, and PK/PD modeling predicted an observed curve-fit EC_{90} corresponding to approximately 221 ng/mL. Therefore, a C_{trough} of 221 ng/mL had been set as the lower limit of exposure to maintain a high degree of CD69 inhibition.

Analysis of the clinical data from Study 257HV101 indicated that QT prolongation is an identified risk with BIIB091. The QT prolongation effect was dose dependent (observed only at higher exposure levels) and was driven primarily by C_{max}. Based on the concentration-QTc analysis in the SAD part of the study, for which the model provided the best fit at high concentrations, a mean ΔΔQTcF (i.e., placebo-corrected ΔQTcF) exceeding 15 ms can be avoided by keeping the C_{max} under approximately 4018 ng/mL. Therefore, a mean C_{max} of less than 4018 ng/mL had been set as the upper limit of exposure based on concentration-QTc analysis.

Part 1B data from the Phase 1 formulation PK study, Study 257HV105, demonstrated that the administration of the BIIB091 IR tablet formulation at 250 mg twice on Day 1 (12 hours apart) in the fasted state and at 350 mg twice on Day 1 (12 hours apart) under the fed state resulted in a mean C_{max} < 4018 ng/mL and a mean C_{trough} > 221 ng/mL. In addition, simulated data at steady state from the popPK model based on Study 257HV101 and Part 1B of Study 257HV105 supported a dose range of 200 to 350 mg with BID dosing based on achieving the above thresholds. The BIIB091 350 mg dose, when administered as a single dose and in a 2-dose regimen in Part 1B of Study 257HV105, was well tolerated and may potentially achieve over > 90% of CD69 inhibition in B cells in > 90% of treated participants at steady state.

Study 257HV105 Part 3 evaluated the PK, PD, and safety of a 7-day treatment with BIIB091 IR 250 mg BID under the fed state in 10 evaluable participants. Based on available data from the 10 participants, the BIIB091 250 mg BID dose showed a favorable safety and tolerability profile. The mean C_{max} and C_{tau} were 2500 ng/mL and 407 ng/mL on Day 7 (steady state), respectively. Mean C_{tau} at steady state was above 221 ng/mL in 9 of the 10 treated participants.

To elucidate the exposure-response relationship, 2 BIIB091 doses were selected for Part 1 of this Phase 2 study. The proposed BIIB091 high dose (350 mg BID) and low dose (250 mg BID) were selected to target a high level of BTK inhibition (represented by > 90% CD69 inhibition) in > 90% and 80% to 90% of participants, respectively. Both doses are expected to have favorable safety and tolerability profiles. Data from Part 1 of the Phase 2 study will be used to select the BIIB091 dose with the optimal benefit-risk profile for Part 2. The selected BIIB091 dose for Part 2 could be different from the Part 1 doses (e.g., 300 mg BID).

3.1.2.2. Rationale for Diroximel Fumarate Doses

The standard dose of DRF in the Phase 2 study will follow the approved DRF dose regimen.

In the context of BIIB091 and DRF combination therapy, it is hypothesized that a lower dose of DRF could potentially reduce some of the possible side effects associated with combination therapy while maintaining a high level of efficacy. Di-ester fumarate therapy mainly modulates T-cell immunity. Given inhibition of B-cell-mediated antigen presentation to T cells following BIIB091 treatment, the degree of direct T-cell immunomodulation required to achieve maximal efficacy within MS patients may be reduced. This could potentially allow for a lower than standard dose of DRF when dosed in combination with BIIB091.

DRF is an aminoethyl ester of MMF that undergoes presystemic hydrolysis through esterases to produce MMF. MMF is also the active metabolite of the approved drug product DMF (Tecfidera®). Both DRF and DMF produce their therapeutic effects primarily by the active metabolite MMF. PK assessment has demonstrated the exposure of MMF after oral administration of 462 mg DRF and 240 mg DMF in adults is bioequivalent.

Studies C-1900, 109MS301, and 109MS302 have demonstrated that DMF 240 mg BID (480 mg daily) and 240 mg TID (720 mg daily) doses had comparable levels of efficacy, whereas the 120 mg TID dose (360 mg daily, i.e., 75% of the approved dose) demonstrated a reduction in the number of T1 GdE lesions from Baseline, although not statistically significant. Therefore, the lower dose of DRF is selected at 350 mg BID, corresponding to approximately 75% of the standard DRF daily dose.

3.1.3. Rationale for the Use of Authorized and/or Unauthorized Auxiliary Medicinal Products

This study uses the auxiliary medicinal products Gd-based contrast agents/media (ATC code: V08CA) and IVMP.

The assessment of GdE lesion endpoints require that MRIs be conducted before and after administration of Gd-based contrast agents/media. Gd-based contrast agents/media must have a marketing authorization. Sites will use the Gd-based contrast agents/media currently approved in the local country, according to the SmPC/USPI/local label, as applicable.

IVMP is authorized for the treatment of MS relapse in the US [SOLU-MEDROL® USPI 2021] and other countries, and is an accepted standard of care in the EU [EMA (EMA/CHMP/771815/2011 Rev. 2) 2015] and other regions. IVMP is typically given as high dose (i.e., 1000 mg/day) over a period of 3 to 5 days and may be followed by an oral taper. Thus, IVMP of 1000 mg/day up to a total of 5 days and with or without an oral taper was chosen in this study protocol.

These products are defined in Section 7.3.4.

3.2. Background

3.2.1. Overview of Multiple Sclerosis

MS is a chronic, autoimmune, demyelinating disorder of the CNS characterized by inflammation, demyelination, and axonal injury as well as oligodendrocyte and neuronal loss. It is the most common demyelinating disorder of the CNS, affecting approximately 2.5 million people worldwide and typically diagnosed in young to middle-aged adults. While there has been substantial progress in MS care over the last 25 years, many people with MS continue to experience disease activity and disability progression that culminates in permanent impairment and loss of independence in performing activities of daily living. Additionally, many currently approved therapies are associated with burdensome monitoring or risk of SAEs. Therefore, there remains an unmet need for tolerable MS therapies that, when initiated early in the disease, minimize the underlying inflammation that drives the disease and its cumulative contribution to disability, yet have an acceptable safety profile with low or no risk of opportunistic infection or secondary autoimmunity.

The pathological changes underlying MS are believed to be mediated by activated circulating lymphocytes, which cross the blood-brain barrier and initiate an immune-mediated cascade of events that injures both the grey and white matter of the brain [Frohman 2006]. Pathogenic activation of B cells is considered a key driver in the maintenance of active inflammation in MS. Recent studies in patients with MS have established B cells as a clinically validated target cell type in MS [Hauser 2017; Milo 2016; Montalban 2017]. In addition to B cells, there is a body of support for the pathological role of myeloid cells (monocytes, macrophages, DCs, mast cells, and granulocytes) in MS [Croxford 2015; Mildner 2009; Yamasaki 2014].

3.2.2. Current Therapies for Multiple Sclerosis

Many currently approved therapies are associated with burdensome monitoring, troublesome side effects, or risk of morbidity resulting from susceptibility to serious opportunistic infection. Approved therapies also vary in terms of respective efficacy, resulting in significantly differing individual benefit-risk profiles.

IFN β therapies and GA, administered by intramuscular or subcutaneous injections, are commonly used therapies for RMS, with well-established safety and efficacy profiles. However, they are associated with known side effects (flu-like symptoms for IFN β; lipoatrophy and other injection site pathologies for GA), which can be a significant burden for some people with MS. Additionally, many people continue to experience significant MS disease activity while on treatment.

DMF, DRF, siponimod, fingolimod, teriflunomide, ozanimod, ponesimod, MMF, and cladribine are oral disease-modifying therapies approved for the treatment of RMS. While these therapies offer an improved route of administration, they each vary in terms of their respective mechanisms of action and benefit/risk profiles. People with MS may continue to experience disease activity while on these treatments, and a variety of side effects, which may include lymphopenia, risk of infections (including rare cases of PML), bradycardia, and hepatotoxicity,

may necessitate exclusion of vulnerable patients and in some cases require specialized monitoring both during and prior to initiation of therapy.

Other available disease-modifying therapies are associated with risk (albeit low) of serious side effects (e.g., PML [natalizumab]; life-threatening autoimmune disorders and autoimmune thyroid disease [alemtuzumab]; and cardiotoxicity [mitoxantrone]). Their use is limited in some regions by a restricted distribution program or risk-management plan, limited to people with more severe diseases, or limited to second- or third-line therapy. Cladribine has also been associated with increased risks of infections and severe and prolonged lymphopenia and a higher risk of malignancies compared to placebo.

Ocrelizumab, a recombinant, humanized, monoclonal antibody directed against CD20 (which is predominantly expressed on B cells), is indicated for the treatment of PPMS as well as RMS and is administered as an IV infusion. It is associated with infusion-associated reactions, infections, and a possible increased risk of malignancy.

In summary, the choice of therapies entails tradeoffs between efficacy, safety, tolerability, and convenience, which makes MS a challenging condition to treat successfully. Based on benefit-risk considerations, the most efficacious therapies in RMS are generally reserved for patients who have already experienced significant disease activity and disability progression. These therapies typically require periodic, ongoing laboratory monitoring and have risks that cannot be fully mitigated. Consequently, there remains a high unmet medical need for new MS drugs with further improved efficacy and safety profiles.

3.2.3. BIIB091

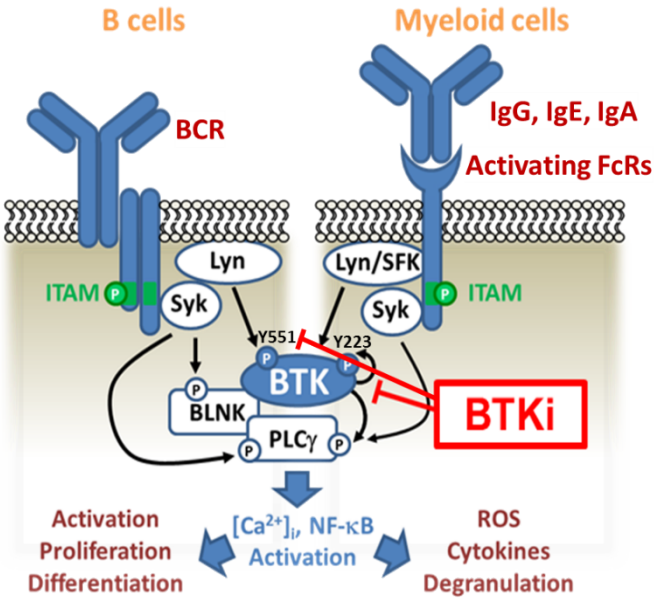
3.2.3.1. BTK Inhibition

Studies in patients with MS have established B cells as a clinically validated target cell type in MS [Hauser 2017; Hauser 1986; Milo 2016; Montalban 2017]. In addition to B cells, there is a body of literature supporting the pathological role of myeloid cells (monocytes, macrophages, DCs, mast cells, and granulocytes) in MS [Croxford 2015; Mildner 2009; Yamasaki 2014].

BTK is a cytoplasmic kinase expressed in many hematopoietic cell types known to be dysregulated in MS; it is a key signaling node immediately downstream of the BCR in B cells and FcRs in myeloid cells. In B cells, BTK mediates B-cell activation and effector functions (such as cytokine secretion and proliferation and differentiation into memory cells and antibody-producing cells) downstream of BCR activation [Corneth 2016] and is required for BCR-mediated antigen presentation to T cells [Benson 2014; Sharma 2009]. In myeloid cells, BTK inhibition blocks FcR-dependent proinflammatory activities (including cytokine secretion by mast cells, monocytes, and macrophages; ROS generation by neutrophils; and degranulation of basophils) triggered by the binding of ICs to FcRs [Koprulu and Ellmeier 2009].

A summary of BTK-dependent signaling in B cells and myeloid cells is presented in Figure 2.

Figure 2: BTK-Dependent Signaling in B Cells and Myeloid Cells



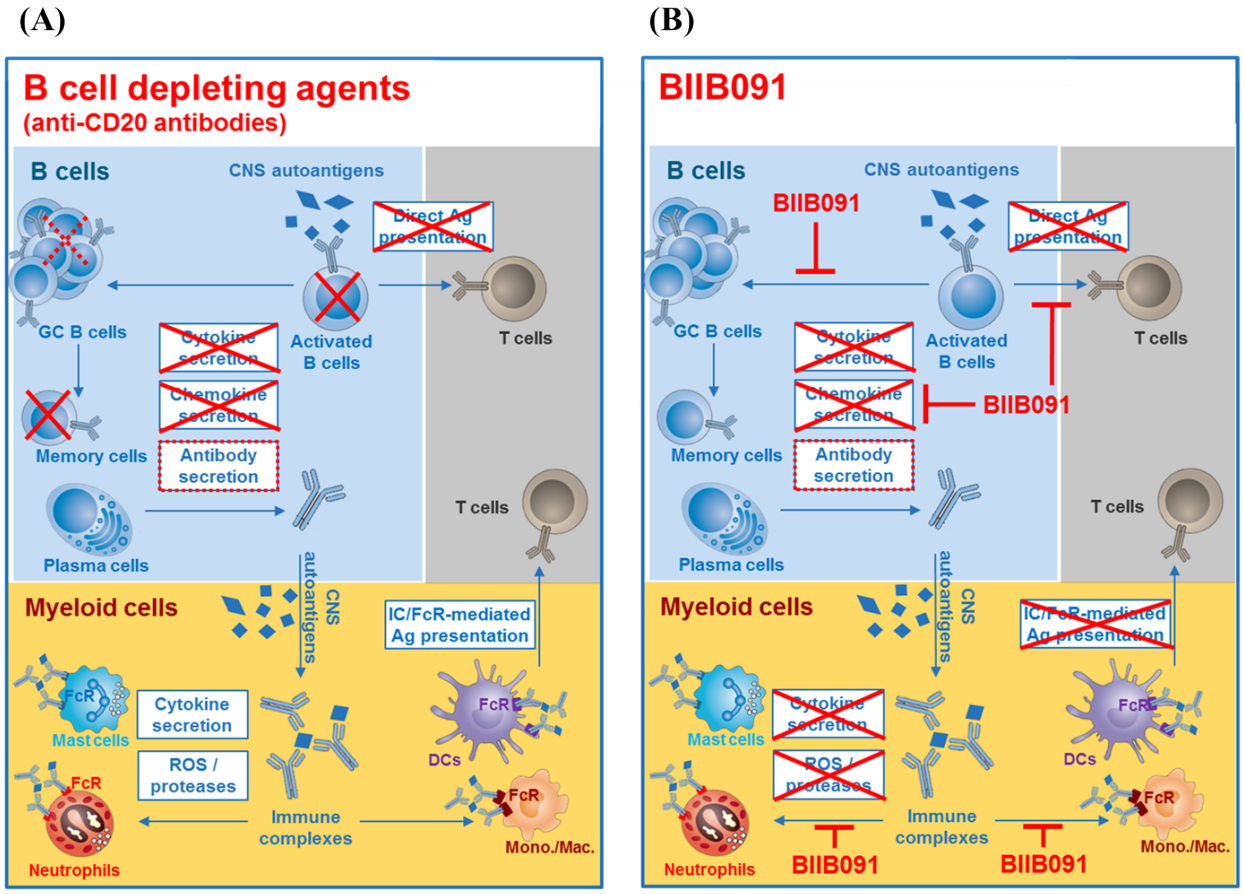
Clinical data demonstrating the benefit of inhibition of the BTK pathway in patients with RMS are starting to emerge in the literature. Results from a Phase 2 clinical trial of the covalent (irreversible) BTK inhibitor evobrutinib in RMS demonstrated significantly fewer T1 GdE lesions during Weeks 12 through Weeks 24 in the evobrutinib 75 mg QD group compared to placebo [Montalban 2019]. Additionally, a Phase 2 clinical trial of the covalent (irreversible) BTK inhibitor tolebrutinib (SAR442168) in RMS demonstrated a significant reduction in the number of new T1 GdE and new or enlarging T2 hyperintense lesions at 12 weeks in the tolebrutinib 60 mg QD group compared to placebo [Reich 2021].

3.2.3.2. BIIB091 Mechanism of Action

BIIB091 is an orally active, potent, selective, reversible (noncovalent), small-molecule BTK inhibitor, a member of the TEC family of protein tyrosine kinases. It is being developed for the treatment of MS, including RMS and PPMS.

Based on its antagonism of BTK-dependent functions in multiple cell types, BIIB091 has the potential to suppress both BCR-mediated and IC/FcR-mediated antigen presentation to T cells, as well as other FcR-dependent functions, such as cytokine secretion, ROS generation, and cell degranulation (Figure 3). As a result, BIIB091 has the potential to inhibit multiple pathological drivers of MS across the spectrum of the disease, from RMS through PPMS.

Figure 3: BIIB091 Targets Myeloid Cells and Shares Mechanisms of Action with B-Cell-Depleting Agents



(A) Due to insufficient saturation of CD20 and lack of the lytic molecular and cellular machinery in CNS, the main MOA of B-cell depleting agents is thought to be peripheral in CNS-draining lymphoid organs, such as cervical lymph nodes. (B) Similar to B-cell depletion, BIIB091 will block peripheral B-cell functions, including cytokine and chemokine secretion, antibody production, and, importantly, antigen presentation to T cells, which is thought to be the critical MOA of B-cell-depleting agents in MS. BIIB091 is anticipated to block B-cell functions without the potential safety liability associated with B-cell depletion. As a second differentiating property, BIIB091 potency will not be impacted by the local tissue environment surrounding target cells, in contrast to antibody-mediated B-cell depletion, which is reported to be less effective in solid tissues than in blood and only partially effective in some cellular contexts, such as GCs. Third, and most importantly, neither B-cell depletion nor BIIB091 is expected to impact plasma cells and pre-existing titers of most autoantibodies. By contrast, BIIB091, but not B-cell-depleting agents, will uniquely block the pathogenic effects of ICs resulting from the binding of autoantibodies to CNS antigens. By blocking FcR signaling, BIIB091 will block IC/FcR-mediated pathogenic effector functions in myeloid cells, among which are IC-mediated antigen presentation to T cells, secretion of cytokine and proinflammatory mediators, and ROS and protease generation.

3.2.3.3. Profile of Previous Experience With BIIB091

BIIB091 is an orally administered, potent, selective, noncovalent (reversible), and peripherally restricted small-molecule inhibitor of BTK. In a biochemical binding assay, BIIB091 exhibited > 500-fold selectivity for BTK relative to all other kinases tested out of a panel of > 400 kinases. When tested in vitro with purified human PBMCs and with human whole blood, BIIB091

inhibited human B-cell activation with IC_{50} at 5.4 nM and 87 nM, respectively, as assessed by inhibition of CD69 upregulation. Based on clinical and nonclinical data, the main pharmacologic activity of BIIB091 depends on the circulating levels of the compound and is quickly reversible as the drug is cleared. Based on data from the first-in-human Study 257HV101 and Study 257HV105 Part 1B, median $t_{½}$ ranged from 6 to 16 hours across all dose levels. Thus, BIIB091 may couple robust efficacy in quieting circulating inflammatory cells with the ability to restore immune functions rapidly after discontinuation when vaccination or management of AEs is needed. The inherent reversibility of the proposed key pharmacologic activity supports the exploration of BIIB091 as an efficacious, differentiated therapy for patients with MS.

Part 1B data from the Phase 1 formulation PK study, Study 257HV105, demonstrated that the administration of the BIIB091 IR tablet formulation at 250 mg twice on Day 1 (12 hours apart) in the fasted state and at 350 mg twice on Day 1 (12 hours apart) under the fed state resulted in a mean C_{max} < 4018 ng/mL and a mean C_{trough} > 221 ng/mL. In addition, simulated data at steady state from the popPK model based on Study 257HV101 and Part 1B of Study 257HV105 supported a dose range of 200 to 350 mg with BID dosing based on achieving the above thresholds. The BIIB091 350 mg dose, when administered as a single-dose and in a 2-dose regimen in Part 1B of Study 257HV105, was well tolerated and is anticipated to achieve > 90% of CD69 inhibition in B cells in > 90% of treated participants at steady state.

