STATISTICAL ANALYSIS PLAN

Product Studied: Daclizumab HYP

Protocol Number: 205MS303/NCT01797965

A Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Safety and Efficacy of BIIB019, Daclizumab High Yield Process (DAC HYP), Monotherapy in Subjects With Multiple Sclerosis (MS) Who Have Completed Study 205MS301

Date of Protocol: 29 September 2017 (Version 5)

Date of Statistical Analysis Plan v1.0: 08 May 2018

Authored By: [redacted] SMT statistician — 08-May-2018 Date

Approved By: [redacted] CDT statistician — 08-May 2018 Date

[redacted] Study Medical Director — 08-May 2018 Date

205MS303

Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN

Product Studied: Daclizumab HYP

Protocol Number: 205MS303

A Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Safety and Efficacy of BIIB019, Daclizumab High Yield Process (DAC HYP), Monotherapy in Subjects With Multiple Sclerosis (MS) Who Have Completed Study 205MS301

Date of Protocol: 29 September 2017 (Version 5)

Date of Statistical Analysis Plan v1.0: 08 May 2018

Authored By:

[redacted], SMT statistician [redacted] — Date

Approved By:

[redacted], CDT statistician [redacted] — Date

[redacted], Study Medical Director [redacted] — Date

TABLE OF CONTENTS

List of Tables

LIST OF ABBREVIATIONS

9HPT	9-hole peg test
AE	adverse event
ALT	alanine aminotransferase
ARR	annualized relapse rate
AST	aspartate aminotransferase
BDI-II	Beck Depression Inventory, Second Edition
bpm	beats per minute
BUN	blood urea nitrogen
C or °C	degrees Celsius
CTC	common toxicity criteria
DAC HYP	daclizumab high yield process
EDSS	Expanded Disability Status Scale
EQ-5D	European Quality of Life, 5 Dimensions
EQ-VAS	European Quality of Life, Visual Analogue Scale
Gd	gadolinium
GGT	gamma-glutamyl transpeptidase
HRPQ	Health related productivity questionnaire
HRU	health resource utilization
HYP	high yield process
ITT	intent to treat
LFT	liver function tests
MedDRA	Medical Dictionary for Regulatory Affairs
mg	milligram
mmHg	millimeters of mercury
MI	multiple imputation
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale-29
NAbs	neutralizing antibodies
PASAT	Paced Auditory Serial Addition Test
PD	pharmacodynamics
PFS	prefilled syringe
PK	pharmacokinetics
PT	Preferred term
QoL	quality of life
SAP	statistical analysis plan
SAE	serious adverse event
SC	subcutaneous
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamate-pyruvate transaminase
SMQ	standardised MedDRA query
SOC	system organ class
T4	thyroxine
TSH	thyroid stimulating hormone
VAS	Visual Analogue Scale
WBC	white blood cell
WHO	World Health Organization

1. Description of Study Objectives and Endpoints

1.1. Primary Objective and Endpoints

The primary objective of the study is to assess the safety and tolerability of long-term treatment with DAC HYP monotherapy in subjects who completed Study 205MS301, Study 205MS203, or Study 205MS302.

The primary endpoints of this study are incidence of adverse events (AEs) and incidence of serious AEs (SAEs).

1.2. Secondary Objective and Endpoints

Secondary objectives of this study in this study population are as follows:

- To describe MS-related outcomes, including MS relapse, disability progression, MS lesion formation, and patient-reported impact of MS, following long-term treatment with DAC HYP
- To assess the long-term immunogenicity of DAC HYP administered by prefilled syringe (PFS)
- To assess the safety, tolerability, and efficacy of switching to DAC HYP in subjects previously on long-term treatment with interferon β-1a (IFN β-1a) in Study 205MS301

The secondary endpoints of this study are as follows:

- Relapse outcomes: annualized relapse rate (ARR), and proportion of subjects who relapse
- Sustained disability progression defined by at least a 1.0-point increase on the Expanded Disability Status Scale (EDSS) score from a baseline EDSS ≥1.0 that is sustained for 24 weeks, or at least a 1.5-point increase on the EDSS from a baseline EDSS <1.0 that is sustained for 24 weeks
- Magnetic Resonance Imaging (MRI) outcomes: total number and volume of new or newly enlarging T2 hyperintense lesions, Gd-enhancing lesions, T1 hypointense lesions, and brain volume change on brain MRI
- Change in Multiple Sclerosis Functional Composite (MSFC) score
- Change in EDSS score
- Change in Symbol Digit Modalities Test (SDMT) score
- Change in 3 Second Paced Auditory Serial Addition Test (PASAT 3) score
- Proportion of subjects who are free from disease activity.

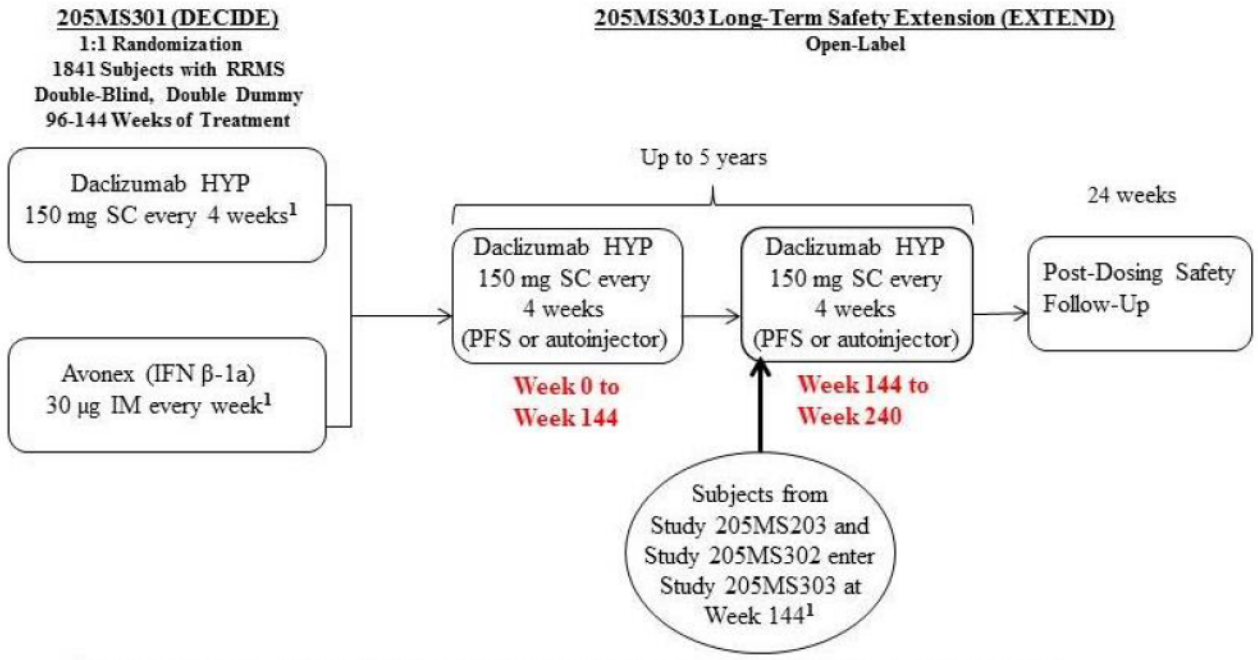
- Change in Multiple Sclerosis Impact Scale-29 (MSIS-29) physical and psychological scores
- Change in quality of life as assessed by the European Quality of Life, 5 dimensions and European Quality of Life, Visual Analogue Scale (EQ-5D and EQ-VAS)
- Change in direct health resource utilization (HRU; hospitalizations, emergency room visits, and unscheduled neurologist visits)
- Change in treatment satisfaction as assessed by the subject
- Change in subject productivity as assessed by the Health Related Productivity Questionnaire (HRPQ)
- Changes in clinical laboratory assessments (hematology and blood chemistry)
- Local tolerability as assessed by subject-reported injection site pain, Visual Analogue Scale (VAS) and clinician injection site assessments
- Incidence of anti-drug antibodies (ADAs) to DAC HYP over time
- Incidence of neutralizing antibodies (NAbs) to DAC HYP over time

2. Study Design

The design of Study 205MS303 is provided in Figure 1. Approximately 1500 subjects will enroll in this study. This includes approximately 1200 subjects who completed Study 205MS301. Additionally, approximately 300 subjects from the other DAC HYP extension studies (205MS203 [SELECTED] and 203MS302 [OBSERVE]) will be eligible to enter Study 205MS303 at Week 144 of Study 205MS303 (Study 205MS301, Study 205MS203, and Study 205MS302 have been referred to as parent studies in the protocol).

All subjects will receive the same dose of DAC HYP as received in the parent studies; i.e., 150 mg by a subcutaneous (SC) injection every 4 weeks. The duration of DAC HYP treatment is up to approximately 5 years, or until availability of commercial product (whichever is sooner). Note that per sponsor discretion, the study was closed early and dosing was terminated by March 30th, 2018.

Figure 1: Study Design for 205MS303 study



[1]Subjects who do not enter Study 205MS303 will complete post-dosing safety follow-up visits per the parent study protocol.

3. Schedule of Events

Table 1: Schedule of Activities: Baseline Through Week 84 for Subjects Enrolling From Study 205MS301 Into Study 205MS303

Note: If study treatment is temporarily suspended or withheld for abnormal liver function tests (LFTs), LFTs must be re-evaluated as specified in Protocol Section 11.7.2. A window of ±4 days applies to all the visits.

Tests and Assessments[1,2]	Week 0/ Day 1 Baseline Visit[3]	Week 4 ±4 days	Week 8 ±4 days	Week 12 ±4 days	Week 24 ±4 days	Week 36 ±4 days	Week 48 ±4 days Start Year 2	Week 60 ±4 days	Week 72 ±4 days	Week 84 ±4 days
Informed Consent	X									
Confirm Eligibility	X									
Medical History Update, including Tobacco Use	X									
Physical Exam	X			X	X		X		X	
Vital Signs (Pre-dose)	X			X	X		X		X	
Weight	X									
Hematology	X			X	X		X		X	
Blood Chemistry (except LFTs)	X			X	X		X		X	
Liver Function Tests[4]		Liver function testing to be performed within the previous 32 days (see Protocol Section 14.4.3)								
Liver Function Tests at Central Laboratory[4, 5]	X	X	X	X	X	X	X	X	X	X
Thyroid Function Panel	X									
DAC HYP Concentration Assessment	X			X	X		X			
Serum Biomarker Sample	X			X	X		X			
Urine Biomarker Sample	X						X			
RNA Assessmen	X			X	X		X			
DNA Collection (Optional)[7]										
Anti-Drug Antibody Sample	X			X	X		X			

Tests and Assessments[1,2]	Week 0/ Day 1 Baseline Visit[3]	Week 4 ±4 days	Week 8 ±4 days	Week 12 ±4 days	Week 24 ±4 days	Week 36 ±4 days	Week 48 ±4 days Start Year 2	Week 60 ±4 days	Week 72 ±4 days	Week 84 ±4 days
Urinalysis	X									
Urine Pregnancy Test[8]	X				X		X		X	
EQ-5D and EQ-VAS	X			X	X		X			
MSIS-29[9]	X			X	X		X			
HRU	X				X		X			
BDI-II	X			X	X		X			
AUDIT-C	X						X			
Treatment Satisfaction Questionnaire for Medication	X[10]			X	X		X			
HRPQ	X			X	X		X		X	
MRI[11]	X						X			
MSFC	X			X	X		X			
EDSS	X			X	X		X		X	
DAC HYP Administration/ Dispensation[12, 13]	X	X[14]	X[14]	X[14]	X	X	X	X	X	X
Dosing Diary	Subject to record observations starting at Week 16 during home dosing only									
Physician Global Assessment Scale	Performed only in subjects with cutaneous AEs (see Protocol Section 11.7.3)									
Concomitant Therapy and AEs	Monitor and record throughout the study.									
Protocol Compliance and DAC HYP Accountability	Monitor and record throughout the study.									

[1]On dosing days, all tests and assessments (other than Treatment Satisfaction Questionnaire for Medication) must be completed prior to administration of study treatment.

[2]When possible, subjects should be evaluated by the same neurologist assigned to them in Study 205MS301.

[3]Baseline Visit must take place within 6 months of completing Study 205MS301. Any test/assessment done at the subject's last visit in Study 205MS301 and within 28 days of the subject's first dose in Study 205MS303 may be used as the baseline and does not need to be repeated at entry into Study 205MS303; for subjects who enroll in Study 205MS303 >28 days after their final Study 205MS301 visit, tests and assessments must be repeated at the Baseline Visit.

[4]ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only.

[5]If local LFTs have been used to determine whether dosing should continue or be suspended at the time of a scheduled clinic visit, LFTs must also be performed at the central laboratory at the time of the scheduled clinic visit (Note: Scheduled clinic visits occur every 4 weeks during the first 12 weeks of the study and every 12 weeks thereafter).

[redacted]

[7]Subjects who did not consent to DNA collection in 205MS301 will be re-approached for this consent upon entry into Study 205MS303. A separate informed consent form may be used for DNA sample collection. Samples for DNA analysis may be collected after the Baseline Visit, if necessary.

[8]Pregnancy test results must be negative prior to dosing.

[9]MSIS-29 to be administered prior to seeing the *Study Neurologist*.

[10]To be performed after the DAC HYP injection at this visit.

[11]MRI scan can be performed up to 4 days prior to the visit.

[12]Before a monthly dose of DAC HYP is given, LFT results from a prior test performed within the previous 32 days must be reviewed by the *Study Neurologist* or their backup.

[13]A window of ±4 days applies to DAC HYP dose even if it is done at home.

[14]At the Week 4, 8, and 12 Visits, subjects will be instructed on DAC HYP self-administration and may administer their scheduled dose under staff supervision. After Week 12, DAC HYP may be dispensed to subjects for at-home administration if the subject chooses.

Table 2: Schedule of Activities: Week 96 through Week 144 for Subjects Enrolling From Study 205MS301 Into Study 205MS303

Note: If study treatment is temporarily suspended or withheld for abnormal LFTs, LFTs must be re-evaluated per Protocol Section 11.7.2. A window of ±4 days applies to all the visits.

Tests and Assessments[1]	Week 96 ±4 days Start Year 3	Week 108 ±4 days	Week 120 ±4 days	Week 132 ±4 days	Week 144[2] ±4 days Start Year 4
Physical Exam	X		X		X
Vital Signs (Pre-dose)	X		X		X
Hematology	X		X		X
Blood Chemistry (except LFTs)	X		X		X
Liver Function Tests[3]	Liver function testing to be performed within the previous 32 days (see Protocol Section 14.4.3)				
Liver Function Tests at Central laboratory[3, 4]	X	X	X	X	X
DAC HYP Concentration Assessment	X				X
Anti-Drug Antibody Sample	X				X
Urine Pregnancy Test[5]	X		X		X
EQ-5D and EQ-VAS	X		X		X
HRU	X				X
HRPQ	X		X		X
MRI[6]	X				X
EDSS[7]	X		X		X
SDMT					X[8]
PASAT 3					X[8,9]
DAC HYP Administration/Dispensation[10, 11]	X	X	X	X	X
Dosing Diary	Subject continues recording observations during home dosing only				
Physician Global Assessment Scale	Performed only in subjects with cutaneous AEs (see Protocol Section 11.7.3)				
Concomitant Therapy and AEs	Monitor and record throughout the study.				