Key aspects of the BIIB091 safety profile are described in Section 3.3; see the BIIB091 IB for detailed information on relevant nonclinical and clinical studies.

3.2.4. Diroximel Fumarate

The di-ester fumarates (including DMF and DRF) have been approved by the US FDA under the trade name Tecfidera and Vumerity for the treatment of RMS, including CIS, RRMS, and active SPMS, in adults [TECFIDERA® USPI 2022; VUMERITY® USPI 2022]. DMF and DRF have been approved by the EMA for the treatment of adult patients with RRMS [Tecfidera™ SmPC 2022 ; Vumerity™ SmPC 2022], and both drugs are also approved in other countries.

3.2.4.1. Diroximel Fumarate Mechanism of Action

DMF and DRF, when orally administered as 240 and 462 mg, respectively, are both metabolized to the same active metabolite MMF with bioequivalent levels of exposure. DRF is also metabolized to HES; however, this is an inactive metabolite. Hence, the systemic safety and efficacy profiles of both treatments are similar. In 2 global Phase 3 studies (EVOLVE-MS-1 and EVOLVE-MS-2), the DRF dose regimen demonstrated favorable safety and tolerability. Additionally, in Study EVOLVE-MS-2, the duration, incidence, and severity of participant-reported GI symptoms were significantly lower compared to treatment with DMF [Wray 2022].

The MOA of fumarate esters is unknown but appears to be partly mediated through activation of the Nrf2 antioxidant response pathway [Nguyen 2003]. DMF has been shown to increase the proportion of naïve T cells and frequencies of T regulatory and Th2 subsets, while decreasing memory T cells, Th1, and Th17 T-cell subsets [Mehta 2019; Mills 2018]. Similarly, B cell,

myeloid, and natural killer populations are also shifted toward a more anti-inflammatory state [Mills 2018]. On the other hand, DMF may have minimal impact on B-cell activation or antibody production. A recent study showed that DMF treatment for 2 years had no effect on Ig isotype concentrations [Longbrake 2020]. In a study comparing the vaccine responses, DMF-treated patients were able to mount immune responses to recall antigens, neoantigens, and T-cell-independent antigens that were comparable to the responses in IFN-treated patients [von Hehn 2018]. In addition, it has been demonstrated that BCR-mediated activation of B cells is not inhibited in DMF-treated MS patients (Biogen internal data).

3.3. Benefit-Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected AEs of BIIB091 and DRF is provided in the BIIB091 IB, the DRF IB, and the ICF for this study. A high-level summary of those benefits and risks known during study design is provided here.

3.3.1. BIIB091 Monotherapy Benefit-Risk Assessment

BIIB091 is hypothesized to provide clinical benefits in people with MS as a group mainly through selectively and reversibly targeting BTK-related functions in B cells and myeloid cells. (See Section 3.3.3 for data on next-generation BTK inhibitors currently in later stages of development in MS.)

The potential risks related to participation in this study are justified by the anticipated benefit to participants.

QTc prolongation is an identified risk with BIIB091. It was dose dependent and observed at the higher exposures in the first-in-human Phase 1 Study 257HV101. Based on that data, the mean C_{max} exposure limit was set at 4018 ng/mL in the formulation development PK study 257HV105 to ensure that participants would not encounter any clinically significant QTc prolongation. Study 257HV105 was designed to optimize and select a BIIB091 formulation.

In Study 257HV101 (BIIB091 IR capsule formulation) and with available data from Study 257HV105 (BIIB091 modified release formulations at doses ranging from 150 to 500 mg and the IR tablet formulation at doses ranging from 150 to 350 mg), there were no AEs reported in association with QT/QTc prolongation, ventricular tachyarrhythmia, or other cardiac AEs. BIIB091 did not have a clinically relevant effect on heart rate or blood pressure. Additionally, there were no deaths, no SAEs, or severe AEs reported.

Moreover, observed mean BIIB091 exposure levels in the formulation development PK study 257HV105 have not exceeded the set C_{max} level, and it is not anticipated that doses selected for this Phase 2 study would result in an exposure that would exceed that set mean C_{max}. Based on nonclinical data, CYP3A4 inhibition is predicted to produce an approximately 2.2-fold increase in BIIB091 exposure. However, clinical data for DDI are not yet available. To avoid higher than expected exposure levels, participants receiving CYP3A4 inhibitors will not be allowed to enter the Phase 2 study, and CYP3A4 inhibitors will not be allowed during the study.

The Phase 2 study will continue to follow risk mitigation measures for QT/QTc prolongation, which will include intensive triplicate 12-lead ECGs during the first month of dosing in all participants. Additional risk mitigations for the QT/QTc prolongation will be reflected in the inclusion and exclusion criteria, discontinuation criteria, and when applicable, study stopping criteria.

The risk of infections with BTK inhibitors varies. Over half of patients taking ibrutinib or acalabrutinib for oncology indications (first- and second-generation BTK inhibitors, respectively) experience an infectious event of any grade. These 2 BTK inhibitors have been associated with serious fungal infections such as aspergillosis in patients with cancer [Alkharabsheh 2021; Lipsky and Lamanna 2020; Tillman 2018; Varughese 2018].
By comparison, next-generation BTK inhibitors such as fenebrutinib and evobrutinib studied in autoimmune diseases show less frequent infectious events. Among fenebrutinib-treated individuals with rheumatoid arthritis, 8% to 15% of patients had any infection at 12 weeks, with a similar percentage in the placebo group (15%) [Cohen 2020]. Among evobrutinib-treated individuals with MS, 19% to 33% of patients had any infection at 24 weeks, with a similar percentage in the placebo group (30%) [Montalban 2019]. This pattern of results may be due to the greater target selectivity of next-generation BTK inhibitors. In addition, much of the data regarding general infections with BTK inhibitors are from studies of individuals with malignancies who may have higher risks of infection, even in the absence of therapy [Weber 2021].

BIIB091 is a next-generation BTK inhibitor that causes reversible and selective immunomodulation of the BTK pathway. As a result of the proposed MOA of BIIB091, there is potential for an increased risk of infection. However, to date, there is no evidence of increased risk of infections in human volunteers based on the available limited clinical data.

General risk mitigation for infections will be implemented. Participants must have a normal WBC and ALC to participate in the study. Symptoms suggestive of infections and temperature checks for signs of a fever (> 37.5˚C) will be assessed at Screening and throughout the study. COVID-19-specific risk mitigations will also be implemented in accordance with the Sponsor's monitoring and prevention control measures for SARS-CoV-2 infection and will be amended based on emerging local, regional, and national guidance. An IDMC will review the clinical data and make recommendations regarding the study conduct.

Additionally, hemorrhage and bleeding have been described as class side effects for earlier generation BTK inhibitors [von Hundelshausen and Siess 2021], hence monitoring for potential BIIB091 effects on platelet function will be implemented in this study. Also, hepatic events have been reported with other BTK inhibitors in late-phase clinical development [Montalban 2019; Sanofi 2022]. A more conservative approach was taken for the relevant inclusion and exclusion criteria (Section 6.1 and Section 6.2, respectively), as well as the monitoring plan for liver function tests, as detailed in Section 8.2.

3.3.2. Diroximel Fumarate Monotherapy Benefit-Risk Assessment

DRF has been approved by the US FDA for the treatment of adults with RMS and in the EU for the treatment of RRMS [VUMERITY® USPI 2022; Vumerity™ SmPC 2022], and it was subsequently approved in several countries. In participants with RRMS, DRF demonstrated safety and tolerability in 2 global Phase 3 studies (see the DRF IB for details). The approval for DRF relied on the efficacy and, in part, on the prior findings of safety for the listed treatment DMF, marketed as Tecfidera [TECFIDERA® USPI 2022; Tecfidera™ SmPC 2022].

The safety profile of DRF relies on the well-known safety profile of DMF. Important identified risks for DMF, and hence DRF, include PML and decreases in leukocyte/lymphocyte counts; flushing and GI events (abdominal pain, nausea, diarrhea, and vomiting) are among the most commonly experienced AEs with DMF. Data from DRF study ALK8700-A302 (EVOLVE-MS-2) showed that over a 5-week treatment period, DRF showed a 46% reduction in the number of days patients experienced GI symptoms when compared with DMF. Moreover, data from Study ALK8700A301, a 96-week open-label study of 1057 MS patients, showed DRF safety data comparable to that of DMF, and no new safety signals have been identified. In conclusion, DRF has a similar efficacy and safety profile as DMF, with fewer GI issues. DRF will be included as monotherapy in Part 1 and Part 2 of this study and also evaluated in a combination therapy regimen with BIIB091 in Part 2 of this study.

Risk mitigation for DRF in this study will include monitoring for ALC, leucocyte counts, liver function, and opportunistic and other infections. It will also include treatment withholding or discontinuation if safety thresholds are met for these items. Additional risk mitigations specific to DRF will be reflected in the inclusion and exclusion criteria, discontinuation criteria, and when applicable, study stopping criteria. An IDMC will review the clinical data and make recommendations regarding the study conduct.

3.3.3. BIIB091 and Diroximel Fumarate Combination Therapy Benefit-Risk Assessment

The combination therapy of BIIB091 and DRF is not expected to have a compounding effect on QTc. The DRF TQT study (Study ALK8700-A110) showed that DRF treatment did not have a clinically relevant effect on QTc in humans. Lymphopenia may be observed with DRF, mostly impacting CD4 and CD8 T cells with an initial decline and stabilization by 24 weeks. While BIIB091 exerts its effects on B cells, it is not a B-cell-depleting agent and, therefore, BIIB091 is not expected to cause additive lymphopenia (no AEs of lymphopenia were reported in > 1 participant in the MAD part of Study 257HV101). Additionally, DRF may cause an elevation in hepatic transaminases as anticipated from the DMF data where the active metabolite is the same as DRF (most were ≤ 3 × ULN, and these abnormalities resolve upon DMF discontinuation). With the limited clinical data available (data from Study 257HV101 and interim data for Part 1 and Part 1B of Study 257HV105), there is no evidence of increased risk of elevation in liver enzymes with BIIB091 treatment (see the BIIB091 IB and DRF IB for details). The monitoring plan for liver enzymes is detailed in Section 8.1.

There is a theoretical risk for increased infections with the combination treatment despite having a minimally overlapping MOA. Based on available data from other next-generation BTK inhibitors clinical studies in later stages of development, there is no anticipated increased risk of serious infections with BIIB091. Fenebrutinib Phase 2 studies in autoimmune diseases reported serious infections in 6 patients (2%) in combined fenebrutinib cohorts and 5 patients (1.8%) in the combined placebo cohorts with no imbalance in pattern, duration, seriousness, or severity of infection in patients receiving fenebrutinib versus placebo despite a background of the use of immunosuppressants [Oh 2021].

Risk mitigations for infections were outlined for each drug separately. Furthermore, there will be additional risk mitigations for serious infections that will be implemented in this study with close monitoring of ALC, leukocytes count, and Ig levels. Additional risk mitigations specific to the combination treatment will be reflected in the inclusion and exclusion criteria, discontinuation criteria, and when applicable, study stopping criteria.

To support the proposed combination clinical study, the Sponsor has conducted a 90-day, GLP-compliant combination toxicology study of BIIB091 and DRF in monkeys. In this combination toxicology study, the following results were observed: nonadverse increases in heart rate (observed in the combination arm; not biologically significant) and nonadverse hematology changes (decreases in red blood cell mass indices and increases in reticulocytes; and observed in the BIIB091 arm and in previous BIIB091 studies, and was, therefore, likely attributable to BIIB091). In this nonclinical combination study, no QTc changes were observed, and no findings were indicative of additive or synergistic effects.

To mitigate risks in the study, an IDMC will review the clinical data and make recommendations regarding the study conduct (Section 14.3.2).

3.3.4. Overall Benefit-Risk Assessment

As with many clinical studies, there is a burden for participants in this clinical study, which includes 12 scheduled study visits, up to 14 blood sample collections, 8 scheduled MRI tests, physical discomfort from participation, and time spent on completing assessment questionnaires. Despite that, participants in this study are expected to benefit from intensive monitoring of their disease and its state. Moreover, all participants will be receiving a form of active drug (either BIIB091, DRF, or both) that is expected to have a positive impact on their disease. This is not a placebo-controlled study (see Section 7.3.3 for details).

In conclusion, BIIB091 has an acceptable safety profile, has an established MOA, and belongs to the class of next-generation BTK inhibitors that are showing promising results in completed Phase 2 MS clinical trials [Montalban 2019; Reich 2021]. Additionally, DRF has an established safety profile and is approved in the US for the treatment of RMS, in the EU for the treatment of RRMS, and in other countries. Considering the minimally overlapping MOA, toxicology combination therapy data, outlined risk mitigation strategies, and the need for highly efficacious oral therapies in MS, testing the combination of BIIB091 with DRF in the Phase 2 study would provide a favorable benefit-risk profile.

4. STUDY OBJECTIVES AND ENDPOINTS

Part 1: Primary and Secondary Objectives

Primary Objective	**Primary Endpoints**
To investigate the safety and tolerability of BIIB091 monotherapy in participants with RMS	• Incidence of AEs from the date of study treatment and incidence of SAEs from the date of signing of ICF through the Follow-Up Visit
Secondary Objectives	**Secondary Endpoints**
To evaluate the effects of BIIB091 monotherapy on the MRI measures of active CNS inflammation	• Cumulative number of new T1 GdE lesions at Weeks 8, 12, and 16 • Cumulative number of new or enlarging T2 hyperintense lesions at Weeks 8, 12, and 16 • Cumulative volume of new or enlarging T2 hyperintense lesions at Weeks 8, 12, and 16
To evaluate the effect of BIIB091 monotherapy on QTc and other ECG parameters	• QTcF, RR, PR, QRS, and QT intervals and heart rate • Incidence of ECG abnormalities as assessed by 12-lead ECG measurements

Part 2: Primary and Secondary Objectives

Primary Objective	**Primary Endpoint**
To evaluate the effects of BIIB091 combination therapy with DRF compared with the DRF monotherapy arm on the key MRI measure of active CNS inflammation	• Cumulative number of new T1 GdE lesions at Weeks 8, 12, and 16

Secondary Objectives	Secondary Endpoints
To evaluate the effects of BIIB091 combination therapy with DRF compared with the DRF monotherapy arm on additional MRI measures of active CNS inflammation	• Cumulative number of new or enlarging T2 hyperintense lesions at Weeks 8, 12, and 16 • Cumulative volume of new or enlarging T2 hyperintense lesions at Weeks 8, 12, and 16
To investigate the safety and tolerability of BIIB091 combination therapy with DRF in participants with RMS	• Incidence of AEs from the date of study treatment and incidence of SAEs from the date of signing of ICF through the Follow-Up Visit
To evaluate the effect of BIIB091 combination therapy with DRF on QTc and other ECG parameters	• QTcF, RR, PR, QRS, and QT intervals and heart rate • Incidence of ECG abnormalities as assessed by 12-lead ECG measurements

Part 1 and Part 2: Exploratory Objectives

Exploratory Objectives	Exploratory Endpoints
To evaluate the maintenance of effect of BIIB091 monotherapy (Part 1) and BIIB091 combination therapy with DRF (Part 2) on additional MRI measures	May include, but are not limited to, the following assessments: • Number and cumulative number of new T1 GdE lesions from Week 8 to Week 48 • Number of T1 GdE lesions from Week 8 to Week 48 • Number, cumulative number, and cumulative volume of new or enlarging T2 hyperintense lesions at each imaging visit • Number, cumulative number, and cumulative volume of new unenhancing T1 hypointense

Exploratory Objectives	Exploratory Endpoints
	lesions at each imaging visit and number that persist for ≥ 24 weeks • Normalized T1-weighted signal intensity in unenhancing T1 hypointense lesions over 48 weeks • SEL-related outcome measures may include number and volume at baseline of SELs and change from baseline in normalized T1-weighted signal intensity and unenhancing T1 lesion volume in SELs over 48 weeks • Change from baseline in tissue characteristics and number of new and disappearing PRLs over 48 weeks • Change in tissue compartment and/or regional brain volume over 48 weeks
To evaluate the effects of BIIB091 monotherapy (Part 1) and BIIB091 combination therapy with DRF (Part 2) on clinical and PRO measures	• ARR over 48 weeks • Proportion of relapsing participants over 48 weeks • ODRS over 48 weeks • Change from baseline over 16 and 48 weeks in the following individual assessments: – EDSS – T25FW – 9HPT-D and 9HPT-ND – SDMT – LCLA

Exploratory Objectives	Exploratory Endpoints
	– PROMIS-29 profile – FSMC
To evaluate the effects of BIIB091 monotherapy (Part 1) and BIIB091 combination therapy with DRF (Part 2) on immune cell activity and PD biomarkers	• May include, but are not limited to, the following assessments: – Change in immune cell subsets over time – B-cell activation (CD69 expression) – Change in serum NfL levels
To evaluate the effects of BIIB091 monotherapy (Part 1) and BIIB091 combination therapy with DRF (Part 2) on digital outcome measures	• Longitudinal change in Konectom-based digital outcome assessments
To evaluate the PK in BIIB091 monotherapy (Part 1), MMF, and HES and BIIB091 combination therapy with DRF (Part 2)	• C_{trough} over time • C_{max} at Week 4 Visit in a subset of participants with intensive PK sampling

This clinical study collects samples that, under separate optional consent, may be used for future scientific and genetic research. Objectives related to this future research have not been determined.

5. STUDY DESIGN

5.1. Study Overview

This is a 2-part, multicenter, randomized, blinded, active-controlled Phase 2 study to sequentially evaluate the safety and efficacy of BIIB091 monotherapy and BIIB091 combination therapy with DRF in approximately 275 participants with RMS. This study will be conducted at approximately 80 sites globally.

Randomization will be performed using IRT. In Part 1, participants will be randomized in a 2:2:1 ratio to the monotherapy of either the proposed high-dose (350 mg) BIIB091 group, the low-dose (250 mg BID) BIIB091 group, or the standard-dose (462 mg BID) DRF group, respectively. In Part 2, participants will be randomized in a 1:1:1 ratio to the selected BIIB091 dose with the standard-dose (462 mg BID) DRF combination therapy group, the selected BIIB091 dose with the low-dose (350 mg BID) DRF combination therapy group, or the standard-dose (462 mg BID) DRF monotherapy group, respectively. (Note: the selected BIIB091 dose for Part 2 will be determined following Part 1 [Week 16] analysis.) In both Part 1 and Part 2, the randomization will be stratified by intensive PK cohort (Yes/No) and region (Eastern Europe vs. Other). For stratification, Eastern Europe will include participants from countries such as Poland and the Czech Republic.

See Figure 1 for a schematic of the study design.

5.1.1. Part 1

Part 1 will include a 4-week screening period; a 16-week double-blind, active-controlled treatment period; a 32-week blinded, active-controlled treatment period; and a 2-week post-treatment safety follow-up period. Participants with active RMS will be randomized to 3 treatment groups: high-dose BIIB091 monotherapy (350 mg BID), low-dose BIIB091 monotherapy (250 mg BID), and DRF monotherapy at the standard dose (462 mg BID).

The primary analysis of the Part 1 primary, secondary, and selected exploratory endpoints will be performed after all participants complete the 16-week visit. The primary objective of Part 1 of the study is to investigate the safety and tolerability of BIIB091 monotherapy in participants with RMS. As detailed in the BIIB091 IB, AESIs include ventricular tachyarrhythmia, clinically significant QT prolongation, and hepatic events. BIIB091 has a relatively short half-life, and multiple dosing periods in the Phase 1 studies have shown that the exposure reaches a steady state within 5 to 7 days. The primary analysis at 16 weeks would allow a sufficient time period for signal detection with intensive monitoring of AEs, safety laboratory assessments, and ECGs. Additionally, subsequent to the Week 16 analysis, a longer period of safety monitoring for BIIB091 monotherapy will continue until Week 48.