Tests and Assessments[1]	Week 96 ±4 days Start Year 3	Week 108 ±4 days	Week 120 ±4 days	Week 132 ±4 days	Week 144[2] ±4 days Start Year 4
Protocol Compliance and DAC HYP Accountability	Monitor and record throughout the study.				

[1]On dosing days, all tests and assessments (other than Treatment Satisfaction Questionnaire for Medication) must be completed prior to administration of study treatment.
[2]Week 144 (start of Year 4) of Study 205MS303 will be the timepoint at which subjects from Study 205MS203 (SELECTED) and Study 205MS302 (OBSERVE) enter Study 205MS303 (see Table 3 for the assessments at Week 144 in these subjects).
[3]ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only.
[4]If local LFTs have been used to determine whether dosing should continue or be suspended at the time of a scheduled clinic visit, LFTs must also be performed at the central laboratory at the time of the scheduled clinic visit (Note: Scheduled clinic visits occur every 4 weeks during the first 12 weeks of the study and every 12 weeks thereafter.)
[5]Pregnancy test results must be negative prior to dosing.
[6]MRI scan can be performed up to 4 days prior to the visit.
[7]When possible, subjects should be evaluated by the same neurologist assigned to them in the parent study.
[8]Prior to the first administration of either SDMT or PASAT 3, a practice SDMT and PASAT 3 should be performed at that visit prior to the test that is scored.
[9]This test will be performed beginning in Week 144 and every 24 weeks thereafter under protocol version 3 and thereafter. Data will be collected only from subjects enrolled from Study 205MS301.
[10]Before a monthly dose of DAC HYP is given, LFT results from a prior test performed within the previous 32 days must be reviewed by the *Study Neurologist* or their backup.
[11]A window of ±4 days applies to DAC HYP dose even if it is done at home.

Table 3: Schedule of Activities: Entry Visit (Week 144) for Subjects Enrolling From Study 205MS203 or Study 205MS302 Into Study 205MS303

Any test/assessment done at the subject's last visit in parent studies and within 28 days of the subject's first dose in Study 205MS303 will be used as the baseline and does not need to be repeated at entry into Study 205MS303; tests/assessments performed >28 days before the Entry Visit must be repeated at the Entry Visit (Note: Central LFT testing is mandatory at the Entry Visit). A window of ±4 days applies to the visit.

Tests and Assessments[1]	Week 144[2] ±4 days Entry Visit[3]
Informed Consent	X
Confirm Eligibility	X
Medical History Update, Including Tobacco Use	X
Physical Exam	X
Vital Signs (Pre-dose)	X
Weight	X
Hematology	X
Blood Chemistry (except LFTs)	X
Liver Function Tests at Central Laboratory[3]	X
Thyroid Function Panel	X
DAC HYP Concentration Assessmen[redacted]	X
Anti-Drug Antibody Sample[redacted]	X
Urinalysis	X
Urine Pregnancy Test[5]	X
EQ-5D and EQ-VAS	X
HRU	X
HRPQ	X
EDSS	X
Physician Global Assessment Scale	Performed only in subjects with cutaneous AEs (see Protocol Section 11.7.3)

DAC HYP Administration/Dispensation[6]	X
Concomitant Therapy and AEs	X
Protocol Compliance and DAC HYP Accountability	X

[1]When possible, subjects should be evaluated by the same *Study Neurologist* assigned to them in the parent studies.
[2]Week 144 (start of Year 4) of Study 205MS303 will be the timepoint at which subjects from Study 205MS203 and Study 205MS302 enter Study 205MS303. Entry Visit must take place within ≤6 months of the last DAC HYP dose in the parent studies (i.e., Study 205MS203 or Study 205MS302).
[3]ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only.
[redacted]
[5]Pregnancy test results must be negative prior to dosing.
[6]Before a monthly dose of DAC HYP is given at the clinic, LFT results from a prior test performed within the previous 32 days must be reviewed by the *Study Neurologist* or their backup.
Note: MRI assessment will not be done at the Week 144/Entry Visit for Study 205MS303.

Table 4: Schedule of Activities: Week 156 through Week 240 (End of Treatment) for Subjects Enrolling From Study 205MS301, Study 205MS203, or Study 205MS302 Into Study 205MS303

Note: Subjects who complete Week 144 of DAC HYP treatment in Study 205MS303 and are in the safety follow-up period per the original protocol, will have the option to restart DAC HYP treatment at Week 156 as long as they meet the eligibility criteria (Protocol Section 8). A window of ±4 days applies to all the visits.

Tests and Assessments	Week 156 ±4 days	Week 168 ±4 days	Week 180 ±4 days	Week 192 ±4 days Start Year 5	Week 204 ±4 days	Week 216 ±4 days	Week 228 ±4 days	Week 240 ±4 days End of Treatment/ Early Termination Visit[1] 4 Weeks After Last Dose
Physical Exam		X		X		X		X
Vital Signs (Pre-Dose)		X		X		X		X
Hematology		X		X		X		X
Blood Chemistry (except LFTs)		X		X		X		X
Liver Function Tests[2]	Liver function testing to be performed within the previous 32 days (see Protocol Section 14.4.3)							
Liver Function Tests at Central Laboratory[2] [3]	X	X	X	X	X	X	X	X
DAC HYP Concentration Assessmen				X				X
Anti-Drug Antibody Sample				X				X

Tests and Assessments	Week 156 ±4 days	Week 168 ±4 days	Week 180 ±4 days	Week 192 ±4 days Start Year 5	Week 204 ±4 days	Week 216 ±4 days	Week 228 ±4 days	Week 240 ±4 days End of Treatment/ Early Termination Visit[1] 4 Weeks After Last Dose
Urine Pregnancy Test[5]		X		X		X		X
EQ-5D and EQ-VAS				X				X
HRU				X				X
HRPQ		X		X		X		X
MRI[6]				X				X[7]
EDSS[8]		X		X		X		X
SDMT[9]		X		X		X		X
PASAT 3[9]		X		X		X		X
DAC HYP Administration/ Dispensation[10 11]	X	X	X	X	X	X	X	
Dosing Diary	Subject to record observations during home dosing only							
Physician Global Assessment Scale	Performed only in subjects with cutaneous AEs (see Protocol Section 11.7.3)							
Concomitant Therapy and AEs	Monitor and record throughout the study.							
Protocol Compliance and DAC HYP Accountability	Monitor and record throughout the study.							

[1] For subjects who prematurely discontinue dosing, the End of Treatment (Early Termination) Visit should be performed 28 ± 4 days following the subject's last dose of study treatment.

[2] ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only.

[3] If local LFTs have been used to determine whether dosing should continue or be suspended at the time of a scheduled clinic visit, LFTs must also be performed at the central laboratory at the time of the scheduled clinic visit (Note: Scheduled clinic visits occur every 12 weeks.)

[redacted]

[5] Pregnancy test results must be negative prior to dosing.

[6] MRI scan can be performed up to 4 days prior to the visit.

[7] MRI assessment is optional for the Early Termination visit. Under protocol version 4, MRI assessments were added at Weeks 192 and 240 to better assess the efficacy of daclizumab on MRI outcomes over a longer period of time as compared to the previous version of the protocol, in which the last MRI assessment was at Week 144.

[8] When possible, subjects should be evaluated by the same neurologist assigned to them in the parent studies.

[9] Performed only for subjects originally enrolled from Study 205MS301 under protocol version 3 and thereafter.

[10] Before a monthly dose of DAC HYP is given, LFT results from a prior test performed within the previous 32 days must be reviewed by the *Study Neurologist* or their backup.

[11] A window of ±4 days applies to DAC HYP dose even if it is done at home.

Table 5: Schedule of Activities: Post-Treatment Safety Follow-Up

Tests and Assessments	Post-Treatment Safety Follow-Up[1]				
	Follow-up Visit 1 8 weeks after last dose ±10 days	Follow-up Visit 2 12 weeks after last dose ±10 days	Follow-up Visit 3 16 weeks after last dose ±10 days	Follow-up Visit 4 20 weeks after last dose ±10 days	Follow-up Visit 5 (Final Study Visit) 24 weeks after last dose ±10 days
Physical Exam		X			X
Vital Signs		X			X
Hematology		X			X
Blood Chemistry (except LFTs)		X			X
Liver Function Tests at Central Laboratory[2, 3]	X	X	X	X	X
Anti-Drug Antibody Sample[4]					X
Urine Pregnancy Test					X
DAC HYP Concentration Assessment[4]					X
EDSS					X
Physician Global Assessment Scale	Performed only in subjects with ongoing cutaneous AEs (see Protocol Section 11.7.3)				
Concomitant Therapy and AEs	Monitor and record throughout the study.				
Protocol Compliance and DAC HYP Accountability	Monitor and record throughout the study.				

[1]Post-treatment follow-up is required for all subjects. An End of Treatment Visit (Week 240) is performed 4 weeks (±4 days) after the subject's last dose of DAC HYP (see Table 4). Therefore, monthly monitoring of LFTs occurs for 6 months after the last DAC HYP dose has been administered. The Follow-up Visit 4 (20 weeks after last dose) is added under protocol version 5.

[2]ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only.

[3]For subjects with elevated LFTs, this should be performed as soon as possible and then at least weekly until stabilization (see Protocol Section 11.7.2).

[redacted]

Table 6: Schedule of Activities: Unscheduled Assessments

Tests and Assessments	Unscheduled Assessments			
	Unscheduled Relapse Assessment Visit (within 72 hours of symptoms)	Unscheduled Hepatic Assessment Visit[1]	Unscheduled Dermatology Assessment Visit[2, 3]	Unscheduled PK/PD Visit[4]
Cutaneous Event Assessment (Rash characteristics and Anatomic distribution), including Physician Global Assessment Scale			X	
Physical Exam	X	X	X	
Vital Signs	X	X	X	
Hematology				X
Liver Function Tests[6]		X		X
Comprehensive Hepatic Panel[7]		X		
Urinalysis	X			
Whole Blood Sample for PK/PD Assessments[8]				X
EDSS[9]	X			
Photographs[10]			X	
Skin Biopsy[10]			X	
Concomitant Therapy and AEs	Monitor and record throughout the study.			
Protocol Compliance and DAC HYP Accountability	Monitor and record throughout the study.			

[1]To be performed as soon as possible (but within 1 week) following permanent discontinuation of study treatment due to elevated LFTs.

[2]Subjects who develop a mild or moderate cutaneous AE that is not associated with more than 1 systemic symptom or sign do not need to be evaluated by the *Study Dermatologist*; the *Study Neurologist* can complete the Unscheduled Dermatology Assessment Visit as soon as possible. Subjects who develop a mild or moderate cutaneous AE that is associated with more than 1 systemic symptom or sign, a severe cutaneous AE (with or without systemic symptoms or signs), or a serious cutaneous AE (with or without systemic symptoms or signs) need to be evaluated by the *Study Dermatologist* at an Unscheduled Dermatology Assessment Visit as soon as possible. Refer to Protocol Section 11.7.3 for detailed information on these visits and information on when to perform the follow-up visits.

[3]If any cutaneous AE is ongoing at the time of the subject terminating from the study, an Unscheduled Dermatology Assessment Visit should be performed if the subject has not had such a visit in the 4 weeks±4 days prior to leaving the study. Refer to Protocol Section 11.7.3.

[4]These assessments will be performed in subjects with significant changes in their medical conditions, as assessed by the Investigator. This visit must be approved by the Biogen Medical Director in advance.

[6]ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only.

[7]Performed as soon as possible after discontinuation of study treatment for subjects who are required to discontinue dosing due to elevated LFTs as described in Protocol Section 11.8.

[8]Whole blood samples will be collected for potential determination of DAC HYP serum concentrations and to isolate and cryopreserve PBMCs for potential profiling of immune cell subsets related to DAC HYP PD activity.

[9]Performed by the *Study Neurologist* or their back-up within 72 hours of a suspected relapse.
[10] Refer to Protocol Section 11.7.3 for information on when to perform these assessments.

4. Interim Analysis

This statistical analysis plan (SAP) is intended to describe the planned analysis methods and considerations for the final analysis based on data after database lock scheduled for Q4 of 2018. One interim analysis was conducted in 2014 for an interim clinical study report. Note that this interim analysis was conducted prior to the protocol amendments to include patients previously enrolled in the 205MS203 and 205MS302 studies, and therefore included data only for patients previously enrolled in the 205MS301 study.

5. Statistical Methods: General Considerations

5.1. Analysis Populations

As this analysis is made up from 3 cohorts of patients obtained from different studies, separate analysis populations will be defined within each cohort.

5.1.1. 205MS301-205MS303 Study Population

205MS301-303 ITT Population

Study 205MS301-303 intent-to-treat (ITT) population consists of all subjects who completed Study 205MS301 and received at least one dose of DAC HYP during the 205MS303 study, which is the population for analyses of efficacy in this cohort.

205MS301-303 Safety Population

Study 205MS301-303 safety population consists of all subjects who participated in Study 205MS301 and received at least one dose of DAC HYP treatment during the 205MS303 study. This is the population for analyses of safety in this cohort.

5.1.2. 205MS203-205MS303 Study Population

205MS203-303 ITT Population

Study 205MS203-303 intent-to-treat (ITT) population consists of all subjects who completed Study 205MS203 and received at least one dose of DAC HYP during the 205MS303 study, which is the population for analyses of efficacy in this cohort.

205MS203-303 Safety Population

Study 205MS203-303 safety population consists of all subjects who completed Study 205MS203 and received at least one dose of DAC HYP during the 205MS303 study, which is the population for analyses of safety in this cohort.

5.1.3. 205MS302-205MS303 Study Population

205MS302-303 ITT Population

Study 205MS302-303 intent-to-treat (ITT) population consists of all subjects who completed Study 205MS302 and received at least one dose of DAC HYP during the 205MS303 study, which is the population for analyses of efficacy in this cohort.

205MS302-303 Safety Population

Study 205MS302-303 safety population consists of all subjects who completed Study 205MS302 and received at least one dose of DAC HYP during the 205MS303 study, which is the population for analyses of safety in this cohort.

5.2. Analysis of baseline data

The definition of baseline will be dependent on the analysis performed and the cohort of patients utilized. The following are the various definitions of baseline that may be used in the analyses:

5.2.1. 205MS301-205MS303 Study Baselines

205MS301 Baseline
Study 205MS301 Baseline is defined as the latest available value prior to or on the date of the first dose of study treatment in Study 205MS301.

205MS303 Baseline
Study 205MS303 Baseline is defined as the latest available value prior to or on the date of the first dose of study treatment in Study 205MS303.

Demographic characteristics, baseline disease characteristics and medical history will be summarized using the 205MS301-303 ITT population at the 205MS301 Baseline and at the 205MS303 Baseline.