An IDMC will review the safety and laboratory data from the Part 1, Week 16 primary analysis and make a recommendation to the Sponsor on whether to initiate Part 2 (see Section 12.8 and

Section 14.3.2 for details). In the event of unfavorable safety findings, the IDMC could recommend pausing or stopping a cohort or the study or recommend a modification to the study design. Details regarding the IDMC review of data will be provided in the IDMC charter.

The Week 16 primary efficacy analysis in Part 1 would allow for a sufficient period to detect a meaningful effect on MRI lesions to support further development of BIIB091. Phase 2 studies with primary endpoints measured after a 12- to 24-week controlled treatment phase are common in RMS [Kappos 2008; Montalban 2019; Traboulsee 2020]. The efficacy signals in tolebrutinib were also observed within this time period [Reich 2021]. Clinical and MRI data from the entire 48-week study treatment period will be analyzed as exploratory endpoints.

Selected Sponsor team members will be unblinded to participate in the primary analysis of Part 1 data at Week 16 (see Section 14.3.1 for details). This team will review the Part 1, Week 16 safety and efficacy data and confirm whether to proceed to Part 2 (based on the overall benefit-risk profile) and select the BIIB091 dose to be used in Part 2 (Figure 1). If the study were to be stopped, participants would not complete Part 1, and the study would not proceed to Part 2.

5.1.2. Part 2

Part 2 will include a 4-week screening period; a 16-week double-blind, active-controlled treatment period; a 32-week blinded, active-controlled treatment period; and a 2-week post-treatment safety follow-up period. Participants with RMS will be randomized to 3 treatment groups: the selected BIIB091 dose in combination with the standard dose (462 mg BID) of DRF, the selected BIIB091 dose in combination with the lower dose (350 mg BID) of DRF, and DRF monotherapy at the standard dose (462 mg BID). The primary analysis comparing the BIIB091/DRF combination therapy to DRF monotherapy will be performed after all participants complete the Week 16 visit in Part 2.

Selected Sponsor team members who were unblinded for the 16-week primary analysis of Part 1 data will also participate in the 16-week primary analysis of Part 2 safety and efficacy data (see Section 14.3.1 for details).

Final analysis of the 48-week data from Part 1 and Part 2 will allow for the assessment of longer-term safety and efficacy (clinical and imaging treatment effects) of BIIB091 monotherapy and BIIB091 combination therapy with DRF. For maintenance of blinding, members of the study management team who are not involved in the Week 16 data review (in Part 1 and Part 2) and the study sites will remain blinded for the entire duration of the study (Section 7.4). Details on how the study blind is maintained will be provided in a separate unblinding plan.

5.2. Study Duration for Participants

Participants in Part 1 of the study cannot participate in Part 2 of the study. In Part 1 and Part 2, the total study duration for each participant will be up to 54 weeks and includes the following:

- 4-week screening period

- 16-week double-blind, active-controlled treatment period
- 32-week blinded, active-controlled treatment period
- 2-week post-treatment safety follow-up period

Participants will have up to 12 scheduled visits during the study. All visits should be performed ± 2 to 5 days from the nominal visit day. Visit days are calculated with respect to Day 1 (the date of the first dose).

The ET Visit is a visit where Week 48 assessments are performed for participants who withdraw from the study early.

The EOT date is the date at which the last dose of study treatment is administered (Week 48 for treatment period completers and at any time during the blinded treatment period for participants who permanently discontinue study treatment early or withdraw from the study early).

The EOS date for a participant may be the last study visit, last follow-up telephone conversation, or last protocol-specified assessment, or if the participant has ongoing AEs that are being followed, the date may be the date of AE resolution.

Participants will complete protocol-specified assessments according to the Schedule of Activities (Table 1).

5.2.1. Screening Period

During the screening period for both Part 1 and Part 2, participants who sign the ICF will undergo all screening procedures to determine their eligibility to participate in the study. Eligible participants who meet all of the inclusion criteria and none of the exclusion criteria as specified in Section 6 will be randomized and enter the Part 1 or Part 2 treatment period (see Section 6.3.2).

Screening of participants for Part 2 will depend on the review of Part 1, Week 16 data by the IDMC and a decision from the select unblinded Sponsor team members to proceed to Part 2 of the study.

5.2.2. Randomization (Day 1)

For both Part 1 and Part 2, on Day 1, the Investigator should ensure that the participant meets the eligibility criteria and undergoes all Day 1 assessments according to the Schedule of Activities (Table 1). Only participants confirmed to be eligible will be randomized and receive study treatment.

Randomization will be performed using IRT. In Part 1, participants will be randomized in a 2:2:1 ratio to the monotherapy of either the proposed high dose (350 mg) BIIB091 group, the low-dose (250 mg BID) BIIB091 group, or the standard-dose (462 mg BID) DRF group, respectively. In Part 2, participants will be randomized in a 1:1:1 ratio to the selected BIIB091 dose with

standard-dose (462 mg BID) DRF combination therapy group, the selected BIIB091 dose with low-dose (350 mg BID) DRF combination therapy group, or the standard dose (462 mg BID) DRF monotherapy group, respectively. (Note: the selected BIIB091 dose for Part 2 will be determined following Part 1 [Week 16] analysis.) In both Part 1 and Part 2, the randomization will be stratified by intensive PK cohort (Yes/No) and region (Eastern Europe vs. Other). For stratification, Eastern Europe will include participants from countries such as Poland and the Czech Republic.

5.2.3. Treatment Period (Day 1 – Week 48)

For both Part 1 and Part 2, participants will visit the study site for safety, MRI, and clinical efficacy assessments from Day -28 to Day 1 (MRI assessments should be completed at least 7 calendar days and no more than 14 calendar days prior to Baseline [Day 1]) and Weeks 4, 8, 12, 16, 24, and 48. Additional specific safety assessments will be performed at Weeks 1, 2, 6, 36, and 50. The primary efficacy endpoint in Part 2 will be the cumulative number of new T1 GdE lesions at Weeks 8, 12, and 16. For Part 1 and Part 2, the last dose of study treatment will be administered on Week 48.

For both Part 1 and Part 2, all participants, Investigators, and the study management team will be blinded to participant treatment assignments before all participants complete the first 16-week visit. Only selected Sponsor team members will be unblinded to participate in the 16-week data analyses (see Section 14.3.1). All participants, Investigators, and the remaining study management team members, especially those directly interacting with study sites, will remain strictly blinded for the study, including the 48-week controlled treatment period and the 2-week safety follow-up period. To further maintain blinding, each study site will have a treating neurologist and an examining neurologist. The treating neurologist will function as the primary treating physician and will conduct all participant safety assessments. The examining neurologist will conduct all EDSS evaluations and relapse assessments but will not be involved in any other aspect of participant care.

Participants will complete protocol-specified assessments according to the Schedule of Activities (Table 1). All screening assessments will be completed prior to administration of study treatment. The PRO questionnaires should be completed by the participant (unassisted by the spouse, family members, legal guardian, friends, site staff, or trained healthcare professionals) prior to all other assessments and prior to the study treatment administration, as disease assessments/clinical evaluations may confound the results.

5.2.4. End of Treatment Period (Week 48/ET)

The end of the blinded, active-controlled treatment period is Week 48 for both Part 1 and Part 2.

Participants who remain in the study through the 48-week treatment period are considered to have successfully completed the treatment period. Participants who complete Part 1 will not participate in Part 2.

Participants in Part 1 and Part 2 who do not remain in the study through Week 48 are considered to have discontinued study treatment early. Participants who discontinue study treatment early are encouraged to remain in the study and continue protocol-required tests and assessments through the EOS and Follow-Up Visits and would not complete an ET Visit.

Participants in Part 1 and Part 2 who withdraw from study participation and do not complete the 48-week treatment period should complete the ET Visit at the time of withdrawal and are also encouraged to complete the blinded post-treatment Follow-Up Visit, unless withdrawal is due to death or withdrawal of consent.

5.2.5. Safety Follow-up Period (2-week Period)

Participants will complete protocol-specified safety assessments according to the Schedule of Activities (Table 1). Participants with ALC < LLN at the 2-week safety Follow-Up Visit will return in 2 weeks for retesting and confirmation, and follow-up will be extended for those participants at intervals of 8 weeks to monitor their lymphocyte counts until their ALC > LLN, or for a period up to 6 months, or until they commence another disease-modifying therapy, whichever occurs first.

5.3. Relapses

An MS relapse is defined as the onset of new or recurrent neurologic symptoms lasting at least 24 hours, accompanied by new objective abnormalities on a neurological examination and not explained solely by non-MS processes, such as associated with fever, infection, severe sepsis, or drug toxicity (adapted from [Schumacher 1965]). The participant must have objective signs on the examining neurologist's examination confirming the event. New or recurrent neurologic symptoms that evolve gradually over months should be considered disease progression, not an acute relapse, and should not be treated with steroids. New or recurrent neurologic symptoms that occur less than 30 days following the onset of a protocol-defined relapse should be considered part of the same relapse and would not be treated with IVMP within the protocol.

Participants who experience new neurologic symptoms must contact the treating neurologist or treating nurse within 48 hours of the onset of symptoms to complete a telephone questionnaire to determine the necessity of an unscheduled Relapse Assessment Visit. If required, the participant will then be evaluated in person by the treating neurologist within 72 hours of the onset of the potential relapse. If, in the opinion of the treating neurologist, an MS relapse may have occurred, the participant must also be evaluated by the examining neurologist within 5 days of the onset of the symptoms. The examining neurologist is to perform a detailed neurologic examination and obtain an EDSS score. New objective findings on a neurological examination performed by the examining neurologist are required to confirm that a protocol-defined relapse has occurred. Participants may not begin corticosteroid treatment of the relapse per protocol until after the examining neurologist has examined them. The examining neurologist is permitted to report the examination findings to the treating neurologist so they can evaluate treatment options.

Relapse Assessment Visits are to be conducted within 72 hours of the onset of any new or worsening neurologic symptom(s) or suspected protocol-defined relapse. Unscheduled Relapse Assessment Visits should not modify or replace the participant's visit schedule.

5.3.1.1. Treatment of Relapses on Scheduled or Unscheduled Visits

Treatment of an acute relapse event may proceed at the discretion of the treating neurologist only after the examining neurologist has completed their examination and after a Gd-enhancing MRI of the brain has been performed (if considered necessary by the treating neurologist) [Table 1]. Participants in the Czech Republic must begin treatment for an acute relapse within 5 days of symptom onset, even if the MRI scan has not yet been performed. The treatment for relapse in this study is IVMP ≤ 1000 mg/day for up to a maximum of 5 days with or without an oral prednisone taper (up to 15 days). Methylprednisolone can be given once a day or in divided doses. Any changes to this treatment should first be discussed with the Sponsor Medical Director or designee. Steroid retreatment of the same relapse (see Section 5.3) is not allowed unless approved by the Sponsor Medical Director or designee. Study treatment dosing is to continue uninterrupted during IVMP treatment.

If the start of treatment for relapse with high-dose corticosteroids falls within 7 days of the next scheduled visit, every attempt should be made to obtain the MRI before administration of the first dose of high-dose corticosteroids. If outside the visit window, the visit should be recorded as unscheduled. The MRI at an unscheduled visit prior to steroid treatment must be ≥ 21 days after the prior MRI. However, if an MRI at an unscheduled visit is < 21 days after a prior MRI, then the use of Gd should be strongly avoided, unless determined by the Investigator to be clinically indicated. In this scenario, the next regularly scheduled MRI should also be obtained.

5.4. Other Considerations

5.4.1.1. SARS-CoV-2 Impact

Details on precautionary measures, including vaccination, because of the ongoing SARS-CoV-2 pandemic are described in Appendix 1.

5.5. Study Stopping Rules

Safety data will be reviewed on a continual basis throughout the study. In the event of unfavorable safety findings, the IDMC could recommend that the Sponsor stop the study or take other actions (see Section 14.3.2 for details).

The Sponsor may terminate this study at any time after informing the Investigators. After reviewing the Part 1, Week 16, safety and efficacy data, the Sponsor may decide to stop the study (remainder of Part 1 and not proceed with Part 2) based on the benefit-risk analysis.

The Sponsor will notify Investigators, ethics committees, and any applicable regulatory agencies when the study is to be placed on hold, terminated, or completed.

Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the participants enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

5.6. Unscheduled Visits

An unscheduled visit to the study site can take place at any time during the Part 1 or Part 2 48-week treatment period. Data collected during the unscheduled visits should be recorded in eCRFs only if the data support protocol objectives and/or are required for safety monitoring. At the unscheduled visit, assessments should be completed as detailed in Table 1.

Unscheduled visits are to be determined at the discretion of the treating neurologist if no relapse is suspected. If a suspected MS relapse occurs during the study, the participant will then be evaluated in person by the treating neurologist within 72 hours of the onset of the potential relapse (see Section 5.3 for details).

5.7. Start of Study

The start of the study is the date the first participant signs the ICF.

5.8. End of Study

The end of study is last participant, last visit, for the final collection of data regardless of the country and site location.

6. STUDY POPULATION

To be eligible to participate in this study, candidates in Part 1 and Part 2 must meet the following eligibility criteria at Screening or at the timepoint specified in the individual eligibility criterion listed.

6.1. Inclusion Criteria

1. Ability of the participant and/or their legally authorized representative (e.g., parent, spouse, or legal guardian), as appropriate and as applicable to local regulations, to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations.

2. Age 18 through 55 years old, inclusive, at the time of informed consent.

3. Diagnosis of MS per the 2010 or 2017 McDonald's criteria [Polman 2011; Thompson 2018].

4. Time since MS symptom onset is < 20 years.

5. Must have EDSS score of 0 through 5.0 at Screening.

6. Must have at least 1 of the following occurring prior to Baseline (Day 1):

   - ≥ 2 clinical relapses in the last 24 months (but not within 30 days prior to Baseline [Day 1]) with at least 1 relapse during the last 12 months prior to randomization.

   - ≥ 1 clinical relapse within the past 24 months (but not within 30 days prior to Baseline [Day 1]) and ≥ 1 new brain MRI lesion (Gd-positive and/or new or enlarging T2 hyperintense lesion) within the past 12 months prior to randomization.
     The screening MRI could be used to satisfy this criterion (if needed for inclusion, local read is required). For new or enlarging T2 hyperintense lesions, the reference scan cannot be > 12 months prior to randomization.

   - ≥ 1 GdE lesion on brain MRI within 6 months prior to randomization.

7. A negative PCR test for SARS-CoV-2 at Screening Visit and within 2 weeks prior to Baseline (Day 1).

8. All WOCBP and all men must practice contraception during the study and for at least 90 days after their last dose of study treatment, as described in Section 11.5. In addition, participants should not donate sperm or eggs during the study and for at least 90 days after their last dose of study treatment.

6.2. Exclusion Criteria

Medical History and Current Health Status

1. Diagnosis of PPMS as defined by the 2010 or 2017 McDonald's criteria [Polman 2011; Thompson 2018].

2. An MS relapse that has occurred within 30 days prior to Baseline (Day 1) or the participant has not stabilized from a previous relapse at the time of Screening.

3. History of severe allergic, anaphylactic reactions or hypersensitivity reaction to BIIB091 or DRF, the excipients contained in the formulation, and if appropriate, any diagnostic agents to be administered during the study, including the following:

   - Known hypersensitivity to any components of the study treatment
   - Known hypersensitivity to previous fumarate or BTK inhibitor treatments
   - History of hypersensitivity to parenteral administration of Gd-based contrast agents

4. History of, or ongoing, malignant disease, including solid tumors and hematologic malignancies (with the exception of basal cell carcinomas and squamous cell carcinomas that have been completely excised and considered cured at least 12 months prior to Baseline [Day 1]).

5. History of any clinically significant cardiac, endocrinologic, hematologic, immunologic, infectious, metabolic, urologic, pulmonary, neurologic (other than MS), dermatologic, psychiatric, renal, or other major disease that is not well-controlled and as determined by the Investigator.

6. History of any clinically significant liver diseases as determined by the Investigator; including but not limited to, viral hepatitis, alcoholic hepatitis and steatosis, non-alcoholic steatohepatitis, cirrhosis, or autoimmune hepatitis.

7. History of any clinically significant pancreatic diseases as determined by the Investigator including, but not limited to, acute provoked pancreatitis in the last 12 months, idiopathic acute pancreatitis, or chronic pancreatitis.

8. History of GI surgery (except appendectomy or cholecystectomy that occurred more than 6 months prior to Screening), irritable bowel syndrome, inflammatory bowel disease (Crohn's disease, ulcerative colitis), or other clinically significant and active GI condition per the Investigator's discretion.

9. Systolic blood pressure > 150 mmHg or < 90 mmHg after sitting for 5 minutes at Screening or prior to dosing. If out of range, testing may be repeated once at Screening and once prior to dosing. Participants must not be dosed if the repeated value is still out of range.

10. Clinically significant 12-lead ECG abnormalities at Screening and at Baseline (Day 1)/prior to the first dose, including confirmed demonstration of QTcF > 450 ms, QRS > 120 ms, PR > 220 ms, or heart rate < 50 bpm based on the average of triplicate measurements, or any other clinically significant 12-lead ECG abnormalities as determined by the Investigator.

11. History of torsades de pointes or additional risk factors for torsades de pointes or ventricular arrhythmias (e.g., heart failure, hypokalemia, family history of long QT syndrome, Mobitz type II heart block, recent myocardial infarction within 6 months, or any medications known to prolong QT interval [based on each drug's product label and other available references such as Woosley et al. [Woosley 2022]] administered within 5.5 half-lives prior to Screening), in the opinion of the Investigator.

12. Receipt of any vaccination within 30 days prior to Screening or plans to receive the same any time from Screening through 30 days after the last study visit; checked at Screening and at Baseline (Day 1)/prior to the first dose. However, non-live COVID-19 vaccination will be permitted if completed at least 21 days or more prior to randomization, as per local regulation and Investigator discretion. See Appendix 1 for details on the COVID-19 vaccination requirements during the study treatment period.

13. Contraindications to MRI, including (but are not limited to) the presence of pacemakers or other implanted metal devices (excluding dental braces), renal impairment, allergies to MRI contrast agent, or claustrophobia that cannot be medically managed.

14. A mental or physical condition that would preclude performing efficacy and safety assessments.

15. Any major surgery within 4 weeks prior to Screening or plans to undergo elective procedures or surgeries at any time after signing the ICF through the Follow-Up Visit.

16. History of bleeding diathesis.

Infection Risk

17. Evidence of SARS-CoV-2 infection within the past 4 weeks prior to Baseline, including, but are not limited to, any of the following:

    - Symptoms consistent with SARS-CoV-2 infection, per the judgment of the Investigator, within 4 weeks prior to Baseline (Day 1), including, but are not limited to, fever (temperature > 37.5°C or 99.5°F), sore throat, new and persistent cough, breathlessness, or loss of taste or smell.

    - Close contact with an individual with SARS-CoV-2 infection within 14 days prior to Baseline (Day 1) [see Appendix 1].

18. History or positive test result at Screening for HIV. HIV testing will be performed at Screening unless prohibited by local regulations.

19. Current hepatitis C infection (defined as positive HCV antibody and detectable HCV RNA). Participants with positive HCV antibody and undetectable HCV RNA are eligible to participate in the study.

20. Current or possible hepatitis B infection (defined as positive for HBsAg and/or total anti-HBc). Participants with immunity to hepatitis B from vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.

21. Chronic or recurrent severe infection (e.g., pneumonia, complicated urinary tract infection, or septicemia) within the 90 days prior to Screening or between Screening and Baseline (Day 1).