DAC HYP Baseline
DAC HYP Baseline is equal to the 205MS301 baseline for subjects randomized to DAC HYP in 205MS301, or the 205MS303 baseline for subjects randomized to IFN β-1a in 205MS301. If no assessments, or if multiple measurements were performed on the day of first dose of DAC HYP, the last measurement prior to the first dose of DAC HYP will be used.

Unless otherwise specified, the DAC HYP Baseline will be utilized in measurements for safety assessments such as laboratory values and vital signs.

5.2.2. 205MS203-205MS303 Study Baselines

205MS303 Baseline is defined as the latest available value prior to or on the date of the first dose of study treatment in Study 205MS303.

DAC HYP Baseline
Subjects enrolled from 205MS203 study had completed the 205MS201, 205MS202, and 205MS203 studies. For subjects randomized to DAC HYP either 150 mg or 300 mg in 205MS201, the DAC HYP Baseline is defined as the 205MS201 baseline. For subjects randomized to placebo in 205MS201, the DAC HYP Baseline is defined as the 205MS202 Baseline. If no assessments, or if multiple measurements were performed on the day of first dose of DAC HYP, the last measurement prior to the first dose of DAC HYP will be used.

5.2.3. 205MS302-205MS303 Study Baselines

205MS303 Baseline
Study 205MS303 Baseline is defined as the latest available value prior to or on the date of the first dose of study treatment in Study 205MS303.

DAC HYP Baseline
DAC HYP Baseline is equal to the 205MS302 baseline for all subjects in the 205MS302-303 safety population. If no assessments, or if multiple measurements were performed on the day of first dose of DAC HYP, the last measurement prior to the first dose of DAC HYP will be used.

5.3. Key Dates Time Period Definitions

The following time periods will be defined for efficacy and safety analyses:

205MS301 Treatment Period
The 205MS301 Treatment Period is the time period as defined in the 205MS301 statistical analysis plan and includes data collected from the first dosing date to the end of treatment period visit in the 205MS301 study. For subjects who completed study treatment this is the date of the last scheduled treatment period visit in that study.

205MS303 Treatment Period refers to the time between the first dose date in 205MS303 and the date of the last available measurement prior to 180 days after the last dose date in 205MS303. This is the time period for most of the efficacy analyses and for all the safety analyses for all the populations.

Combined Study Period

For the 205MS301-303 ITT population, the Combined Study Period is the combined period of the 205MS301 and 205MS303 studies, that is the time between the first dose date in 205MS301 and the date of the last available measurement prior to 180 days after last dose date in 205MS303.

Note that for the 205MS203-303 ITT population and the 205MS302-303 ITT population, the combined study period is not necessary due to the limited number of patients in each population.

5.4. General Methods of Analysis

For the 205MS301-303 ITT population, efficacy analyses will focus on data from the 205MS303 treatment period but will include some additional analyses across the combined study period. In general, summary statistics will be presented by previous treatment group of the 205MS301 study (IFN β-1a 30 µg and 150 mg DAC HYP). Safety analyses will include subjects in the 205MS301-303 Safety Population and use the data from the 205MS303 Treatment period only. Analyses will be presented by previous treatment group of the 205MS301 study (IFN β-1a 30 µg and 150 mg DAC HYP) and for all subjects combined.

For the 205MS203-303 ITT population, efficacy analyses will focus on data from the 205MS303 treatment period. Summary statistics will be summarized for all subjects combined. Safety analyses will include the data from the 205MS303 Treatment period, and will be presented for all subjects combined. Note that subjects enrolled from the 205MS203 study may receive DAC HYP at a higher dose (300 mg) during the 205MS201 and/or 205MS202 studies. Given the long duration time since last exposure to high dose of DAC HYP and to be consistent with the analyses in the 205MS203 clinical study report, analyses will not be presented by high/low dose level in previous studies.

For the 205MS302-303 ITT population, efficacy and safety analyses will focus on subject data from the 205MS303 treatment period, and will be presented for all subjects combined.

Analyses will generally be descriptive in nature. For relevant efficacy analyses, confidence intervals will be provided for each treatment group where appropriate to characterize the variability around the point estimates. Statistical hypothesis testing may be completed for selected analyses [redacted]

Visit Windows

For by-visit analyses, visit windows will be utilized. Data will be windowed to the nearest scheduled visit. If two or more evaluations occur in the same visit window, the evaluation measured on a day closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations are equally close to the target visit day, then the evaluation with an earliest day will be selected for inclusion in the analysis. If several samples are collected on the same day but at different times, the earliest time will be used.

Missing measurements

In general, no imputation for missing measurements will be performed, unless specified otherwise.

Missing dates

For start date of adverse events, if all available start date information is the same as that of the date of first dose in 205MS303, and the event did not end prior to first dose, the date of first dose in 205MS303 will be used as the imputed date. Otherwise for adverse events, and always for the start of concomitant medications, the earliest possible start date based on available partial information will be used. Namely, if only the day is missing, the 1st of the month will be used; if the month is also missing, January 1st will be used. End dates for concomitant medications and adverse events will not be imputed. For evaluations other than adverse events and concomitant medications, missing or incomplete dates that are needed for analysis will also be imputed. If the day is missing for a study procedure or assessment but the month and year are present, the day will be imputed as the 15th of the month. Month and year will not be imputed for study procedures or assessments. These same rules will be applied to missing or incomplete dates for relapses.

6. Study Subjects

6.1. Subject Accountability

The disposition of subjects will be summarized for the 205MS301-303 ITT population, including the number and percentage of subjects who received treatment, discontinued treatment, or withdrew from the study. Reasons for withdrawal or treatment discontinuation will also be summarized.

The disposition of subjects enrolling from Study 205MS203 or Study 205MS302 Into Study 205MS303 will be summarized, including the number and percentage of subjects who received treatment, discontinued treatment, or withdrew from the study. Reasons for withdrawal or treatment discontinuation will also be summarized.

6.2. Demography and Baseline Disease Characteristics

6.2.1. Demography and Baseline Disease Characteristics for the 205MS301-303 ITT Population

Demographic data collected at the start of 205MS301 study (205MS301 Baseline) and at the start of 205MS303 study (205MS303 Baseline) for the 205MS301-303 ITT population will be summarized by previous 205MS301 treatment group and for all subjects combined. Demographic data will include age at baseline (years), age category (<18, 18-19, 20-29, 30-39, 40-49, 50-55, and >55, also $\leq$ 35, > 35), gender, height, race category and weight (kg).

Medical history (collected at the start of 205MS301 and updated since) will be summarized by prior treatment group in the 205MS301 study and for all subjects combined for the 205MS301-303 ITT population. Other baseline characteristic data at 205MS301 Baseline and at 205MS303 Baseline (e.g., EDSS test scores, the number of relapses in a year prior to baseline, MRI endpoints) will also be summarized for the 205MS301-303 ITT population using descriptive statistics by 205MS301 treatment group and for all subjects combined.

EDSS test score at the 205MS303 baseline is defined as score at the most recent assessment prior to the first dose in 205MS303, excluding assessments occurring within 29 days after a relapse onset.

The following MRI characteristics will be presented for the 205MS301 baseline and the 205MS303 baseline in the 205MS301-303 ITT population: the number of Gd lesions, the number and volume of T2 hyperintense lesions, and the number and volume of T1 hypointense lesions.

6.2.2. Demography and Baseline Disease Characteristics for the 205MS203-303 ITT Population

Demographic data collected at the start of 205MS303 study (205MS303 Baseline) for the 205MS203-303 ITT population will be summarized for all subjects combined.

Medical history (collected at the start of 205MS201 and updated since) will be summarized for all subjects combined for the 205MS203-303 ITT population. Other baseline characteristic data at 205MS303 Baseline (e.g., EDSS test scores, the number of relapses in a year prior to baseline) will

also be summarized for the 205MS203-303 ITT population using descriptive statistics for all subjects combined.

6.2.3. Demography and Baseline Disease Characteristics for the 205MS302-303 ITT Population

Demographic data collected at the start of 205MS303 study (205MS303 Baseline) for the 205MS302-303 ITT population will be summarized for all subjects combined.

Medical history (collected at the start of 205MS302 and updated since) will be summarized for the 205MS302-303 ITT population. Other baseline characteristic data at 205MS303 Baseline (e.g., EDSS test scores, the number of relapses in a year prior to baseline) will also be summarized for the 205MS302-303 ITT population.

6.3. Extent of Exposure

6.3.1. Extent of Exposure for the 205MS301-205MS303 Study Population

The number of doses of DAC HYP received in 205MS303 and in total, per subject, will be summarized for the 205MS301-303 ITT population by prior treatment group in the 205MS301 study and for all subjects combined.

Time on study (days) will be computed for each subject as (date of study completion or withdrawal) – (date of first dose in 205MS303) + 1 day.

6.3.2. Extent of Exposure for the 205MS203-205MS303 Study Population

The number of doses of DAC HYP received in the 205MS303 study and in total, per subject, will be summarized for all subjects combined.

Time on study (days) in the 205MS303 study will be computed for each subject as (date of study completion or withdrawal) – (date of first dose in 205MS303) + 1 day.

6.3.3. Extent of Exposure for the 205MS302-205MS303 Study Population

The number of doses of DAC HYP received in the 205MS303 study and in total, per subject, will be summarized for all subjects combined.

Time on study (days) in the 205MS303 study will be computed for each subject as (date of study completion or withdrawal) – (date of first dose in 205MS303) + 1 day.

6.4. Concomitant Therapy

Medications (prescribed or over-the-counter) and non-drug therapies are considered concomitant if they are used during the study (i.e., either started prior to the study and continued while on study or started after the first dose of study treatment). Medications started more than 180 days after the last dose of study treatment are not considered concomitant. The World Health Organization (WHO) dictionary will be used for coding concomitant medication, and the Medical Dictionary for Regulatory Affairs (MedDRA) will be used for coding concomitant non-drug therapies.

The number and percentage of subjects taking any concomitant medications in 205MS303 will be reported for the 205MS301-303 safety population, the 205MS203-303 Safety Population, and the 205MS302-303 Safety Population, respectively. The most frequent concomitant medications, defined as those taken by at least 10% of subjects, and use of alternative MS medications and steroids may also be summarized.

The list of potential hepatotoxic medications is defined and agreed by SABR prior to data base lock. The number and percentage of subjects taking any potential hepatotoxic concomitant medications in 205MS303 will be reported for the 205MS301-303 safety population, the 205MS203-303 Safety Population, and the 205MS302-303 Safety Population, respectively.

7. Efficacy Data

7.1. Summary of Efficacy Analyses

Table 7 shows the overall summary of the efficacy analyses.

For the 205MS301-303 ITT population, efficacy analyses will be performed in the 205MS303 Treatment Period and the Combined Study Period. Selected analyses will be also done for the 205MS301-303 ITT population in the 205MS301 Treatment Period for evaluation with corresponding results in the 205MS303 Treatment period (e.g., for the annualized relapse rate). For the combined study period, data from the last dose of study treatment in 205MS301 to the first dose of study treatment in 205MS303 will also be included in the analysis.

For the 205MS203-303 ITT population, efficacy analyses will be performed in the 205MS303 Treatment Period, and will be summarized for all subjects combined. For the 205MS302-303 ITT population, efficacy analyses will be performed in the 205MS303 Treatment Period. Note that for subjects in the 205MS203-303 ITT population and the 205MS302-303 ITT population, due to the inherent difference in dosing and treatment in their previous studies, efficacy analyses will only be performed in the 205MS303 Treatment Period.

Table 7: Summary of populations and treatment periods for efficacy analyses

Population	Study/Treatment Period	Baseline
205MS301-303 ITT population	205MS301 Treatment Period	205MS301 Baseline
	205MS303 Treatment Period	205MS303 Baseline
	Combined Study Period	205MS301 Baseline
205MS203-303 ITT population	205MS303 Treatment Period	205MS303 Baseline
205MS302-303 ITT population	205MS303 Treatment Period	205MS303 Baseline

The following three tables include endpoints, analysis populations, baseline type with a short summary of statistical methods for the efficacy analyses. Sections below include more details about these analyses.

Table 8: Summary of efficacy analyzes for the 205MS301-303 ITT population

Endpoint	Population	Study/Treatment Period	Baseline	Statistical Methods
Annualized relapse rate	205MS301-303 ITT population	Combined Study Period	205MS301 Baseline	Unadjusted and adjusted ARR. Adjusted ARR will be estimated from the negative binomial model, adjusting for age, prior IFN beta, baseline EDSS and baseline relapse rate at the 205MS301 Baseline.
		205MS301 Treatment Period	205MS301 Baseline	As above
		205MS303 Treatment Period	205MS303 Baseline	As above. Covariates will include prior IFN beta at the 205MS301 Baseline, age at the 205MS303 Baseline, baseline EDSS, and the number of relapses in a year prior to 205MS303 baseline.
Annualized relapse rate by year	205MS301-303 ITT population	205MS301 Treatment Period	205MS301 Baseline	Unadjusted and adjusted ARR. Adjusted ARR will be estimated from the Poisson model, adjusting for age, prior IFN beta, baseline EDSS and baseline relapse rate at the 205MS301 Baseline.
		205MS303 Treatment Period	205MS303 Baseline	As above. Covariates will include prior IFN beta at the 205MS301 Baseline, age at the 205MS303 Baseline, baseline EDSS, and the number of relapses in a year prior to 205MS303 baseline.
Proportion of subjects who relapsed at selected time points	205MS301-303 ITT population	Combined Study Period	205MS301 Baseline	Kaplan-Meier curve of time to first relapse will be used to estimate the proportion at selected time points.
		205MS303 Treatment Period	205MS303 Baseline	As above
Proportion of subjects with 6-month sustained disability progression measured by EDSS at selected time points	205MS301-303 ITT population	Combined Study Period	205MS301 Baseline	Kaplan Meier analysis of time to the 6-month sustained disability progression will be used to estimate the proportion at selected time points.
		205MS303 Treatment Period	205MS303 Baseline	As above