22. Symptoms of bacterial, fungal, or viral infection (including upper respiratory tract infection) within 14 days prior to Screening or between Screening and Day -1. Participants with local fungal infection (e.g., candidiasis, tinea) are eligible to be rescreened after successful treatment of the infection.

23. History of TB or a positive diagnostic TB test result prior to enrollment (Baseline [Day 1]), defined as a positive IFN γ release assay test (positive QuantiFERON® or T-SPOT® [ELISPOT] results or 2 successive indeterminate QuantiFERON test results).

Laboratory Values

24. Any of the following abnormal blood/urine tests at Screening and at Baseline:

    - Blood ALT or AST > the ULN
    - Blood lipase ≥ 2 times the ULN
    - Any value for blood platelets, hemoglobin, ALC, or neutrophil count that is < LLN
    - Any value for blood prothrombin time or activated partial thromboplastin time that is > ULN
    - Urine albumin-to-creatinine ratio > 200 mg/g (22.6 mg/mmol)
    - eGFR ≤ 60 mL/min/1.73 m^2 (using the CKD-EPI equation [Levey 2009]).

Medications

25. History of treatment with or has received the following:

    - Any history of treatment with BTK inhibitors (including BIIB091)
    - Anti-CD20 antibodies (e.g., ocrelizumab, ofatumumab, rituximab, and ublituximab) within 6 months of Baseline (Day 1)

  - Participant must demonstrate blood B-lymphocyte count > LLN at Screening or Baseline (Day 1). Discontinuation of prior anti-CD20 treatment must not be due to severe infections, as determined by the Investigator.

- DMF-, DRF-, or any MMF-containing product within 2 months prior to Baseline (Day 1)

  - Participant's reason for treatment discontinuation must not be due to intolerability/safety concerns.

- Cladribine, T cell or T-cell receptor vaccination, total body irradiation, total lymphoid irradiation, or stem cell transplantation at any time

- Alemtuzumab within 4 years prior to Baseline (Day 1)

- Mitoxantrone or other immunosuppressant agents (e.g., azathioprine, cyclosporine, cyclophosphamide, methotrexate, and mycophenolate mofetil) within 1 year prior to Baseline (Day 1)

- Teriflunomide within 3 months of Baseline (Day 1), unless an accelerated elimination procedure for teriflunomide with cholestyramine is completed during Screening

- Natalizumab and other anti-integrin alpha-4-beta-1 antibodies within 3 months prior to Baseline (Day 1)

  - Participants with more than 2 years of treatment history require proof of a JCV antibody index < 0.90 within 6 months of natalizumab discontinuation or at Screening (performed at a local laboratory), and no prior treatment history with other immunosuppressants.

- IVIg, plasmapheresis, or cytapheresis within 3 months prior to Baseline (Day 1)

- S1P receptor modulators:

  - Fingolimod and ozanimod within 2 months prior to Baseline (Day 1)

  - Siponimod and ponesimod within 4 weeks prior to Baseline (Day 1)

- GA or IFN β within 2 weeks prior to Baseline (Day 1)

- IV corticosteroid treatment and oral corticosteroid treatment within 4 weeks prior to Screening or during the Screening period

- Treatment with dalfampridine (Ampyra®) unless on a stable dose for ≥ 30 days prior to Screening. Wherever possible, participants should remain on stable doses throughout the 48-week treatment period

26. Use of agents known to significantly inhibit or induce drug-metabolizing enzymes (e.g., barbiturates, phenothiazines) within 4 weeks prior to the Screening Visit.

27. Use of any traditional and/or unlicensed medicines and/or therapies and/or herbal preparations, which are known or considered by the treating neurologist to affect MS and MS endpoints that are being considered in the study, including safety, PK, and efficacy, within 4 weeks or 5 half-lives prior to randomization, whichever is longer.

28. Use of any prescription medications that are known to prolong QT/QTc interval (based on each drug's product label and other available references such as Woosley et al. [Woosley 2022]; also see the BIIB091 IB) or use of nutraceutical compounds (St. John's Wort, ginseng, or ginkgo biloba) within 4 weeks or 5 half-lives prior to randomization, whichever is longer.

29. Receipt of opioid treatment within 28 days prior to Screening.

30. Use of anticoagulation therapy or antiplatelet therapy within 4 weeks prior to randomization. (Note: low-dose aspirin [up to 100 mg] is permitted.)

31. Use of CYP3A4 inducers or inhibitors, including hormonal contraceptives as applicable, OATP1B1 or OATP1B3 substrates, and proton pump inhibitors, within 14 days before the first dose of study treatment. (Note: see the BIIB091 IB, Appendix C for examples of clinical inhibitors for CYP3A4.)

32. Current enrollment or plan to enroll in any other drug, biological, device, clinical study, or treatment with an investigational drug or approved therapy for investigational use within 90 days prior to randomization or 5 half-lives of the drug or therapy, whichever is longer.

Other

33. Blood donation (1 unit or more) within 90 days prior to Screening and Day 1, plasma donation from 1 week prior to Screening and Day 1, and platelet donation from 6 weeks prior to Screening and Day 1.

34. Female participants who are pregnant or currently breastfeeding or intending to become pregnant during the study and for 90 days after the last dose of study treatment.

35. Male participants with pregnant partners or male participants planning to father children during the period of the study and for 90 days after the last dose of study treatment.

36. Consumption of any product containing grapefruit, pomelos, or Seville oranges (e.g., marmalade) within 14 days prior to Baseline (Day 1) and an unwillingness to refrain from such products during study participation unless specifically permitted elsewhere within this protocol.

37. History of alcohol or substance abuse (as determined by the Investigator) within 24 months prior to Screening or an unwillingness to refrain from illicit or recreational drugs during the study (note: treatment with medical marijuana for MS symptoms is not exclusionary if it is consistent with local MS treatment guidelines and local regulations).

38. Clinically significant history of suicidal ideation or suicidal behavior occurring in the past 12 months (as assessed by the C-SSRS at Screening) in the opinion of the Investigator.

39. Inability to comply with study requirements in the opinion of the Investigator.

40. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the participant unsuitable for enrollment.

6.3. Screening, Retesting, and Screen Failures

6.3.1. Screening

Once informed consent is obtained, screening assessments can occur. At this time, a unique identification number is assigned that will be used on study-related documents pertaining to the participant. Any identification numbers that are assigned will not be reused even if the participant fails screening, does not receive treatment, or does not continue in the study. Study sites are required to document all screened participants initially considered for inclusion in the study.

6.3.2. Retesting

Participants who have an out-of-range result that is not clinically significant at the Screening Visit can be retested once at the discretion of the Investigator. In addition, eligible participants who are not able to complete the Baseline Visit (Day 1) within 4 weeks of starting their screening assessments may be rescreened. Participants who had a relapse within 30 days prior to randomization (Day 1) and who received disallowed concomitant medications can be rescreened at a later timepoint to meet the enrollment criteria.

If the participant fails screening twice, they may not undergo further screening for this study.

6.3.3. Screen Failures

Participants who fail the following screening criteria cannot be retested and are considered screen failures:

- Positive HIV, hepatitis B, or hepatitis C testing
- AST or ALT $\geq 2 \times$ ULN

Screen failures are defined as participants who sign the ICF but are not subsequently randomized or dosed. If a participant is considered a screen failure, the reasons for exclusion must be documented in the participant's source documents and on the screening log. 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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria evaluations, and any SAEs.

7. STUDY TREATMENT

7.1. Regimen

In both Part 1 and Part 2, BIIB091 will be dosed with the IR tablet formulation BID via oral administration after regular meals (within 30 to 60 minutes after meals) for a total of 48 weeks. BIIB091 should not be taken in the fasted state. In Part 1, BIIB091 350 mg BID and 250 mg BID will be used as the high dose and low dose, respectively. In Part 2, the BIIB091 dose will be selected based on benefit-risk evaluation of Part 1 data (rationale for dosing is discussed in Section 3.1.2).

DRF will be supplied as HPMC capsules consisting of enteric-coated, pH-sensitive DRF minitablets. In both Part 1 and Part 2, participants treated with the standard-dose DRF will take the starting dose of 231 mg BID for the first 7 days and then 462 mg BID thereafter. In Part 2, participants receiving the BIIB091 and low-dose DRF combination therapy will take DRF 231 mg BID for the first 7 days and then 350 mg BID thereafter.

In Part 1 and Part 2, participants will be dosed with study treatment every 12 hours. Missed doses should be taken within 4 hours. If the participant does not remember to take the dose within 4 hours, this dose should be skipped and the next dose should be taken as scheduled. Any 2 doses of study treatment should be separated by ≥ 8 hours. Doses should not be doubled to make up for the missed doses. All doses administered, whether in the clinic or at home, must be recorded on the Patient Diary; see Section 7.6 for further details.

Participants will be randomized into treatment groups as shown below. Individual participants will have up to 12 scheduled study visits. Participants in Part 1 of the study cannot participate in Part 2 of the study. The randomization will be stratified by intensive PK cohort (Yes/No) and region (Eastern Europe vs. Other). For stratification, Eastern Europe will include participants from countries such as Poland and the Czech Republic.

Part 1:

BIIB091 monotherapy

- high dose (350 mg) BID (N = 50)
- low dose (250 mg) BID (N = 50)

DRF monotherapy

- standard dose (462 mg) BID (N = 25)

Part 2:

BIIB091 and DRF combination therapy

- BIIB091 selected dose with DRF standard dose (462 mg) BID (N = 50)

- BIIB091 selected dose with DRF low dose (350 mg) BID (N = 50)

DRF monotherapy

- standard dose (462 mg) BID (N = 50)

See Section 3.1.2 for the rationale for dose selection.

7.2. Modification of Dose and/or Treatment Schedule

The dosage of BIIB091 or DRF cannot be modified.

7.3. Study Treatment Management

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice.

Site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA aligns with all other references, including the protocol.Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once study treatment is prepared for a participant, it can be administered only to that participant. After administration, any study treatment remaining in the bottle should not be used for another participant.

7.3.1. BIIB091

BIIB091 is supplied as an IR formulation in tablets containing 50, 150, or 250 mg of BIIB091 that will be combined as necessary to obtain 250 mg (low dose) or 350 mg (high dose), or an intermediate level of BIIB091 per dose. BIIB091 contains the following excipients: silicified microcrystalline cellulose, sodium starch glycolate, sodium stearyl fumarate, and colloidal silicon dioxide. BIIB091also contains a film coating which consists of titanium dioxide, hypromellose, macrogol, iron oxide yellow, and ferrosoferric oxide.

The contents of the BIIB091 label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with the local law. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to site staff. Study treatment should not be used after the expiry or use-by date.

7.3.1.1. Preparation

The individual preparing BIIB091 should carefully review the instructions provided in the DHA.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the bottles or study treatment, do not use the study treatment. The bottles in question should be saved at the study site and the problem immediately reported to the Sponsor.

Contact information for reporting a problem is provided in the Study Reference Guide (or comparable study document).

7.3.1.2. Storage

Study treatment must be stored in a secure location.

BIIB091 is to be stored at 15°C to 30°C (59°F to 86°F) in a locked cabinet with limited access. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

7.3.1.3. Handling and Disposal

The Investigator must return all used and unused bottles of BIIB091 as instructed by the Sponsor, unless approved for onsite destruction.

If any BIIB091 supplies are to be destroyed at the study site, the institution or appropriate site staff must obtain prior approval from the Sponsor, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

7.3.1.4. Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed, amount returned by the participant, and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all bottles, both used and unused, must be saved for study treatment accountability. By the end of the study, reconciliation must be made between the amount of BIIB091 supplied, dispensed, and subsequently destroyed, lost, or returned to the Sponsor. A written explanation must be provided for any discrepancies.

7.3.2. Diroximel Fumarate

DRF is formulated as enteric-coated minitablets in HPMC capsules for oral administration. Each capsule consists of 33 minitablets and contains 231 mg DRF. DRF contains the following excipients: crospovidone, colloidal silicon dioxide, magnesium stearate (nonbovine), methacrylic acid and ethyl acrylate copolymer, microcrystalline cellulose, talc, and triethyl citrate [VUMERITY® USPI 2022].

DRF delayed-release, gastro-resistant capsules are supplied in 120 count, 200 cc induction sealed, high-density polyethylene bottles.

The contents of the DRF label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with the local law. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to site staff. Study treatment should not be used after the expiry or use-by date.

7.3.2.1. Preparation

The individual preparing DRF should carefully review the instructions provided in the DHA.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the bottles or the capsules, do not use the capsules. The bottle in question should be saved at the study site and the problem immediately reported to the Sponsor.

Contact information for reporting a problem is provided in the Study Reference Guide.

7.3.2.2. Storage

Study treatment must be stored in a secure location.

DRF is to be stored at room temperature not to exceed 25°C (77°F) in a locked cabinet with limited access. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

7.3.2.3. Handling and Disposal

The Investigator must return all used and unused bottles of DRF as instructed by the Sponsor, unless approved for onsite destruction.

If any DRF supplies are to be destroyed at the study site, the institution or appropriate site staff must obtain prior approval from the Sponsor by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

7.3.2.4. Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed, amount returned by the participant, and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all bottles, both used and unused, must be saved for study treatment accountability. By the end of the study, reconciliation must be made among the amount of DRF supplied, dispensed, and subsequently destroyed, lost, or returned to the Sponsor. A written explanation must be provided for any discrepancies.

7.3.3. Placebo

In order to maintain blinding for participants in the study (to disguise both the type of study drug and dose level), active study treatment (BIIB091 or DRF) will be administered together with placebo. Placebo will be of the same appearance (BIIB091 placebo matching the appearance of the BIIB091 tablet and DRF placebo matching the appearance of the DRF capsule).

Corresponding information as provided for the active study treatment (BIIB091 or DRF) is applicable to the matching placebos (BIIB091 placebo or DRF placebo, respectively), with the exception that the placebos contain listed excipients only.

7.3.4. Other Protocol-Designated Products

7.3.4.1. Auxiliary Medicinal Products: Gadolinium and Intravenous Methylprednisolone

An auxiliary medicinal product is a medicinal product used for the needs of a clinical trial as described in the protocol but is not an investigational medicinal product. It could include medicinal products used for background treatment, challenge agents, or rescue medication, or it could be used to assess endpoints in a clinical trial. Authorized auxiliary medicinal product refers to a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC. An unauthorized auxiliary medicinal product is one without such authorization.

This study uses the auxiliary medicinal products Gd-based contrast agents/media (ATC code: V08CA) and IVMP.

Gd-based contrast agents/media must have a marketing authorization. Sites will use the Gd-based contrast agents/media currently approved in the local country, according to the SmPC/USPI/local label, as applicable.

IVMP of 1000 mg/day up to a total of 5 days and with or without an oral taper was chosen in this study protocol. IVMP is authorized for the treatment of MS relapse in the US [SOLU-MEDROL® USPI 2021]. IVMP is authorized in all participating geographic regions of this study. Use in MS relapses at a dose of up to 1000 mg/day for 3 to 5 days is considered an acceptable standard of care as noted in EU guidance [EMA (EMA/CHMP/771815/2011 Rev. 2) 2015], although the indication may not contain MS relapse in all regions.

Accountability of both products will be conducted as described for the study treatments and placebo.

7.4. Blinding Procedures

For both Part 1 and Part 2, the Investigator, study staff, and participants will remain blinded to the treatment assignments during the 48-week study period. To maintain the study blind, it is imperative that treatment assignments are not shared with the participants, their families, or any member of the blinded study team, both at the site and at the Sponsor and CRO, if applicable. Selected Sponsor team members, including Sponsor representatives from Clinical Development, Safety, Biomarkers, and Biostatistics will be unblinded to participate in the 16-week data analyses in Part 1 and Part 2 (see Section 14.3.1 for details). All participants, Investigators, and the remaining study management team members, especially those directly interacting with study sites, will remain strictly blinded for the study, including the 48-week controlled treatment period and the 2-week safety follow-up period.

To further maintain blinding, each study site will have a treating neurologist and an examining neurologist. The treating neurologist will function as the primary treating physician and will conduct all participant safety assessments. The examining neurologist will conduct all EDSS evaluations and relapse assessments but will not be involved in any other aspect of participant care.

At the end of the study (i.e., once the clinical study report is finalized), if unblinding will not jeopardize the results of ongoing related studies, the Sponsor will provide the randomization codes to Investigators, who then can inform their participants about the treatment received.

In the event of a medical emergency that requires unblinding of a participant's treatment assignment, refer to Section 11.4.5.

7.5. Precautions

Medications for the treatment of severe hypersensitivity reactions (e.g., epinephrine for subcutaneous injections, diphenhydramine for injection) must be available for immediate use.

See the DHA for detailed instructions.

7.6. Compliance

Participants will receive instructions on compliance with study treatment at the first study visit (Baseline Day 1). A Patient Diary will be given to the participant to record intake at home; this will be collected by the Investigator or site staff at each visit and a new one will be given to the participant for the next visit record. Doses administered at the study site will also be recorded in the Patient Diary. Compliance will be monitored by tablet (BIIB091 and the matching placebo) or capsule (DRF and the matching placebo) count, conducted by study personnel at protocol-scheduled visits. Compliance will be assessed by direct questioning, counting of returned tablets and capsules, review of the Patient Diary, etc. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF. Insufficient compliance with the protocol-specified dosing regimen is defined as taking less than 80% of study medication during any part of the study treatment period. Any dose of study drug in excess of that specified in this protocol is considered

to be an overdose. Participants should make every effort to complete the Patient Diary as soon as they have taken the study medication, but no later than 12 hours afterwards.

7.7. Concomitant Therapy and Procedures

7.7.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the participant's Baseline Visit and the last study visit.

7.7.1.1. Allowed Concomitant Therapy

Participants should be instructed to contact their Investigators before taking any new medications, including nonprescription drugs and herbal preparations.

Participants may take up to 3000 mg/day acetaminophen (paracetamol) and up to 100 mg/day low-dose aspirin during the study at the discretion of the Investigator. During the study, female participants may also take hormone replacement therapy or oral contraceptives that are not known to prolong QT/QTc interval (based on each drug's product label and other available references such as Woosley et al. [Woosley 2022]), do not induce or inhibit CYP3A4 [FDA 2022], and are not OATP1B1 or B3 substrates. Symptomatic therapy, such as treatment for spasticity, depression, or fatigue, is not restricted but should be optimized as early as possible during screening to maintain consistent treatment for the duration of the study.

Clinical evidence from non-live COVID-19 vaccine studies showed that highly protective immunologic effects are expected within 14 to 21 days after administration of the COVID-19 vaccine. Since BIIB091 treatment may reduce the immune response to the vaccine if given within 21 days after vaccine administration, it is recommended that participants receive the SARS-CoV-2 vaccine 21 days or more prior to randomization (for the vaccine to exert its effect), as per local regulation, and/or Investigator guidance.

After Week 16 in Part 1 and Part 2, the non-live COVID-19 vaccine may be administered at the discretion of the PI. In this case, participants may remain off-treatment for a maximum of 21 days after administration of the COVID-19 vaccine (for the vaccine to exert its effect) (see Appendix 1).

The yearly non-live influenza (flu) vaccine is permitted during the study. Study treatment should not be withheld due to the influenza vaccination during the study treatment period. Participants are encouraged to receive influenza vaccination 2 to 3 weeks prior to randomization, when feasible.

7.7.1.2. Disallowed Concomitant Therapy

Medications and therapies that are prohibited prior to dosing as indicated in Section 6.2 are prohibited during the study. Participants should be instructed to contact their Investigators before taking any new medications, including nonprescription drugs and herbal preparations.

Participants should not receive any vaccination within 30 days prior to screening, during the study, and up to 30 days after the last study visit. However, non-live COVID-19 vaccination and the non-live influenza (flu) vaccine will be permitted as described in Section 7.7.1.1.