Endpoint	Population	Study/Treatment Period	Baseline	Statistical Methods
EQ-5D: EQ5D VAS, EQ-5D index score and EQ-5D individual questions	205MS301-303 ITT population	205MS303 Treatment Period	205MS303 Baseline	Descriptive statistics by previous treatment group in 205MS301 and by study visit in 205MS303.
MRI endpoints at selected visits of the 2015MS301 and 2015MS303 studies: 1) total number of new or newly-enlarging T2 hyperintence lesions	205MS301-303 ITT population	205MS301 Treatment Period	205MS301 Baseline	Descriptive statistics by previous treatment group in 205MS301 and by study visit in 205MS301 study. For the total number of new or newly enlarging T2 lesions and the total number of new T1 lesions: negative binomial model, adjusted for 301 baseline characteristics.
2) total number of new T1 hypointense lesions 3) total number of Gd lesion 4) total volume of T2 hyperintence lesions 5) the volume of new or newly enlarging T2 lesions 6) total volume of new T1 hypointense lesions 7) Percent Brain Volume Change (PBVC)	205MS301-303 ITT population	205MS303 Treatment Period	205MS303 Baseline	Descriptive statistics by previous treatment group in 205MS301 and by study visit in 205MS303 study. For the total number of new or newly enlarging T2 lesions and the total number of new T1 lesions: negative binomial model, adjusted for 303 baseline characteristics. PBVC will be analyzed during the 205MS303 treatment period and with either 205MS301 or 205MS303 baseline.
EDSS: actual score and change from baseline	205MS301-303 ITT population	205MS303 Treatment Period	205MS303 Baseline	Descriptive statistics by previous treatment group in 205MS301 and by study visit in 205MS303.
MSFC z-score and component z-scores: actual value and change from baseline	205MS301-303 ITT population	Combined Study Period	205MS301 Baseline	Descriptive statistics by previous treatment group in 205MS301 and by study visit in 205MS301 and 205MS303. See section 8.4.3.
		205MS303 Treatment Period	205MS303 Baseline	Descriptive statistics by previous treatment group in 205MS301 and by study visit in 205MS303. See section 8.4.3.
PASA 3: actual value and change from baseline	205MS301-303 ITT population	Combined Study Period	205MS301 Baseline	Descriptive statistics by previous treatment group in 205MS301 and by study visit in 205MS301 and 205MS303.

Endpoint	Population	Study/Treatment Period	Baseline	Statistical Methods
		205MS303 Treatment Period	205MS303 Baseline	Descriptive statistics by previous treatment group in 205MS301 and by study visit in 205MS303.
SDMT: actual score and change from baseline; proportion of subjects with a ≥ 3 or ≥ 4 decline from baseline; proportion of subjects with a ≥ 3 or ≥ 4 increase from baseline.	205MS301-303 ITT population	Combined Study Period	205MS301 Baseline	Descriptive statistics by previous treatment group in 205MS301 and by study visit in 205MS301 and 205MS303.
		205MS303 Treatment Period	205MS303 Baseline	Descriptive statistics by previous treatment group in 205MS301 and by study visit in 205MS303.
MSIS-29 physical score and MSIS-29 psychological score: actual score and change from baseline; proportion of subjects with a >= 7.5 worsening from baseline in MSIS-29 physical score.	205MS301-303 ITT population	205MS303 Treatment Period	205MS303 Baseline	Descriptive statistics by previous treatment group in 205MS301 and by study visit in 205MS303.
Proportion of subjects who are free from disease activity	205MS301-303 ITT population	205MS303 Treatment Period	205MS303 Baseline	Descriptive statistics by previous treatment group in 205MS301
HRU: MS-related and non-MS related visits	205MS301-303 ITT population	205MS301 Treatment Period		Descriptive statistics for the number of unscheduled site visits by previous treatment group in 205MS301 and by visit in 205MS301 study.
		205MS303 Treatment Period		Descriptive statistics for the number of unscheduled site visits by previous treatment group in 205MS301 and by visit in 205MS303 study.
HRPQ	205MS301-303 ITT population	205MS303 Treatment Period		Descriptive statistics by previous treatment group in 205MS301 and by study visit in 205MS303 study.

Table 9: Summary of efficacy analyzes for the 205MS203-303 ITT population

Endpoint	Study/Treatment Period	Baseline	Statistical Methods
Annualized relapse rate	205MS303 Treatment Period	205MS303 Baseline	Unadjusted and adjusted ARR for all subjects combined. Adjusted ARR will be estimated from the negative binomial/Poisson model, adjusting for baseline relapse rate at the 205MS303 Baseline
Annualized relapse rate by 48-week time interval	205MS303 Treatment Period	205MS303 Baseline	Unadjusted and adjusted ARR for all subjects combined. Adjusted ARR will be estimated from the Poisson model, adjusting for baseline relapse rate at the 205MS303 Baseline.
Proportion of subjects who relapsed at selected time points	205MS303 Treatment Period	205MS303 Baseline	Kaplan-Meier curve of time to first relapse will be used to estimate the proportion at selected time points for all subjects combined
Proportion of subjects with 6-month sustained disability progression measured by EDSS at selected time points	205MS303 Treatment Period	205MS303 Baseline	Kaplan Meier analysis of time to the 6-month sustained disability progression will be used to estimate the proportion at selected time points for all subjects combined
EDSS: actual score and change from baseline	205MS303 Treatment Period	205MS303 Baseline	Descriptive statistics by study visit in 205MS303 for all subjects combined.
EQ-5D: EQ5D VAS, EQ-5D index score and EQ-5D individual questions	205MS303 Treatment Period	205MS303 Baseline	Descriptive statistics by study visit in 205MS303 for all subjects combined.
MRI endpoints at selected visits of the 205MS303 study	205MS303 Treatment Period		Descriptive statistics by study visit in 205MS303 study for all subjects combined.
HRU: MS-related and non-MS related visits	205MS303 Treatment Period		Descriptive statistics for the number of unscheduled site visits by visit in 205MS303 study.
HRPQ	205MS303 Treatment Period		Descriptive statistics by study visit in 205MS303 study.

Table 10: Summary of efficacy analyzes for the 205MS302-303 ITT population

Endpoint	Study/Treatment Period	Baseline	Statistical Methods
Annualized relapse rate	205MS303 Treatment Period	205MS303 Baseline	Unadjusted and adjusted ARR. Adjusted ARR may be estimated from the negative binomial/Poisson model, adjusting for baseline relapse rate at the 205MS303 Baseline.
Annualized relapse rate by 48-week interval	205MS303 Treatment Period	205MS303 Baseline	Unadjusted and adjusted ARR. Adjusted ARR may be estimated from the Poisson model, adjusting for baseline relapse rate at the 205MS303 Baseline.
Proportion of subjects who relapsed at selected time points	205MS303 Treatment Period	205MS303 Baseline	Kaplan-Meier curve of time to first relapse will be used to estimate the proportion at selected time points.
Proportion of subjects with 6-month sustained disability progression measured by EDSS at selected time points	205MS303 Treatment Period	205MS303 Baseline	Kaplan Meier analysis of time to the 6-month sustained disability progression will be used to estimate the proportion at selected time points.
EDSS: actual score and change from baseline	205MS303 Treatment Period	205MS303 Baseline	Descriptive statistics by study visit in 205MS303.
EQ-5D: EQ5D VAS, EQ-5D index score and EQ-5D individual questions	205MS303 Treatment Period	205MS303 Baseline	Descriptive statistics by study visit in 205MS303.
MRI endpoints at selected visits of the 205MS303 study	205MS303 Treatment Period		Descriptive statistics by study visit in 205MS303 study.
HRU: MS-related and non-MS related visits	205MS303 Treatment Period		Descriptive statistics for the number of unscheduled site visits by visit in 205MS303 study.
HRPQ	205MS303 Treatment Period		Descriptive statistics by study visit in 205MS303 study.

7.2. Annualized Relapse Rate

7.2.1. Annualized Relapse Rate in the 205MS301-303 ITT Population

In Study 205MS301, relapses were defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the *Examining Neurologist*. In addition, these relapses must have been reviewed and confirmed by the Independent Neurology Evaluation Committee (INEC).

In Study 205MS303, relapses are defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the *Study Neurologist*. The subject must have objective signs on the examination confirming the event.

Therefore, Studies 205MS301 and 205MS303 utilize essentially the same definition for objective (i.e., protocol-defined) relapses, with the exception that there is no Independent Neurology Evaluation Committee (INEC) in Study 205MS303. Because relapses in 205MS303 were not evaluated by an independent committee, all investigator-confirmed relapses from 205MS301 are included whether or not independently confirmed. New or recurrent neurological symptoms that occurred less than 30 days following the onset of a protocol-defined relapse will be considered part of the same relapse (i.e., relapses with onset days ≤29 days of one another, will be counted as 1 relapse).