During the first 16 weeks of study treatment periods in Part 1 and Part 2, non-live COVID-19 vaccines are not permitted. COVID-19 vaccines may prompt temporary withholding or discontinuation of study treatment in order for the vaccine to exert its effect. Since temporary withholding or discontinuation could affect the primary analysis of safety and efficacy of the study treatment, COVID-19 vaccines are not allowed during the first 16 weeks of Part 1 and Part 2 (see Appendix 1).

Participants who receive any restricted medications (Section 6.2) without approval from the Medical Monitor may be required to permanently discontinue study treatment and withdraw from the study. If specific medical conditions necessitate the use of any disallowed concomitant medications, the Sponsor or Sponsor designee must be contacted for approval. Participants who withdraw from the study due to a disallowed concomitant therapy must complete an ET Visit.

For participants who complete the study, permanently discontinue study treatment, or withdraw from the study, starting any of these disallowed medications should be based on discretion of the treating neurologist, with consideration of the PK/PD profile of the study treatment.

7.7.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the participant is enrolled in the study and the last study visit.

Concomitant procedures are allowed in appropriate situations:

- In an emergency situation, concomitant procedures should be reported accordingly.
- In a non-emergency situation, concomitant procedures should be authorized by the Investigator in collaboration with the Medical Monitor and approved by the Sponsor.

Any concomitant procedures administered should be recorded.

7.8. Continuation of Treatment

No further provisions are made for access to the study treatment after the study, and participants will continue to receive standard of care at that time. If BIIB091 monotherapy or BIIB091 combination therapy with DRF is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

8. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF PARTICIPANTS FROM THE STUDY

8.1. Discontinuation of Study Treatment

A participant *must* permanently discontinue study treatment for any of the following reasons:

- The participant withdraws consent to continue study treatment.
- The participant becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 11.4.1.
- The participant is not compliant with the study treatment or study procedures.
- The Sponsor decides to stop the study prematurely.
- The participant experiences a medical emergency that necessitates unblinding of the participant's treatment assignment.
- The Investigator discontinues participant study treatment for medical reasons.
- The participant experiences an AE that necessitates permanent discontinuation of study treatment.
- The participant develops ventricular arrhythmia that requires hospitalization or urgent intervention.
- The participant experiences a serious hypersensitivity reaction that may be related to study treatment.
- The participant has either of the following:
  - a QTcF > 500 ms or uncorrected QT interval > 600 ms
  - a confirmed increase in QTcF of > 60 ms from Baseline
- The participant is diagnosed with acute pancreatitis.
- The participant is diagnosed with PML.

The primary reason for discontinuation of study treatment must be recorded in the participant's CRF.

Participants who discontinue treatment must remain in the study and continue protocol-required tests and assessments, where possible.

8.2. Temporary Withholding Criteria

If the participant experiences a serious infection other than PML, study treatment is withheld for a maximum of 4 weeks until the serious infection has resolved, as determined by the Investigator, otherwise, study treatment will be permanently discontinued. Participants who recover from serious or opportunistic infections with prophylaxis measures may resume treatment at the discretion of the Sponsor, in concordance with the Investigator and the Medical Monitor.

Study treatment must also be temporarily withheld if any of the following laboratory parameters meet the threshold limits described below:

- AST or ALT > 3 × ULN. Study treatment must be withheld, and liver function (ALT, AST, alkaline phosphatase, and total bilirubin) must be retested within 48 to 72 hours for confirmation. Study treatment will be permanently discontinued for an individual participant if any of the following criteria are met:
  - AST or ALT ≥ 3 × ULN and (total bilirubin level > 2 × ULN or INR > 1.5)
  - AST or ALT > 3 × ULN for ≥ 4 weeks after withholding of study treatment
  - AST or ALT > 5 × ULN for more than 2 weeks after withholding of study treatment
  - AST or ALT ≥ 8 × ULN
  - AST or ALT > 3 × ULN associated with the appearance or worsening of rash or hepatitis symptoms (i.e., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia).

  If study treatment is permanently discontinued because of liver abnormalities, the event will be appropriately investigated to determine the potential cause.
- eGFR < 60 mL/min/1.73 m^2, confirmed by repeat testing as soon as possible. If the eGFR remains < 60 mL/min/1.73 m^2 for ≥ 4 weeks after withholding study treatment, the participant must permanently discontinue study treatment.
- ALC < 0.5 × 10^9/L, confirmed by repeat testing as soon as possible. If the value remains < 0.5 × 10^9/L for ≥ 6 months, the participant must permanently discontinue study treatment. Participants who completed the study with a last measured lymphocyte count < 0.8 × 10^3/μL will require additional follow-up approximately every 8 weeks to monitor their lymphocyte counts until their ALC > LLN, or for a period up to 6 months, or until they commence another disease-modifying therapy, whichever occurs first.
- Neutrophil count < 500/mm^3 (Grade 4) or neutrophil count 500 to 999/mm^3 (Grade 3) with fever, confirmed by repeat testing. Study treatment must be withheld if the result

is confirmed upon retest within 48 hours. If the value remains < 999/mm^3 for ≥ 4 weeks after withholding study treatment, then the participant must permanently discontinue study treatment and the event must be recorded as an AE.

- Platelet count < 25,000/mm^3 (Grade 4) or platelet count 25,000 to 49,999/mm^3 (Grade 3) with bleeding, confirmed by repeat testing. Study treatment must be withheld if the result is confirmed upon retest within 48 hours. If the value remains < 49,999/mm^3 for ≥ 4 weeks after withholding study treatment, then the participant must permanently discontinue study treatment, and the event must be recorded as an AE.

- Urine albumin-to-urine creatinine ratio > 200 mg/g (22.6 mg/mmol), confirmed by repeat testing within 7 days. If the urine albumin-to-urine creatinine ratio remains > 200 mg/g (22.6 mg/mmol) for ≥ 4 weeks after withholding study treatment, the participant must permanently discontinue study treatment.

- After Week 16, study treatment may be temporarily suspended for a maximum of 21 days after administration of COVID-19 vaccine for the vaccine to exert its effect.

8.3. Lost to Follow-Up

Participants will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, and 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.

- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.

Should the participant continue to be unreachable, that participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.4. Withdrawal of Participants From the Study

Participants must be withdrawn from the study for any one of the following reasons:

- The participant withdraws consent for participation in the study.

- The participant enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.

- The participant is unwilling or unable to comply with the protocol.

The primary reason for the participant's withdrawal from the study must be recorded in the participant's CRF.

Participants should undergo an ET Visit unless withdrawal is due to death or withdrawal of consent.

Participants who withdraw from the study may not be replaced.

9. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

See Section 1.3 for the timing of all assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, participants will be asked to return to the study site to have the evaluations repeated.

9.1. Efficacy Assessments

9.1.1. Brain Magnetic Resonance Imaging

MRI scans will be assessed according to the Schedule of Activities (see Table 1).

Brain MRI scans will be performed according to a standardized imaging protocol before and after the administration of single-dose Gd. Images will be assessed and reported by an independent, blinded, centralized MRI vendor. Further details, including the scans required and the optimal MRI workflow, will be provided in a separate Imaging Manual.

Brain MRI measurements include, but are not limited to, the following:

- T1-weighted MRI before Gd infusion
- T1-weighted MRI after Gd infusion
- T2-weighted MRI
- susceptibility-weighted MRI (if available at site)

The cumulative number of new T1 GdE brain lesions, the cumulative number of new or enlarging T2 lesions, and the cumulative volume of new or enlarging T2 hyperintense lesions will be collected and reported. Number of GdE lesions at each visit, numbers and volumes of new unenhancing T1 hypointense lesions that persist for ≥ 24 weeks, normalized T1-weighted intensity in unenhancing T1 hypointense lesions, SEL-related outcomes (including number and volume and normalized T1-weighted intensity and unenhancing T1 lesion volume), number of new and disappearing PRLs, tissue characteristics of PRLs, tissue compartment, and regional brain volume may be collected and reported. Additional lesion types may be studied by machine learning/artificial intelligence, and analyses of the number and volume of lesions may be collected and reported as exploratory endpoints.

SELs are a longitudinal MRI measure of disease. SELs are identified as pre-existing T2-weighted hyperintense lesions that slowly expand over time using deformation-based analyses that simultaneously use the T1-weighted and T2-weighted scans [Elliott 2018]. The reported volume of SELs is the baseline volume of lesions detected as SELs at various postbaseline timepoints.

PRLs are identified by a conspicuous rim around the lesion as seen on susceptibility-weighted MRI. The paramagnetic rim is generally reflective of accumulating iron-laden macrophages/activated microglia associated with chronic inflammation at the lesion edge. PRLs are thus considered a putative measure of chronic active lesions.

If the start of a treatment for a relapse with high-dose corticosteroids falls within 7 days of the next scheduled visit, every attempt should be made to obtain the MRI before administration of the first dose of high-dose corticosteroids. If outside the visit window, the visit should be recorded as unscheduled. The MRI at an unscheduled visit prior to steroid treatment must be ≥ 21 days after the prior MRI. However, if an MRI at an unscheduled visit is < 21 days after a prior MRI, then the use of Gd should be strongly avoided, unless determined by the Investigator to be clinically indicated. In this scenario, the next regularly scheduled MRI should also be obtained.

9.1.2. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of BIIB091 in all study participants:

- MS relapses (see Section 5.3)
- EDSS
- T25FW
- 9HPT: 9HPT-D and 9HPT-ND (both the right and left hands are tested, with the D hand tested before the ND hand)
- SDMT
- LCLA [Balcer 2017]

9.1.3. Patient-Reported Outcomes

PRO questionnaires must be completed under the supervision of the primary treating nurse or study coordinator during clinical visits before objective test performance is tested. Refer to the Study Reference Guide for additional instructions. The following PROs will be collected to evaluate the efficacy of BIIB091 in all study participants:

- PROMIS-29 profile
- FSMC [Penner 2009]

9.1.4. Digital Outcome Measure

The current study will explore a wide range of digital smartphone-based disease outcome assessments derived from remote at-home monitoring assessments, including electronic PROs

that may collect self-assessments of mood and quality of life; performance-based outcomes from a battery of active tests evaluating cognition (information processing speed), upper extremity function, and ambulation; and participants' walk step counts and variance in overall mobility features (devoid of absolute geolocation information) recorded passively. The smartphone application is called Konectom.

Konectom has received CE mark certification in the EU and remains an NSR investigational device in the US. In Canada, Konectom is classified as Medical Device Exempt (see the Konectom IB for details).

Data recorded through the application will not be used to determine patient care. Any digitally collected outcomes will only be exploratory.

9.1.4.1. Konectom™

Konectom is an at-home (and in-clinic) smartphone-based application intended to be used as a self-assessment tool to objectively quantify motor and cognitive function and their impairments associated with MS.

Continuous sensor-based passive mobility data is also collected.

Where local regulations and ethics committee approval allow, smartphone-based digital assessments will be completed by all participants, both in-clinic during scheduled study visits and remotely (at-home tests). Digital assessments include tests evaluating motor and cognitive functions that are enabled on consumer mobile devices that are provided to participants. At-home tests will be requested daily for the first-week post-Baseline (Day 1) and weekly for the remainder of the trial. At-home tests will not be requested for weeks with in-clinic Konectom administration.

Additional details on the use of Konectom to perform digital assessments will be provided in the Instruction for Use.

Details for the collection of complaints about the device and ADEs are provided in Section 11.5.3.

The Konectom assessments include ambulation tests, fine motor tests, cognition tests, and PROs.

Ambulation Tests

- 6MWT: to evaluate walking performance, fatigability, and limitations in walking distance
- UTT: to evaluate gait and balance while turning
- SBT: to evaluate static balance

Fine Motor Tests

- Drawing Test: clinical study participants will be asked to draw a set of shapes on the smartphone touchscreen. Upper extremity function will be evaluated.
- Pinching Test: to evaluate grasping and dexterity. The participant will be asked to pinch as many of the randomly displayed circular shapes as possible over 30 seconds.

Cognition Test

- CPST (based on previously clinically validated SDMT): clinical study participants will be asked to complete a series of cognitive tasks (e.g., matching symbols to numbers) within a fixed period of time. Cognitive performance speed will be evaluated.

Patient-Reported Outcome

- Mood questionnaires: clinical study participants will be asked to self-report their emotional and physical states.
- MSIS-29 v2 physical and psychological scores.

9.2. Pharmacokinetic Assessments

Sparse PK sampling will be conducted to measure plasma BIIB091, MMF, and HES concentrations at predetermined timepoints, and intensive PK sampling post-steady state will be conducted at Week 4, as provided in the Schedule of Activities (Table 1). The PK sampling timepoints for BIIB091, MMF, and HES are -15 minutes (predose) and 1, 2, 3, 4, and 5 hours (postdose; relative to the first BID [morning dose]) administered on that day (Table 2).

PK will be assessed as C_{max} measured postdose and C_{trough} measured predose at specific timepoints. PopPK, PK/PD, and C-QT analyses, if conducted, will be reported separately.

9.3. Pharmacodynamic Assessments

The PD properties of BIIB091 monotherapy or BIIB091 in combination with DRF will be evaluated using assessments that include, but may not be limited to, the following:

- Serum and whole blood will be collected for potential biomarkers related to MS or evaluated as treatment response biomarkers in response to BIIB091 or DRF at the Sponsor's discretion.
- The PD properties of BIIB091 and DRF will be evaluated using assessments that include, but may not be limited to, the following:
  - changes in immune cell subsets (TBNK)
  - B-cell activation (CD69 expression)
- Disease activity biomarkers include, but may not be limited to, the following biomarker associated with the disease MS:
  - serum NfL levels

9.4. Pharmacogenetic and Genetic Assessments

Where local regulations and ethics committee approval allows and if the participant accepts, a DNA sample will be collected for future exploratory genetic analysis related to MS and/or the response to BIIB091 or DRF. This one-time required blood collection is listed in the Schedule of Activities. In addition, where allowed by local, regional, and national regulatory authorities and ethics committees, participants will be offered the option for residual DNA samples to be retained for future exploratory unspecified genetic research that may be used to understand the biology of other diseases and traits of interest to the Sponsor and/or to develop diagnostic and analytical tests. Participants who consent to their samples being retained for future genetic research will be required to sign a separate, written pharmacogenomics ICF.

Genetic polymorphism in genes encoding drug targets or the downstream pathways, as well as proteins that impact drug absorption, distribution, metabolism, and elimination, may affect the safety and efficacy of the study treatment.

In the event of an unusual response or observation of unexplained AEs, DNA samples may be used to determine if there are any pharmacogenetic associations with drug response.

In the future, as the understanding of MS and/or BIIB091 or DRF increases, additional genetic analyses may be warranted to refine the knowledge of the molecular basis of the disease and the drug response and to advance the development of novel therapeutics.

The DNA samples will be coded with the participant's identification number and stored for up to 25 years after the end of the main study years or a duration dictated by local, national, or regional laws or regulations. No genotyping or genetic data will be provided to the participant.

Participants may withdraw consent and request to have their sample destroyed at any time and no further genetic data will be generated; any data already generated will not be destroyed.

9.5. Future Scientific Research Assessments

Where allowed by local, regional, and national regulatory authorities and ethics committees, participants will be offered the option for residual serum samples to be retained for future, unspecified, exploratory biomarker analysis. In addition, MRI scans may be stored for future analysis. Participants who opt for samples and scans to be retained for such use will be required to sign a separate, written Future Scientific Research ICF.

The samples may be utilized to identify or verify putative, prognostic, and predictive markers associated with disease and markers of therapeutic response to treatment and/or to develop diagnostic and analytical tests. Background and dynamic clinical disease characteristics and associated biomarker data may be utilized to predict subsequent disease worsening (severity), identify high-risk patient subgroups, and identify predictors of response to treatment.

Serum will be collected and stored for future exploratory analyses to measure proteins of interest related to MS disease, BIIB091, and/or DRF treatment response. DNA samples may be collected for any future exploratory genomics analyses (Section 9.4). The collected samples will be tested at the Sponsor's discretion.

The serum samples will be coded with the participant's identification number (but are otherwise anonymized) and stored for 15 years or a duration dictated by local, national, or regional laws or regulations. Participants may withdraw consent and request to have their sample destroyed at any time and no further data will be generated; any data already generated will not be destroyed.

10. SAFETY ASSESSMENTS

See Section 1.3 for the timing of all safety assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, participants will be asked to return to the study site to have the evaluations repeated.

10.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BIIB091 monotherapy and BIIB091 combination therapy with DRF:

- AE and SAE recording
- Medical history and prior MS treatment
- MS signs and symptoms (including relapses)
- Physical examinations (head, ears, eyes, nose, mouth, skin, heart and lung, lymph nodes, and GI, musculoskeletal, and neurological systems)
- Vital signs measurements: body temperature, pulse rate, respiratory rate, and diastolic and systolic blood pressure measured. Participants must remain in the sitting position for 5 minutes prior to having their pulse rate and blood pressure taken
- Triplicate 12-lead ECG parameters: heart rate, uncorrected QT, QTcF, PR, and QRS intervals. ECG should be recorded after the participant has been supine for at least 5 minutes. Triplicate ECGs will be recorded at the 2-hour and 5-hour intensive PK sampling timepoints (Week 4 Visit)
- C-SSRS will be administered by the trained site staff. The Baseline screening C-SSRS version will be used at Screening, and the Since Last Visit C-SSRS version will be used for subsequent visits.
- Concomitant therapy and procedure recording

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Measures taken during the course of the study due to the ongoing SARS-CoV-2 pandemic are detailed in Appendix 1.

10.2. Laboratory Safety Assessments

Samples will be analyzed using GLP-validated assays. Laboratory safety assessments will be conducted at the central laboratory. The platelet function test may be conducted at the central

laboratory or local laboratory, as applicable. All sites are required to conduct the platelet function test if they have the capability to perform it on site or at an external laboratory.

The following laboratory assessments will be performed to evaluate the safety profile of BIIB091 monotherapy and BIIB091 combination therapy with DRF:

- hematology: complete blood count with differential (ALC and absolute neutrophil count) and platelet count
- coagulation parameters: aPTT, PT, platelet function test (PFA 100/200)
- blood chemistry: total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, 1,25-$(OH)_2$ vitamin D_3, total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, ALT, AST, gamma-glutamyl transferase, lipase, amylase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium
- urinalysis: color, clarity/appearance, specific gravity, pH, urine protein, urine creatinine, and urine microalbumin testing; urine dipstick test for blood, protein, ketones, bilirubin, urobilinogen, glucose, bacteria, nitrite, and leukocyte esterase (with microscopy examination if abnormal)
- serum and urine pregnancy tests (WOCBP only)
- serum quantitative Ig: total Ig, IgM, IgG (including subtypes), IgA, and IgE
- serology for antibody titers: anti-tetanus, anti-pneumococcal, and anti-influenza antibody titers

11. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs and ADEs. If an AE or ADE occurs, the first concern should be for the safety of the participant. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each participant and/or their legally authorized representative must be given the names and telephone numbers of site staff for reporting SAEs, UADEs, pregnancies, overdoses, and medical emergencies. Throughout the protocol, the Sponsor is named, but reporting may be done through a CRO.

Konectom is classified as a Medical Device in EU, carrying the CE mark. Therefore, in European countries, AEs and product complaints will be handled according to the Sponsor's technical product complaint management process and reported according to standard local postmarketing channels. For the classification of Konectom in other countries, refer to the Konectom IB.

11.1. Definitions

11.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject (participant) administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal assessment such as an abnormal laboratory value), symptom, or disease temporally associated with the use of a medicinal (investigational) product or auxiliary medicinal products defined in Section 7.3.4, whether or not related to the medicinal (investigational) product or auxiliary medicinal product.

Determination of whether an abnormal assessment (e.g., laboratory value, vital sign, and ECG) result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

- The result meets the criteria for an SAE.
- The result requires the participant to receive specific corrective therapy.
- The result is considered by the Investigator to be clinically significant.

11.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.

- In the view of the Investigator, places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Is a medically important event.

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

11.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the participant is hospitalized. The study site must document all the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the participant's consent to be in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the participant's consent to be in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a participant is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 11.1.2 is met.

11.2. Safety Classifications

11.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 11.1.2.

- The relationship of the event to study treatment and/or auxiliary medicinal product, as defined in Section 11.2.2.
- The severity of the event as defined in Section 11.2.3.

11.2.2. Relationship of Events to Study Treatment and/or Auxiliary Medicinal Products

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment and/or auxiliary medicinal products. Definitions for auxiliary medicinal products are provided in Section 7.3.4.

Relationship of Event to Study Treatment and/or Auxiliary Medicinal Product(s)	
Not related	An AE will be considered "not related" to the use of the investigational product or auxiliary medicinal product if there is not a reasonable possibility that the event has been caused by the product. Factors pointing toward this assessment include, but are not limited to, the lack of reasonable temporal relationship between administration of the investigational product or auxiliary medicinal product and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational product or auxiliary medicinal product if there is a reasonable possibility that the event may have been caused by the product. Factors that point toward this assessment include, but are not limited to, a positive rechallenge, a reasonable temporal sequence between administration of the investigational product or auxiliary medicinal product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

11.2.3. Severity of Events

The severity of AEs and SAEs will be graded using the National Cancer Institute CTCAE, version 5.0. Any AE not listed in the CTCAE will be graded as follows:

Severity of Event	
Grade	Definition
1	Mild AE (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)
2	Moderate AE (minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living)
3	Severe or medically significant AE (not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living)
4	Life-threatening AE (urgent intervention indicated)
5	Death related to AE

11.2.4. Expectedness of Events

Expectedness of all SAEs will be determined by the Sponsor as follows:

- For study treatment, according to the BIIB091 IB and the DRF IB, as applicable.
- For authorized auxiliary medicinal products Gd-based contrast agents/media (ATC code: V08CA) and IVMP, according to the SmPC/USPI/local label, as applicable.

These products are defined in Section 7.3.4.

11.3. Monitoring and Recording Events

11.3.1. Adverse Events

Investigators are responsible for eliciting AEs experienced by participants as per the study design/schedule of activities. Any AE experienced by the participant between the time of first dose of study treatment (BIIB091, DRF, or both) and/or auxiliary medicinal product and the participant's EOS date is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment and/or auxiliary medicinal product. At each study visit, the Investigator will assess the participant for AEs and will record any new AEs or updates to previously reported AEs on the CRF.

AEs that are ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcome will be recorded on the CRF, as applicable.

11.3.2. Adverse Events of Special Interest

An AESI is an AE of scientific and medical concern specific to this study, for which ongoing monitoring and reporting to the Sponsor within 24 hours are required.

Events considered AESIs for BIIB091 will include the following events:

- QT prolongation (based on the average of triplicate QTcF measured at the same timepoint) that is considered to be clinically significant (change from baseline > 60 ms and/or QTc > 500 ms)
- ventricular tachyarrhythmia
- hepatic events

The following laboratory criteria will be considered evidence of a hepatic event AESI:

- AST or ALT ≥ 8 × ULN

  OR

- Total bilirubin > 2 × ULN with AST or ALT ≥ 3 × ULN

Hepatic events included as AESIs of BIIB091 were not based on current knowledge of BIIB091, but were based on emerging data from other BTK inhibitors in development.

Events considered AESIs for DRF will include the following events:

- PML and all related terms according to MedDRA
- Pancreatitis and all related terms according to MedDRA

All cases (serious and nonserious) of PML, pancreatitis, hepatic event AESI, ventricular tachyarrhythmia, and clinically significant QT prolongation (change from baseline > 60 ms and/or QTc >500 ms) should be reported to the Sponsor's safety group on the AESI form within 24 hours of the site staff becoming aware of the AESI and recorded in the participant's CRF.

11.3.3. Serious Adverse Events

Any SAE experienced by the participant between the time of the signing of the ICF and the participant's EOS date is to be recorded on an SAE form and recorded in the participant's CRF, regardless of the severity of the event or its relationship to study treatment and/or auxiliary medicinal product. Thereafter, the event should be reported to the Sponsor only if the Investigator considers the SAE to be related to study treatment.

SAEs must be reported to the Sponsor within 24 hours (as described in Section 11.3.4 or according to national law). Follow-up information regarding an SAE also must be reported within 24 hours.

An SAE that is also an AESI is to be reported per Section 11.3.4.

Any SAE that is ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

11.3.4. Immediate Reporting of Serious Adverse Events and Adverse Events of Special Interest

In order to adhere to all applicable laws and regulations for reporting an SAE and AESIs, the study site must formally notify the Sponsor within 24 hours of the site staff becoming aware of the SAE or AESI, or according to national law. It is the Investigator's responsibility to ensure that the SAE and AESI reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs and AESIs
A report ***must be submitted*** to the Sponsor regardless of the following:

- whether or not the participant has undergone study-related procedures
- whether or not the participant has received study treatment
- the severity of the event
- the relationship of the event to study treatment

To report initial or follow-up information on an SAE or AESI, fax or email the respective completed form; refer to the Study Reference Guide's Official Study Contact List for complete contact information.

11.3.5. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event or according to national law. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the Sponsor. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

11.3.6. Suspected Unexpected Serious Adverse Reactions

SUSARs are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Appropriate personnel at the Sponsor will unblind SUSARs for the purpose of regulatory reporting. The Sponsor will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. The Sponsor will submit SUSARs to Investigators in a blinded fashion.

Procedures for Handling Special Situations

11.4.1. Public Health Emergency Due to the SARS-Cov-2 Pandemic

In the event that a public health emergency due to the SARS-CoV-2 pandemic results in study site closure, travel restrictions, and/or the study being deprioritized at the site such that clinic visit(s) cannot occur, applicable local guidances on clinical trials during the SARS-CoV-2 pandemic within each country or region should be followed, for example the EU Guidance [EMA 2022]. A protocol deviation would be incurred for any deviation from the protocol-specified visits and assessments, with the additional notation that this protocol deviation is due to the SARS-CoV-2 pandemic.

If a protocol-specified clinical visit cannot occur due to a SARS-CoV-2 pandemic-related public health emergency, the following mitigating options should be pursued, in order of preference (in which the highest preference option that is feasible should be done): 1) transfer to another active study site that is open, 2) home visit, 3) telemedicine visit (e.g., by telephone or web conference), and 4) local laboratory visit. These mitigating options only apply in the setting of a SARS-CoV-2 pandemic-related public health emergency in which a protocol-specified clinic visit cannot occur

and should not be pursued solely due to the participant's preference. If the participant does not participate in one of these options, a Safety Telephone call must be conducted within 14 days of the scheduled visit that is impacted.

Details on which visits and procedures are eligible to be performed at alternative medical facilities will be provided by the Sponsor in writing. All procedures performed at alternative medical facilities will need to be performed as described in this protocol, and medical staff will need to be trained accordingly.

The Sponsor will determine appropriate start and end dates for each contingency measure, where the duration of the mitigations may begin at the onset of site restrictions for a specific site and/or country and may end once those restrictions are lifted and in accordance with local laws and regulations. The adaptations to the visits and procedures described are alternatives or deviations to the main protocol procedures.

These contingency measures will only be implemented in exceptional cases and after the site has received written notification from the Sponsor. In situations where written notification may be delayed, alternate communications (e.g., telephone) may be used until written notification is available. The Sponsor will have the final authority to decide what mitigations can be implemented, in accordance with local laws and regulations.

The Sponsor will communicate decisions to the Principal Investigator(s) and study site(s) via protocol clarification letters. The protocol clarification letter will include details such as which visits are eligible to be conducted via televisits. Study sites will be responsible for notifying any required boards or committees.

11.4.2. Pregnancy

Participants should not become pregnant or impregnate their partners during the study and for 90 days after their last dose of study treatment. If a female participant becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female participant and/or female partner of a male participant from first dose of study treatment to 90 days after their last dose of study treatment by faxing or emailing the pregnancy form to the Sponsor within 24 hours of the site staff becoming aware of the pregnancy. Refer to the Study Reference Guide's Official Study Contact List for complete contact information. The Investigator or site staff must report the outcome of the pregnancy to the Sponsor. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

If awareness of a pregnancy occurs after the participant completed the EOS Visit, the Investigator should report pregnancies where conception occurred during the study treatment period or within 90 days from their last dose of study treatment.

Every reasonable effort will be made by the Investigator to follow up the pregnancy of a female subject or a consented female partner until delivery. A pregnancy notification form and follow-

up will be completed. The Investigator or site staff must report the outcome of the pregnancy to the Sponsor.

Congenital abnormalities and birth defects in the offspring of male or female participants should be reported as an SAE if conception occurred during the study treatment period or within 5 times the half-life or 90 days from their last dose of study treatment, whichever is longer.

11.4.3. Overdose

An overdose is any dose of study treatment administered to a participant or taken by a participant that exceeds the dose assigned to the participant according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded in an Overdose form and faxed or emailed to the Sponsor within 24 hours of the site becoming aware of the overdose. An overdose must be reported to the Sponsor even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or emailed to the Sponsor. All study treatment-related dosing information must be recorded in the dosing CRF.

11.4.4. Abuse, Misuse, Medication Error, and Accidental or Occupational Exposure

Abuse, misuse, medication error, and accidental or occupational exposure events (defined below) are not considered AEs and should not be recorded as an AE on the CRF; however, all occurrences of abuse, misuse, medication error, and accidental or occupational exposure with any study treatment and/or unauthorized auxiliary medicinal product administered must be recorded on a Clinical Trial Special Situation(s) Report form and faxed or emailed to the Sponsor within 24 hours of the site becoming aware of the event. Abuse, misuse, medication error, and accidental or occupational exposure must be reported to the Sponsor from first dose of study treatment and/or auxiliary medicinal product to last study visit, even if the event does not result in an AE. If an abuse, misuse, medication error, or accidental or occupational exposure event results in an AE, the AE must be recorded on the CRF. If an abuse, misuse, medication error, or accidental or occupational exposure event results in an SAE, both the SAE and the Clinical Trial Special Situation(s) Report forms must be completed and faxed or emailed to the Sponsor within 24 hours of awareness. All study treatment-related dosing information must be recorded on the dosing CRF.

These events are defined as follows:

- Abuse: persistent or sporadic, intentional excessive use of the study treatment and/or auxiliary medicinal product that is accompanied by harmful physical or psychological effects.

- Misuse: medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.

- Medication error: any preventable incident that may cause or lead to inappropriate study treatment and/or auxiliary medicinal product use or participant harm while the product is in the control of the health care professionals or participants. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

- Accidental/occupational exposure: the unintentional exposure to a study treatment and/or auxiliary medicinal product as a result of one's professional or nonprofessional occupation, or accidental exposure to a nonprofessional to whom exposure was not intended (i.e., product given to wrong participant).

11.4.5. Medical Emergency

In a medical emergency requiring immediate attention, the site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Reference Guide's Official Study Contact List for complete contact information.

11.4.5.1. Unblinding for Medical Emergency

In this study, treatment assignment information is provided electronically and will be accessible by the Investigator (or designee) in case of a medical emergency where knowledge of a participant's treatment assignment may influence that participant's clinical care. If such an event occurs, the date and the reasons for opening the code-break file must be submitted to the Sponsor within 24 hours of the unblinding. All treatment assignment information, including electronic or hard copies, must be kept in a secure location with limited access.

The Investigator must document the reasons for unblinding in the participant's source documents. The Investigator is strongly advised not to divulge the participant's treatment assignment to any individual not directly involved in managing the medical emergency, or to personnel involved with the analysis and conduct of the study. The Investigator can contact the Sponsor to discuss such situations.

11.5. Device Definition and Reporting Requirements

Follow this section for reporting events during the use of Konectom.

11.5.1. Adverse Device Effect

An ADE is defined as any AE related to the use of an investigational medical device.

Any ADE experienced by a participant after the participant signs the ICF and before study completion or premature study withdrawal is to be recorded in the eCRF.

11.5.2. Unanticipated Adverse Device Effect

A UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

The criteria for seriousness include the following:

- requires inpatient hospitalization or prolongation of existing hospitalization
- causes disability or permanent damage
- results in persistent or significant disability/incapacity
- requires intervention to prevent permanent impairment/damage
- results in congenital anomaly/birth defect
- any other medically important event that, in the opinion of the Investigator, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above

Any UADE experienced by a participant after the participant signs the ICF and before study completion or premature study withdrawal is to be recorded on the AE eCRF and on a Clinical Trial Device Reporting Form and faxed or emailed to the Sponsor within 24 hours of the site staff becoming aware of the UADE; refer to the Study Reference Guide's Official Study Contact List for complete contact information. Follow-up information regarding a UADE must be reported on the AE CRF and on the Clinical Trial Device Reporting Follow-up Form. Additionally, in the US, the study site must formally notify the IRB/ethics committee of UADEs within 10 working days of the site staff becoming aware of the UADE.

Participants will be followed for all UADEs until the study completion or premature study withdrawal. Any UADE that is ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

11.5.3. Product Complaints

For information on product complaints/device deficiencies related to Konectom, please refer to the Konectom IB.

11.5.4. Relationship of Device Effects to Konectom

The following should be considered when evaluating if an effect is caused by or associated with Konectom:

- The event has a temporal relationship with investigational device use/application or procedures.
- The event involves a body site or organ that:
  - the investigational device or procedures are applied to
  - the investigational device or procedures have an effect on
- The serious event follows a known response pattern to the medical device (if the response pattern is previously known).
- Discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure) have an impact on the serious event (when clinically feasible).
- Other possible causes (e.g., an underlying or concurrent illness/clinical condition and/or an effect of another device, drug, or treatment) have been adequately ruled out.
- Harm to the participant is due to an error in use.

In order to establish the relatedness, not all the criteria listed above might be met at the same time. Depending on the type of device/procedures and the serious effect, an event may be assessed as related even if all the criteria listed above are not met.

11.5.5. Severity of Device Effects

The following definitions should be considered when evaluating the severity of ADEs/UADEs:

Severity of Event	
Mild	Symptoms barely noticeable to participant or do not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms.
Moderate	Symptoms of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of device use; treatment for symptoms may be given and/or participant hospitalized.

11.5.6. Expectedness of Device Effects

Refer to the Konectom IB for information on any expected/anticipated ADEs associated with the use of Konectom.

11.6. Contraception Requirements

All WOCBP and all men with WOCBP partners must ensure that highly effective contraception is used during the study and for at least 90 days after their last dose of study treatment, unless in conflict with local or country rules and guidelines. In addition, participants should not donate sperm or eggs for the duration of the study and for at least 90 days after their last dose of study treatment.

For the purposes of this study, WOCBP are defined as all women physiologically capable of becoming pregnant, UNLESS they meet 1 of the following conditions:

- Postmenopausal
    - 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical cause and a serum FSH level >40 mIU/mL
    - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation), where applicable, according to local guidelines

For the purposes of the study, highly effective contraception is defined in agreement with the current Clinical Trial Facilitation and Coordination Group guidance [HMA 2020] as use of one of the following and achieves a failure rate of less than 1% when used consistently and correctly.

For females:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation
- Established use of oral, injected, or implanted hormonal methods of contraception associated with the inhibition of ovulation
- Placement of an intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate)

For males:

- Vasectomy with negative semen analysis at follow-up. If documentation is not available, the participant must use contraception

- Condoms with or without spermicide, where applicable according to local guidelines
- Sex with a woman who uses the methods described for females if she is of childbearing potential

Note: Contraceptives and hormone replacement therapies that are known to prolong QT/QTc interval (based on each drug's product label and other available references such as Woosley et al. [Woosley 2022]), induce or inhibit CYP3A4 [FDA 2022], or are OATP1B1 or B3 substrates are not permitted. A current comprehensive list of medications, including oral contraceptives, known to prolong QT/QTc interval is available in the aforementioned citation.

True abstinence, when this is consistent with the preferred and usual lifestyle of the participant, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical study (abstinence would be required during the study and for 90 days after the last dose of study treatment). Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Women who are breastfeeding cannot take part in this study.

Pregnancy reporting is described in Section 11.4.1.

11.7. Safety Responsibilities

11.7.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, SAEs, AESIs, ADEs, and UADEs on the CRF regardless of the severity or relationship to study treatment and/or auxiliary medicinal products.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies in female participants and (where consent is granted) in female partners of male participants and follow up on the outcome of all pregnancies.
- Monitor and record all cases of abuse, misuse, medication error, and accidental or occupational exposure with any study treatment and/or unauthorized auxiliary medicinal product administered, and record on a Clinical Trial Special Situation(s) Report form and fax or email to the Sponsor within 24 hours of the site becoming aware of the event.
- Complete the Overdose form if applicable

- Complete the appropriate form for each SAE (and if applicable, also the Special Situation Form), AESI, and UADE and email it to the Sponsor within 24 hours of the site staff becoming aware of the event or according to national law.

- Pursue follow-up information actively and persistently for reported events (SAE, AESI, and UADE). Follow-up information must be reported to the Sponsor within 24 hours of the site staff becoming aware of new information or according to national law.

- Report AESIs, SUSARs, and UADEs if applicable, according to the respective requirements for these events.

- Ensure all AE, SAE, AESI, ADE, and UADE reports are supported by documentation in the participants' medical records.

- Pursue AE and ADE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the CRF, as applicable.

- Report SAEs to local ethics committees, as required by local law.

- Formally notify the IRB/ethics committee within 10 working days of the site staff becoming aware of a UADE, if applicable.

11.7.2. The Sponsor

The Sponsor's responsibilities include the following:

- Before a site can enroll any participants, the Medical Monitor is responsible for reviewing with site staff the definitions of AE, SAE, AESI, ADE, UADE, product complaints, pregnancy, overdose, and other special situations, as well as the instructions for monitoring, recording, and reporting of these events.

- The Sponsor is to notify all appropriate regulatory authorities, EU Eudra Vigilance Database, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

- The Sponsor is to manage and evaluate ADEs and UADEs, including collection and evaluation of data of all UADEs transmitted by the Investigator.

- The Sponsor is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of the result of all UADE evaluations as required by local law, within the required time frames.

- The sponsor will task an IDMC with safety monitoring (see Section 14.3.2).

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1. General Considerations

Continuous variables will be summarized using descriptive statistics, including mean, SD, median, minimum, and maximum, by treatment group. Categorical variables will be presented using frequency distributions by treatment group. The stratification factor of region (Eastern Europe vs. Other) will be included in the statistical models for adjustment, unless otherwise specified. For stratification, Eastern Europe will include participants from countries such as Poland and the Czech Republic. Other covariates, if included in the model, will be specified in the respective sections.

No multiplicity adjustment will be performed for all analyses because of the exploratory nature of Phase 2 trials.

12.2. Analysis Sets

The populations of study participants used in the analyses are defined in the following analysis sets. For each set, study treatment refers to BIIB091, DRF, or placebo.

12.2.1. Full Analysis Set

The FAS includes all randomized participants who receive at least 1 dose of study treatment. In analyses performed on the FAS, participants will be analyzed according to their randomized treatment assignment regardless of treatment received.

12.2.2. Safety Analysis Set

The Safety Analysis Set includes all randomized participants who have received at least 1 dose of study treatment. In analyses performed on the Safety Analysis Set, participants will be analyzed according to their actual treatment received.

12.2.3. PK Analysis Set

The PK Analysis Set includes all randomized participants who have received at least 1 dose of study treatment and have at least 1 measurable study drug concentration in serum. In analyses performed on the PK Analysis Set, participants will be analyzed according to their actual treatment received.

12.2.4. Intensive PK Analysis Set

The Intensive PK Analysis Set includes the subset of randomized participants who have received at least 1 dose of study treatment and have at least 1 measurable concentration in serum from the intensive PK sampling. In analyses performed on the Intensive PK Analysis Set, the participants

who are selected as the intensive PK cohort will be analyzed according to their actual treatment received.

12.2.5. PD Analysis Set

The PD Analysis Set includes all randomized participants who have received at least 1 dose of study treatment and who have a baseline measurement and at least 1 postbaseline measurement of the parameter of interest. In analyses performed on the PD Analysis Set, participants will be analyzed according to their actual treatment received.

12.3. Methods of Analysis for Efficacy Endpoints

In general, the efficacy endpoints will be summarized using descriptive statistics and will be analyzed with appropriate statistical models. Efficacy analyses will be based on participants in the FAS population.

Except for adjusting region, all analysis models will include a relevant baseline factor for the specified endpoint as a covariate. For example, it is baseline T1 GdE lesion number for the cumulative number of new T1 GdE lesions; baseline T2 lesion volume for the cumulative number of new or enlarging T2 lesions; baseline T2 lesion volume for the cumulative volume of new or enlarging T2 lesions; baseline relapse rate for ARR and time to first relapse; and baseline EDSS, T25W, and 9HPT for ODRS. Other baseline factors that may be added in the models include prior anti-CD20 therapy and age. If additional variables are added, they will be prespecified in the SAP.

12.3.1. Analysis of the Primary Endpoint (Part 2 Only)

The analysis of the primary endpoint will be performed under the estimand framework described in the SAP, where relevant intercurrent events and corresponding handling strategies will be specified.

12.3.1.1. Cumulative Number of New T1 GdE Lesions Over Weeks 8, 12, and 16

The cumulative number of new T1 GdE lesions over Weeks 8, 12, and 16 will be analyzed based on the negative binomial regression model, with offset given by the log number of available scans, adjusted for the baseline number of GdE lesions and region (Eastern Europe vs. Other). For stratification, Eastern Europe will include participants from countries such as Poland and the Czech Republic. Treatment groups will be included as a fixed-effect factor for the treatment comparison of each treatment group versus DRF monotherapy. Details on missing data imputation will be provided in the SAP. The same statistical model will be used to evaluate the cumulative number of new T1 GdE lesions over Weeks 8, 12, and 16 in Part 1 and in Part 2 (primary endpoint).

12.3.2. Analysis of the Secondary Efficacy Endpoints (Part 1 and Part 2)

12.3.2.1. Cumulative Number of New or Enlarging T2 Lesions

The cumulative number of new or enlarging T2 lesions is derived by summing up the numbers of new or enlarging T2 lesions at Weeks 8, 12, and 16. The cumulative number of new or enlarging T2 lesions over Weeks 8, 12, and 16 will be analyzed based on the negative binomial regression model. The baseline volume of T2 lesions and stratification factor of region will be included as covariates.

12.3.2.2. Cumulative Volume of New or Enlarging T2 Hyperintense Lesions

The secondary efficacy endpoint is derived by summing up the volumes of new or enlarging T2 lesions at Weeks 8, 12, and 16. The cumulative volume of new or enlarging T2 hyperintense lesions at Weeks 8, 12, and 16 will be analyzed by using ANCOVA with adjustment for the baseline T2 lesion volume and region. If the data are not normally distributed, then the rank ANCOVA model will be used. Treatment group will be included as a fixed factor for the treatment comparison of each BIIB091 dose to DRF.

12.3.3. Analysis of Key Exploratory Efficacy Endpoints (Part 1 and Part 2)

For the Part 1 and Part 2 key exploratory efficacy endpoints, the Kaplan-Meier method will be used to estimate the proportion of relapsing participants, and a Cox proportional hazards model will be used for time-to-event data (e.g., time to relapse, time to confirmed disability progression); a mixed-effect repeated measures model will be used for continuous repeatedly measured outcomes (e.g., MSIS-29 v2 physical and psychological scores). In general, all models will be adjusted for stratification factor for region and relevant baseline measurements (baseline relapse rate for time to first relapse, baseline EDSS for progression, baseline MSIS-29 for analyses on the MSIS-29 physical, and psychological scores).

12.3.3.1. Annualized Relapse Rate

The analysis of ARR will be based on the relapses that are determined to meet the protocol-defined definition from Baseline up to the timepoint according to the analysis (or early withdrawal). New or recurrent neurological symptoms that occur less than 30 days following the onset of the relapse will be considered part of the same relapse. That is, if 2 relapses have onset days less than or equal to 30 days of one another, they will be counted as 1 relapse. ARR will be analyzed by using a negative binomial regression model with the logarithmic transformation for the time on study included as an offset parameter and will be adjusted for baseline relapse rate and region.

12.3.3.2. Overall Disability Response Score

The ODRS is a multicomponent score that assesses the overall change in disability over time and is derived based on 4 components: EDSS, T25FW, 9HPT-D, and 9HPT-ND. At each visit, each component is given a score relative to baseline: -1 (if threshold is met for worsening), 0 (no changes meet threshold criteria), or +1 (if threshold is met for improvement). The scores of

individual assessments are summed up to provide a total ODRS that ranges from +4 to -4 for each visit. A mixed-effect repeated measures will be used to analyze the ODRS with adjustment for region, and baseline EDSS, T25FW, and 9HPT.

12.3.3.3. Smartphone Digital Outcomes

Due to the innovative nature of smartphone assessments, analyses of the digital clinical outcomes are considered exploratory. Details of derived features of the digital outcomes will be specified in a priori, separate, digital data processing plan. The prespecified features will be summarized and analyzed per the SAP.

12.3.4. Pooled Analysis of Part 1 and Part 2 Efficacy Endpoints

Key efficacy endpoints including T1 GdE lesion number, ARR, and ODRS, will also be evaluated after pooling data from Part 1 and Part 2. Analysis models will be similar to those specified for the Part 1 and Part 2 analyses, except that the models will include 5 treatment groups (BIIB091 low-dose monotherapy, BIIB091 high-dose monotherapy, BIIB091 selected-dose and DRF low-dose combination therapy, BIIB091 selected-dose and DRF standard-dose combination therapy, and DRF standard-dose monotherapy [with the pooled data and as reference group for treatment comparison]). Analysis models will be adjusted by region and relevant baseline factors for the specified endpoint. Other baseline factors that may be included in these models include prior anti-CD20 therapy, age, baseline number of GdE lesions, and baseline EDSS.

12.4. Methods of Analysis for Pharmacokinetic Endpoints

Results from the analysis of PK endpoints will be summarized using descriptive statistics by treatment group. Details of the additional analyses of PK and exposure-response and exposure-safety will be described in a separate analysis plan, and the results of the analyses will be documented in a separate report.

12.5. Methods of Analysis for Pharmacodynamic Endpoints

Results from the analysis of PD endpoints will be summarized using descriptive statistics by treatment group. Mean change from baseline time profiles for CD69 expression and inhibition and absolute count or proportion of immune cell subsets may be plotted on linear and/or semi-logarithmic scales. Additional analyses, if any, may be summarized in a separate report.

12.6. Methods of Analysis for Biomarkers/Pharmacogenetics

Results from any unspecified exploratory pharmacogenetic or biomarker research, if performed, will be documented separately, and details related to the analyses will not be described in the protocol.

Exploratory potential biomarker candidates related to BIIB091 biological activity will be summarized using descriptive statistics and will be presented by dose group.

Sampling for this analysis will be approved at the discretion of each site's ethics committee. If a site's ethics committee does not approve the sampling for the analysis, this section will not be applicable to that site.

12.7. Methods of Analysis for Safety Endpoints

The safety endpoints, including AEs, SAEs, and ECGs, will be summarized by treatment group using descriptive statistics.

12.7.1. Adverse Events

The incidence of TEAEs and treatment-emergent SAEs are the primary endpoints for safety in Part 1 of this study and are also endpoints for safety in Part 2 of the study.

Only TEAEs will be summarized. A TEAE is any new or worsening AE experienced by the participant between the time of first dose of study treatment and the participant's EOS date recorded in the eCRF.

The incidence of all TEAEs and that of all treatment-emergent SAEs will be summarized by treatment group, severity, and relationship to study treatment. The summary tables will include incidence by system organ class and preferred term, as well as by preferred term only, in descending order of frequency. AEs will be coded using MedDRA.

12.7.2. Adverse Device Events

The incidence of ADEs and UADEs are safety endpoints for this study due to the use of Konectom. Both will be summarized by treatment group, severity, and relationship to the medical device. The summary tables will include incidence by system organ class and preferred term, as well as by preferred term only, in descending order of frequency. ADEs will be coded using MedDRA.

12.7.3. Clinical Laboratory Results

Clinical laboratory evaluations include hematology, blood chemistry, and urinalysis. Laboratory data will be summarized by treatment group and visit using descriptive statistics for both recorded values and changes from baseline. Laboratory data will also be summarized using shift tables. Shifts from baseline to high/low status for hematology and blood chemistry parameters and shifts from baseline to high/positive status for urinalysis will be presented. Summaries of laboratory values categorized based on potentially clinically significant abnormalities will be provided. Graphical presentations of aggregate data may also be provided for selected parameters of interest.

12.7.4. Vital Signs

Vital signs will be summarized by treatment group and visit using descriptive statistics for values and changes from baseline. The incidence of clinically relevant abnormalities will also be summarized by treatment group.

The analysis of vital signs will focus on clinically relevant abnormalities.

The definitions of these clinically relevant abnormalities are shown in Table 3.

Table 3: Criteria Used to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	> 38°C or an increase from baseline of at least 1°C
Pulse Rate	> 100 bpm or an increase from baseline of > 30 bpm < 40 bpm or a decrease from baseline of > 20 bpm
Systolic Blood Pressure	> 160 mmHg or an increase from baseline of > 40 mmHg < 90 mmHg or a decrease from baseline of > 30 mmHg
Diastolic Blood Pressure	> 100 mmHg or an increase from baseline of > 30 mmHg < 45 mmHg or a decrease from baseline of > 20 mmHg

12.7.5. Physical Examinations

Clinically significant abnormal findings on physical examinations will be reported as AEs and included in the AE analyses.

12.7.6. Electrocardiograms

The number and percentage of participants with shifts to the categorical values in ECG results (abnormal not AE, or abnormal AE) will be summarized by treatment group.

12.7.7. Multiple Sclerosis Signs and Symptoms

Changes from baseline in MS signs and symptoms will be summarized by treatment group.

12.7.8. C-SSRS

C-SSRS data will be summarized using descriptive statistics (number of participants, mean, SD, median, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables.

12.8. Planned Analyses

12.8.1. Part 1: Primary and Secondary Endpoint Analysis (Week 16)

An analysis of efficacy, safety, and selected exploratory endpoints will be completed after all participants in Part 1 complete Week 16. The overall benefit-risk will be assessed in order to determine if the study will proceed to Part 2 and to select a BIIB091 dose for Part 2 (see Section 14.3 for details). No alpha adjustment will be made. Decision criteria for dose selection will be prespecified in the SAP.

The participants, site staff, and Sponsor team members responsible for site monitoring and data management will remain blinded to treatment assignment during the ongoing data review, as well as during the Week 16 analysis in order to minimize the potential for bias in the data cleaning process.

12.8.2. Part 2: Primary and Secondary Endpoint Analysis (Week 16)

The primary analysis of the study will be based on data after all participants in Part 2 complete the Week 16 Visit. For this analysis of Part 2 data, the reference cohort will be the Part 2 DRF monotherapy cohort with approximately 50 randomized participants. Primary and secondary efficacy endpoints will be analyzed comparing each combination therapy group to DRF. The efficacy superiority of BIIB091 combination therapy to DRF will be examined, by testing if statistical significance is in the coefficient estimate of treatment groups in relevant models. Safety, PK, PD, and (selected) other efficacy endpoints may also be analyzed in the primary analysis. At the end of Part 2, Week 16, selected study management team members will be unblinded to complete the analysis (see Section 14.3.1 for details). However, the blind will continue to be strictly maintained for all study personnel at sites and for all study participants until the end of the study.

12.8.3. Final Analysis

Analyses will be completed at the end of the study, and analyses of efficacy endpoints for this final analysis will be considered exploratory.

In general, analysis methods will be the same as those used in the interim analyses of Part 1 and Part 2 (mentioned in Section 12.3 to Section 12.7). For example, descriptive statistics by treatment groups will be used for the data of safety endpoints and PK/PD endpoints; negative binomial models and ANCOVA (or rank-based ANCOVA) will be utilized respectively for lesion count-type and volume-type endpoints; mixed-effect repeated measures models will be employed for continuous repeatedly measured outcomes (e.g., clinical and PRO measures) and associated changes from baseline.

12.9. Sample Size Considerations

The planned sample size is 275 participants.

Accounting for a 12% dropout rate, 275 participants are planned to be enrolled in the study. Of these, 125 participants will be randomized in Part 1 and 150 participants will be randomized in Part 2.

In Part 2, a sample size of 50 participants per group (44 evaluable) was designed to detect an 80% reduction from the mean number (SD) of 1.2 (3) cumulative new T1 GdE lesions over MRI scans at Weeks 8, 12, and 16 in the standard dose of DRF monotherapy with approximately 90% power and a 10% Type 1 error rate. The sample size of 44 evaluable participants per group was derived via negative binomial rate ratio test where the cumulative number of new T1 GdE lesions was assumed to follow a negative binomial distribution.

A sample size of 50 participants (44 evaluable) per treatment group will allow for an 80% or greater probability of observing at least 1 occurrence of an AE with an event rate of 3.6%.

In Part 1, intensive PK will be collected in up to 25 participants (approximately 10 participants in each BIIB091 group and approximately 5 participants in the DRF group). In Part 2, intensive PK will be collected in up to 30 participants (approximately 10 participants in each group).

13. ETHICAL AND REGULATORY REQUIREMENTS

The Sponsor, any contracted third party, and the Investigator must conduct the clinical trial in compliance with all instructions, regulations, and agreements in this protocol; the principles of applicable ICH and GCP guidelines; and conduct the study according to local regulations, including the requirements of Clinical Trials Regulation (EU) No 536/2014 or, if applicable, Clinical Trials Directive 2001/20/EC.

The Investigators are responsible for demonstrating timely oversight of all clinical trial data from their site, including data external to the EDC system, such as laboratory, imaging, and electronic clinical outcomes assessment data. Investigators must approve all their data on completed CRFs by signing electronically, at the participant, visit, or casebook level, at any time prior to an interim lock or database lock, as well as before any subsequent re-lock. The EDC system does not prohibit Investigator approval or signing in any way.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

13.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

13.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study.The Sponsor will submit documents on behalf of the study sites in countries other than the US.If the Investigator makes any changes to the ICF, the Sponsor must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to the Sponsor. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and the Sponsor.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

The Sponsor must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, where required, the study site must submit a close-out letter to the ethics committee and the Sponsor.

13.3. Changes to Final Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect participant safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, the Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a participant. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 13.4).

13.4. Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, informed consent with the approved ICF must be obtained.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the participant must be explained to the participant and/or the participant's legally authorized representative, as applicable, in accordance with local practice and regulations. The participant and/or the participant's legally authorized representative, as applicable, in accordance with local practice and regulations, must be given sufficient time to consider whether to participate in the study.

Where allowed, additional consents for future exploratory genetic research or future scientific research may also apply, if the participant opts for residual samples or MRI scans to be retained for possible use for such research (see Section 9.4 and Section 9.5). If the participant opts for such use, the Genetic Research ICF and/or Future Scientific Research ICF should be signed at the same visit as the main ICF, before the samples are collected.

A copy of the signed and dated ICF must be given to the participant. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the participant's medical record.

When additional information that may affect participants' willingness to continue in the study becomes available, the Investigators will be notified in a timely manner, according to all local and applicable law. An updated ICF may be required.

13.5. Participant Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by applicable national and local privacy regulations (e.g., Protected Health Information authorization in North America).

During the study, participants' race and ethnicity will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). These data will be used in the analysis of the safety and/or PK profile of the study treatment.

Study reports will be used for research purposes only. The participant will not be identified by name in CRFs, study-related forms, study reports, or any related publications. The Sponsor, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the participant's personal medical data confidential.

The Sponsor will conduct this study, and process all personal data, according to the Sponsor policies related to data privacy, records retention and disposition, and information security. The Sponsor has developed and implemented and will maintain a comprehensive, documented information security program that requires the implementation of administrative, physical, and technical safeguards to protect personal data against unauthorized or inappropriate use, access, or transmission. Such technical and organizational measures (including organizational processes and procedures) are designed to protect personal data from unauthorized use or access, accidental loss, damage, destruction, theft, or disclosure, and to ensure that such measures are commensurate with the harm that may result from this. The Sponsor's information security controls are compliant with the NIST SP 800-53 (or the ISO equivalent) framework to protect the confidentiality of personal data.

In case of a suspected data security breach, the Sponsor will follow the procedure outlined in its data privacy and information security policies, which require immediate reporting to the Sponsor's Global Privacy Office so that risk and next steps (including reporting to data protection authorities and/or data subjects) can be assessed.

13.6. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

13.7. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in the Sponsor) with the participant before the participant makes a decision to participate in the study.

13.8. Study Report Signatory

The Sponsor will designate 1 or more of the participating Investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to, the

Investigator's experience and reputation in the studied indication; the Investigator's contribution to the study in terms of design, management, and/or participant enrollment; or by other factors determined to be relevant by the Sponsor.

The Sponsor will follow all applicable local regulations pertaining to study report signatories.

13.9. Registration of Study and Disclosure of Study Results

The Sponsor will register the study and post study results regardless of outcome, on a publicly accessible website within 12 months after the final data lock date, in accordance with the applicable laws and regulations. Since both parts of the study are blinded, interim analysis results after Part 1 will not be released.

The Sponsor also will notify, when required, the applicable regulatory authorities and ethics committees about the completion or termination of this study and will send a copy of the study synopsis in accordance with necessary timelines.

13.10. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

14. KEY ROLES AND STUDY GOVERNANCE COMMITTEES

14.1. Site Staff

For each participant, the PI of the site will designate the following study site staff:

- a primary and backup **treating neurologist**
- a **treating nurse** (or study coordinator; may be performed by **treating neurologist**)
- a primary and backup **examining neurologist**
- an **examining technician** (may be performed by **examining neurologist**)
- an **MRI technician**

Both the examining neurologist and the treating neurologist must have a minimum of 2 years of neurology specialty training and, at study initiation, do not anticipate leaving the study within at least 1 year. Where specified, evaluations described in this section must be performed only by the personnel indicated. Treating neurologists may review neurological examination results obtained by examining neurologists. The examining neurologist and examining technician should not administer study treatment.

The **primary treating neurologist** will be responsible for the following:

- Management of the routine neurological care of the participant
- Assessment (including assignment of causality) and treatment of AEs and MS relapses
- Reading MRIs should be read at their discretion or following local procedures
- Review of hematology and blood chemistry results from the central laboratory to assess whether the participant's study treatment should be discontinued per the criteria detailed in Section 8.1
- Providing education to participants on signs and symptoms of potential delayed reactions after study treatment administration, signs and symptoms of a relapse, and providing information to the participant on how to contact the site to report any AE

The **primary treating nurse** (or study coordinator; may be performed by the treating neurologist) will be responsible for the following:

- Assisting the treating neurologist in participant management, including the treatment of AEs, the treatment and assessment of MS relapses, and the recording of AEs and concomitant medications

- Administering the PROs
- Administering the C-SSRS (must be performed by a certified examiner or trained study coordinator; may be performed by the treating neurologist)
- Collecting blood samples and obtaining vital sign measurements

The **examining neurologist (EDSS-certified rater)** will be responsible for the following:

- Performing the assessment of the EDSS based on a detailed neurological examination at the scheduled timepoints required in the protocol
- Performing the assessment of the EDSS at every unscheduled visit for relapse assessment if referred by the treating neurologist when an MS relapse is suspected
- The following guidelines must be strictly followed:
  - The examining neurologist must not be involved with any other aspect of participant care and management. Further, the examining neurologist is not to serve as treating neurologist for any participants at a given study site.
  - The examining neurologist must remain blinded to AEs, concomitant medications, laboratory data, MRI scan/data (including any local reads), and any other data that have the potential of revealing the treatment assignment.
  - To ensure consistency across sites, examining neurologists and the backup examining neurologists must receive standardized training and obtain certification of EDSS scoring prior to enrollment of participants at their site.
  - After receiving approval from the Sponsor Medical Director or designee, nurse practitioners or physician assistants who have at least 2 years of practice experience in a neurology clinic and have prior experience and certification in EDSS scoring may also function as examining neurologists in this study.
  - The backup examining neurologist will conduct participant evaluations ONLY if the primary examining neurologist is unavailable due to illness, vacation, or travel. All sites should attempt to maintain the same examining neurologist throughout the study.
  - If an examining neurologist has to be replaced, the new examining neurologist must receive standardized training and obtain certification of EDSS scoring prior to performing an EDSS assessment.
  - The communication of new findings on the neurological examination from the examining neurologist to the treating neurologist is permitted (because findings

on the neurological examination may be important in the routine care of the participant, e.g., medical management of relapses).

– The roles of the treating and examining neurologists (primary and backup) are NOT interchangeable, even for different participants.

– The examining neurologist may also act as the examining technician (see below).

The **examining technician** will be responsible for the following:

- Administering the in-clinic (Konectom) smartphone-based test battery (can also be performed by the examining neurologist) which includes a CPST, 2 fine motor tests (Pinching and Drawing), U-Turn Test, SBT, 6MWT, mood scale, and MSIS-29 v2

- Administering the nondigital clinical assessments which includes the T25FW, 9HPT, SDMT, and LCLA tests

The **MRI technician** will be responsible for the following:

- Performing a brain MRI scan with and without contrast, in accordance with the study-specific MRI manual, at all protocol-required timepoints

14.2. Vendors

The Sponsor will ensure oversight of any study-related duties and functions carried out on its behalf and will specify in writing all duties and functions that are transferred.

14.2.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, management of SAE reports, monitoring, and data management.

14.2.2. Interactive Response Technology

IRT will be used in this study. Before participants are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

14.2.3. Electronic or Remote Data Capture

Participant information will be captured and managed by study sites on eCRFs by a web-based EDC tool configured by the Sponsor and hosted by Medidata Solutions.

The EDSS will be administered using a separate tablet device hosted by WCG MedAvante.

PROs will be completed by the participant on paper forms and subsequently entered into the EDC tool by the site staff.

14.2.4. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by the Sponsor to analyze all hematology, blood chemistry, and urine samples collected for this study. PK samples will be analyzed at a laboratory selected by the Sponsor.

Samples for PD assessments will be analyzed at laboratories selected by the Sponsor.

14.2.5. Central Facility for Other Assessments

14.2.5.1. Central Imaging Facility

A central MRI reader has been selected by the Sponsor to read and interpret all MRI scans for the MRI endpoints for this study. All sites will need to perform a dummy scan for qualification of the site's MRI machine; a separate ICF will be used for this scan. If there is a change in MRI machine during the study, this process will need to be repeated.

14.2.5.2. Central Facility for Reading ECGs

A central facility has been selected by the Sponsor to read and interpret all ECG reports for this study.

14.2.6. Central Review of Raters

The Sponsor has selected a rater management group to establish rater qualifications, provide study-specific training about the rater process, and provide oversight. As part of the oversight process, the rater management group will incorporate a central review of the raters to ensure that data are consistently rated across sites.

14.3. Study Committees

14.3.1. Sponsor Study Management Team

Selected Sponsor team members, including Sponsor representatives from Clinical Development, Safety, Biomarkers, and Biostatistics, will be unblinded at Week 16 to participate in the 16-week data analyses. After Week 16 in Part 1, this team will determine whether the study will proceed to Part 2 (based on the overall benefit-risk profile of the Part 1, Week 16 analyses) and to select the BIIB091 dose to be used in Part 2. Details on how the study blind is maintained during, who is unblinded, and the timing of unblinding in Part 1 and Part 2 will be provided in a separate unblinding plan.

14.3.2. Independent Data Monitoring Committee

An IDMC will be formed to review ongoing safety and tolerability data during the study and make recommendations to the Sponsor about any existing or potential issues and will be able to access unblinded data as needed. In particular, the IDMC will review the participants' safety data from the Part 1, Week 16 primary analysis and make a recommendation whether to proceed with

enrollment of participants into Part 2 without modification, proceed with enrollment of participants into Part 2 with certain modifications (e.g., protocol amendment), or discontinue the study. The IDMC charter will provide full guidance on the function and practices to be followed by the IDMC.

The IDMC will meet periodically during the study to review AE listings, vital signs, 12-lead safety ECGs, C-SSRS, and laboratory results for all enrolled participants. In addition to the periodic meetings, the IDMC may meet on an ad hoc basis to address any issues of concern. At any time during the study, the IDMC may make additional recommendations regarding continuation of the study without modification, discontinuation of further enrollment into a treatment group, or discontinuation of further enrollment for the study.

15. ADMINISTRATIVE PROCEDURES

15.1. Study Site Initiation

The Investigator must not screen any participants prior to the Sponsor completing a study initiation visit. This initiation visit with the Investigator and other site staff, as appropriate, will include a detailed review of the protocol, study procedures, and study responsibilities.

15.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate. The Investigator is responsible for endorsing all CRF data prior to any interim or final database lock.

During and/or after completion of the study, quality assurance officers named by the Sponsor or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

15.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the participants' medical histories. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The Medical Monitor will visit the study site at regular intervals during the study and after the study has been completed, as appropriate. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on participant safety, data integrity, and critical data and processes.

During these visits, CRFs, supporting documentation, and essential documentation related to the study will be reviewed and any discrepancies or omissions will be resolved. Documentation of results will be provided to the Sponsor in a timely fashion to allow follow-up and verification of compliance with the monitoring plan. Remote evaluation of data (centralized monitoring) may also be conducted and reported as defined in the monitoring plan.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of participant rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

15.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and Biogen.**Publication Policy**

Details are included in the clinical trial agreement for this study.

The Sponsor is committed to ensuring that its publications are of the highest quality and that the integrity of the research and its reporting is maintained. To fulfill this commitment, the Sponsor publications will be developed, reviewed, and approved in accordance with current good publications practice guidelines and industry standards (e.g., International Committee of Medical Journal Editors recommendations; Good Publication Practice guidelines; The International Federation of Pharmaceutical Manufacturers and Associations Position; the CONSORT guidelines; and the Pharmaceutical Research and Manufactures of America Principles) to ensure that the publications reflect accurate, balanced, timely, and transparent reporting and interpretation of research data.

16. REFERENCES

Alkharabsheh O, Alsayed A, Morlote DM, et al. Cerebral Invasive Aspergillosis in a Case of Chronic Lymphocytic Leukemia with Bruton Tyrosine Kinase Inhibitor. Curr Oncol. 2021;28(1):837-841. Epub 20210208.

Balcer LJ, Raynowska J, Nolan R, et al. Validity of low-contrast letter acuity as a visual performance outcome measure for multiple sclerosis. Mult Scler. 2017;23(5):734-747. Epub 2017/02/16.

Bame E, Tang H, Burns JC, et al. Next-generation Bruton's tyrosine kinase inhibitor BIIB091 selectively and potently inhibits B cell and Fc receptor signaling and downstream functions in B cells and myeloid cells. Clin Transl Immunology. 2021;10(6):e1295. Epub 20210614.

Benson MJ, Rodriguez V, von Schack D, et al. Modeling the clinical phenotype of BTK inhibition in the mature murine immune system. J Immunol. 2014;193(1):185-97. Epub 2014/06/04.

Cohen JA, Trojano M, Mowry EM, et al. Leveraging real-world data to investigate multiple sclerosis disease behavior, prognosis, and treatment. Mult Scler. 2020;26(1):23-37. Epub 2019/11/28.

Corneth OB, Klein Wolterink RG, Hendriks RW. BTK Signaling in B Cell Differentiation and Autoimmunity. Curr Top Microbiol Immunol. 2016;393:67-105.

Croxford AL, Lanzinger M, Hartmann FJ, et al. The Cytokine GM-CSF Drives the Inflammatory Signature of CCR2+ Monocytes and Licenses Autoimmunity. Immunity. 2015;43(3):502-14. Epub 2015/09/01.

Elliott C, Wolinsky J, Hauser S, et al. Slowly expanding/evolving lesions as a magnetic resonance imaging marker of chronic active multiple sclerosis lesions. Multiple Sclerosis Journal. 2018;25(14):1915-1925.

European Medicines Agency. Guidance for conduct of clinical trials of medical products during the COVID-19 public health emergency.

European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis. EMA/CHMP/771815/2011. 26 Mar 2015.

FDA. Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers, Table 3-2. U.S. Food & Drug Administration. Food and Drug Administration. Published 2022 [Accessed 08 Aug 2022]. Available from: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Frohman EM, Racke MK, Raine CS. Multiple sclerosis--the plaque and its pathogenesis. The New England journal of medicine. 2006;354(9):942-55.

Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376(3):221-234. Epub 2016/12/21.

Hauser SL, Bhan AK, Gilles F, et al. Immunohistochemical analysis of the cellular infiltrate in multiple sclerosis lesions. Ann Neurol. 1986;19(6):578-87.

HMA. Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials V1.1.

Kappos L, Gold R, Miller DH, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet. 2008;372(9648):1463-72.

Koprulu AD, Ellmeier W. The role of Tec family kinases in mononuclear phagocytes. Crit Rev Immunol. 2009;29(4):317-33.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Lipsky A, Lamanna N. Managing toxicities of Bruton tyrosine kinase inhibitors. Hematology Am Soc Hematol Educ Program. 2020;2020(1):336-345.

Longbrake EE, Mao-Draayer Y, Cascione M, et al. Dimethyl fumarate treatment shifts the immune environment toward an anti-inflammatory cell profile while maintaining protective humoral immunity. Mult Scler. 2020:1352458520937282. Epub 2020/07/27.

Mehta D, Miller C, Arnold DL, et al. Effect of dimethyl fumarate on lymphocytes in RRMS: Implications for clinical practice. Neurology. 2019;92(15):e1724-e1738. Epub 2019/03/27.

Mildner A, Mack M, Schmidt H, et al. CCR2+Ly-6Chi monocytes are crucial for the effector phase of autoimmunity in the central nervous system. Brain. 2009;132(Pt 9):2487-500. Epub 2009/06/16.

Mills EA, Ogrodnik MA, Plave A, et al. Emerging Understanding of the Mechanism of Action for Dimethyl Fumarate in the Treatment of Multiple Sclerosis. Front Neurol. 2018;9:5. Epub 2018/01/23.

Milo R. Therapeutic strategies targeting B-cells in multiple sclerosis. Autoimmun Rev. 2016;15(7):714-8. Epub 2016/03/09.

Montalban X, Arnold DL, Weber MS, et al. Placebo-Controlled Trial of an Oral BTK Inhibitor in Multiple Sclerosis. The New England journal of medicine. 2019;380(25):2406-2417. Epub 2019/05/10.

Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. N Engl J Med. 2017;376(3):209-220. Epub 2016/12/21.

Nguyen T, Sherratt PJ, Pickett CB. Regulatory mechanisms controlling gene expression mediated by the antioxidant response element. Annu Rev Pharmacol Toxicol. 2003;43:233-60.

Oh J, Cohen S, Isenberg D, et al. The safety of fenebrutinib in a large population of patients with diverse autoimmune conditions supports Investigation in multiple sclerosis. Presented at the AAN 2021 Virtual Annual Meeting; Virtual.

Owens TD, Smith PF, Redfern A, et al. Phase 1 clinical trial evaluating safety, exposure and pharmacodynamics of BTK inhibitor tolebrutinib (PRN2246, SAR442168). Clin Transl Sci. 2022;15(2):442-450. Epub 20211112.

Penner IK, Raselli C, Stöcklin M, et al. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. Mult Scler. 2009;15(12):1509-17.

Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292-302.

Reich DS, Arnold DL, Vermersch P, et al. Safety and efficacy of tolebrutinib, an oral brain-penetrant BTK inhibitor, in relapsing multiple sclerosis: a phase 2b, randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2021;20(9):729-738.

Sanofi. Patient enrollment of phase III tolebrutinib trials paused in the U.S.: Sanofi; 2022. p. 1-2.

Schumacher G, Beebe G, Kibler R, et al. Problems of experimental trials of therapy in multiple sclerosis: Report by the Panel on the Evaluation of Experimental Trials of Therapy in Multiple Sclerosis. Ann NY Acad Sci. 1965;122(1):552-568.

Sharma S, Orlowski G, Song W. Btk regulates B cell receptor-mediated antigen processing and presentation by controlling actin cytoskeleton dynamics in B cells. J Immunol. 2009;182(1):329-39.

SOLU-MEDROL® (methylprednisolone sodium succinate for injection, USP) Package Insert. New York, NY: Pfizer.

TECFIDERA® (dimethyl fumarate) Package Insert. Cambridge, MA: Biogen, Inc.

Tecfidera™ Summary of Product Characteristics, 29 Jun 2022.

Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-173. Epub 2017/12/21.

Tillman BF, Pauff JM, Satyanarayana G, et al. Systematic review of infectious events with the Bruton tyrosine kinase inhibitor ibrutinib in the treatment of hematologic malignancies. Eur J Haematol. 2018;100(4):325-334. Epub 20180206.

Traboulsee A, LaGanke C, Montalban X, et al. Design of a Phase 2b Dose-finding Trial to Evaluate Safety and Efficacy of the CNS-penetrant BTK Inhibitor SAR442168 in Patients with Relapsing Forms of Multiple Sclerosis. Presented at the AAN 2020.

Varughese T, Taur Y, Cohen N, et al. Serious Infections in Patients Receiving Ibrutinib for Treatment of Lymphoid Cancer. Clin Infect Dis. 2018;67(5):687-692.

von Hehn C, Howard J, Liu S, et al. Immune response to vaccines is maintained in patients treated with dimethyl fumarate. Neurol Neuroimmunol Neuroinflamm. 2018;5(1):e409. Epub 2017/11/15.

von Hundelshausen P, Siess W. Bleeding by Bruton Tyrosine Kinase-Inhibitors: Dependency on Drug Type and Disease. Cancers (Basel). 2021;13(5) Epub 20210304.

VUMERITY®(diroximel fumarate) delayed-release capsules, for oral use. Cambridge, MA: Biogen, Inc.

Vumerity ™ Summary of Product Characteristics, 05 Apr 2022.

Weber MS, Nicholas JA, Yeaman MR. Balancing Potential Benefits and Risks of Bruton Tyrosine Kinase Inhibitor Therapies in Multiple Sclerosis During the COVID-19 Pandemic. 2021;8(6):e1067.

Werdenberg D, Joshi R, Wolffram S, et al. Presystemic metabolism and intestinal absorption of antipsoriatic fumaric acid esters. Biopharm Drug Dispos. 2003;24(6):259-73.

Woosley R, Heise C, Gallo T, et al. QTdrugs List. AZCERT Inc. Published 2022 [Accessed 24 Aug 2022]. Available from: https://www.crediblemeds.org/

Wray S, Then Bergh F, Wundes A, et al. Efficacy and Safety Outcomes with Diroximel Fumarate After Switching from Prior Therapies or Continuing on DRF: Results from the Phase 3 EVOLVE-MS-1 Study. Adv Ther. 2022;39(4):1810-1831. Epub 20220224.

Yamasaki R, Lu H, Butovsky O, et al. Differential roles of microglia and monocytes in the inflamed central nervous system. J Exp Med. 2014;211(8):1533-49. Epub 2014/07/07.

17. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A 2-Part, Multicenter, Randomized, Blinded, Active-Controlled Phase 2 Study to Sequentially Evaluate the Safety and Efficacy of BIIB091 Monotherapy and BIIB091 Combination Therapy With Diroximel Fumarate in Participants With Relapsing Forms of Multiple Sclerosis," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date (DDMMMYYYY)

_____

Investigator's Name (Print)

_____

Study Site (Print)

APPENDIX 1. SARS-COV-2 CONSIDERATIONS

Because of the ongoing SARS-CoV-2 pandemic, there will be measures taken during the course of the study as given below. Where available, PCR testing should be used. Testing may be conducted by the central laboratory selected by the Sponsor or locally.

1. At Screening:

    - Participants will not be allowed to participate in the study if they have a SARS-CoV-2 infection within 4 weeks prior to randomization.

    - A SARS-CoV-2 PCR test must be done at the Screening Visit and within 14 days prior to randomization. A negative test is required at the Screening Visit and within 14 days of randomization to confirm participant eligibility.

    - Clinical evidence from non-live COVID-19 vaccine studies showed that highly protective immunologic effects are expected within 14 to 21 days after administration of the COVID-19 vaccine. Since BIIB091 treatment may reduce the immune response to the vaccine if given within 21 days after vaccine administration, it is recommended that participants receive the SARS-CoV-2 vaccine 21 days or more prior to randomization (for the vaccine to exert its effect), as per local regulation, and/or Investigator guidance.

2. At Randomization: Participants will not be allowed to participate in the study in the following instances:

    - Positive SARS-CoV-2 test (within 14 days prior to randomization); or

    - Evidence of SARS-CoV-2 infection within 4 weeks prior to randomization. Symptoms suggestive of SARS-CoV-2 infection, per the judgment of the Investigator, may include, but are not limited, to any of the following:

        – Fever (temperature > 37.5°C or 99.5°F), chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea. The Investigator should assess participant's condition holistically when determining evidence of SARS-CoV-2 infection; or

    - Close contact with an individual with SARS-CoV-2 infection within 14 days prior to randomization, even if vaccinated. Close contact is defined as follows or according to local guidance:

        – Being within 6 feet (1.8 meters) of an infected individual (as confirmed by laboratory assessment or clinical diagnosis) for a cumulative total of 15 minutes or more over a 24-hour period. Of note, an infected person can spread

SARS-CoV-2 starting 2 days before they have any symptoms or, for asymptomatic individuals, 2 days before the positive specimen collection date; or

– Other situations as indicated by local risk assessments.

As the pandemic evolves, these instructions may change. Consult local guidance.

3. During the Study

- Additional testing during the study may be performed per local regulations and/or at the discretion of the Investigator. Study treatment should be temporarily suspended if SARS-CoV-2 infection is diagnosed. If a participant receives SARS-CoV-2 treatment, consult the Medical Monitor and/or the Sponsor's study Medical Director prior to restarting study treatment.

- During the first 16 weeks of study treatment periods in Part 1 and Part 2, non-live COVID-19 vaccines are not permitted. COVID-19 vaccines may prompt temporary withholding or discontinuation of study treatment in order for the vaccine to exert its effect. Since temporary withholding or discontinuation could affect the primary analysis of safety and efficacy of the study treatment, COVID-19 vaccines are not allowed during the first 16 weeks of Part 1 and Part 2.

- After Week 16 in Part 1 and Part 2, the non-live COVID-19 vaccine may be administered at the discretion of the PI. In this case, participants may remain off-treatment for a maximum of 21 days after administration of the COVID-19 vaccine (for the vaccine to exert its effect).

4. Statistical Considerations

- Because of the ongoing SARS-CoV-2 pandemic, the Sponsor plans to monitor the missing data attributed to SARS-CoV-2 external factors, such as restriction on travel as per local regulation for SARS-CoV-2.

Additional measures will be determined as per evolving local and regulatory requirements.

General risk mitigation against SARS-CoV-2 may be implemented in accordance with the study site’s institutional review board approved monitoring and prevention control measures. The risk mitigation measures, where applicable, will be amended based on emerging local, regional, and national guidance.