The annualized relapse rate will be summarized using the following study population and study periods:

- 205MS301-303 ITT population in the combined study period
- 205MS301-303 ITT population in the 205MS301 Treatment Period and the 205MS303 Treatment period.

The relapse rate will be reported using relapses that occurred on or after the first dose date during the applicable study period. Relapses that occur after subjects receive alternative MS medications will be excluded from the analyses of relapse rate, and the subject's time on study will be censored at the time the alternative MS medication is added. For each analysis period, the subject's time on study will be censored at the time the alternative MS medication in the given period. For example, if a subject from the 205MS301-303 ITT population took alternative medication in the 205MS301 study before the first dose in study 205MS303 and in the 205MS303 study, this subject will be included in the analyses of the 205MS303 Treatment period and will be censored at the time the alternative MS medication in the 205MS303 study.

The unadjusted ARR will be calculated as the total number of relapses experienced during the given period, divided by the total number of days in the study period or the time of censoring, and the ratio then multiplied by 365.25. Relapse rate may be tabulated by the 205MS301 study treatment group (IFN β-1a 30 µg and 150 mg DAC HYP).

For the combined study period and the 205MS301 Treatment Period, the relapse rate will also be estimated using a negative binomial model, with adjustment for the following characteristics at the 205MS301 Baseline: baseline relapse rate (number of relapses in the 3-years prior to study entry divided by 3), history of prior IFN β use (yes/no, collected as a stratification variable in IVRS), baseline EDSS (EDSS ≤ 2.5 versus EDSS > 2.5) and baseline age (age ≤ 35 versus age >35). The logarithmic transformation of the number of days in the study will be included in the model as the "offset" parameter. If the data are under-dispersed (assessed using the Pearson Chi-Squared statistic) or if the negative binomial model does not converge, a Poisson regression model will be used instead. The Poisson model will be adjusted for over-dispersion using a Pearson scale parameter. The treatment group is the previous treatment group of the 205MS301 study. For the 205MS303 Treatment Period, a similar analysis will be done. The adjustment will be performed with the following characteristics: number of relapses in a year prior to the first dose in 205MS303, history of prior IFN β use at the 205MS301 baseline, age (age ≤ 35 versus age >35) at the 205MS303 Baseline and EDSS (EDSS ≤ 2.5 versus EDSS > 2.5) at the 205MS303 Baseline.

To further assess the durability of treatment, the relapse rate will also be summarized by year for the 205MS301-303 ITT population in the 205MS301 Treatment Period and the 205MS303 Treatment Period. For these analyses, rates will be tabulated by evaluating the number of relapses in each time period and the amount of follow-up time in the time period. A Poisson model will be used to estimate the relapse rate in each time period unless data are over-dispersed in which case a negative binomial model will be used.

7.2.2. Annualized Relapse Rate in the 205MS203-303 ITT Population

The annualized relapse rate will be summarized for the 205MS203-303 ITT population in the 205MS303 Treatment period. The relapse rate will be reported using relapses that occurred on or after the first DAC HYP dose date in the 205MS303 Treatment period. Relapses that occur after subjects receive alternative MS medications will be excluded from the analyses of relapse rate, and the subject's time on study will be censored at the time the alternative MS medication is added.

The unadjusted ARR will be calculated as the total number of relapses experienced during the given period, divided by the total number of days in the period or the time of censoring, and the ratio then multiplied by 365.25. Relapse rate will be tabulated for all subjects combined.

For the 205MS303 Treatment period, the relapse rate will also be estimated using a negative binomial model, with adjustment for the number of relapses in a year prior to the first dose in 205MS303. The logarithmic transformation of the number of days in the study will be included in the model as the "offset" parameter. If the data are under-dispersed (assessed using the Pearson Chi-Squared statistic) or if the negative binomial model does not converge, a Poisson regression model will be used instead. The Poisson model will be adjusted for over-dispersion using a Pearson scale parameter.

To further assess the durability of treatment, the relapse rate will also be summarized by 48-week time intervals defined in the 205MS303 Treatment Period. For these analyses, rates will be tabulated by evaluating the number of relapses in each time interval and the amount of follow-up time in the time interval. A Poisson model will be used to estimate the relapse rate in each time interval unless data are over-dispersed in which case a negative binomial model will be used.

7.2.3. Annualized Relapse Rate in the 205MS302-303 ITT Population

The annualized relapse rate will be summarized for the 205MS302-303 ITT population in the 205MS303 Treatment Period. The relapse rate will be reported using relapses that occurred on or after the first dose date during the 205MS303 Treatment period. Relapses that occur after subjects receive alternative MS medications will be excluded from the analyses of relapse rate, and the subject's time on study will be censored at the time the alternative MS medication is added.

The unadjusted ARR will be calculated as the total number of relapses experienced during the given period, divided by the total number of days in the study period or the time of censoring, and the ratio then multiplied by 365.25.

The relapse rate may also be estimated using a negative binomial model, with adjustment for the number of relapses in a year prior to the first dose in 205MS303. The logarithmic transformation of the number of days in the study will be included in the model as the "offset" parameter. If the data are under-dispersed (assessed using the Pearson Chi-Squared statistic) or if the negative binomial model does not converge, a Poisson regression model will be used instead. The Poisson model will be adjusted for over-dispersion using a Pearson scale parameter.

To further assess the durability of treatment, the relapse rate may also be summarized by 48-week intervals in the 205MS303 Treatment Period. For these analyses, rates will be tabulated by evaluating the number of relapses in each time interval and the amount of follow-up time in the time interval. A Poisson model will be used to estimate the relapse rate in each time interval unless data are over-dispersed in which case a negative binomial model will be used.

7.3. Proportion of Subjects who Relapsed

7.3.1. Proportion of Subjects with Relapse in the 205MS301-303 ITT Population

The proportion of subjects who relapsed will be summarized using the following study population and study periods

- 205MS301-303 ITT population in the combined study period
- 205MS301-303 ITT population in the 205MS303 Treatment period

Relapse will be defined using the same definition that was used for the annualized relapse rate endpoint. The proportion of subjects who relapsed at selected time points, by treatment group of the 205MS301 study, will be estimated.

Kaplan-Meier curve of time to the first relapse during the study period (i.e., the Kaplan-Meier product-limit estimator) will be used to estimate the proportion of subjects who relapsed. If there are no early withdrawals, the Kaplan-Meier estimate of the proportion of subjects relapsed is same as the observed proportion of subjects relapsed. If there are early withdrawals, the Kaplan-Meier estimate has the advantage of taking into account the length of follow-up for the early withdrawals, without having any assumptions about whether those subjects relapsed or not.

Subjects without a confirmed relapse will be censored at either early withdrawal or the end of the corresponding study period. If a subject took an alternative MS medication before the first relapse, the subject will be censored at the time of the alternative MS medication. Kaplan-Meier plots of the

time to first relapse will also be presented and used to estimate the median time (and/or the 25th percentile) by the previous treatment group of the 205MS301 study.

7.3.2. Proportion of Subjects with Relapse in the 205MS203-303 ITT Population

The proportion of subjects who relapsed will be summarized for the 205MS203-303 ITT population in the 205MS303 Treatment period. Relapse will be defined using the same definition that was used for the annualized relapse rate endpoint. The proportion of subjects who relapsed at selected time points will be estimated and presented for all subjects combined. Kaplan-Meier curve of time to the first relapse during the study period will be used to estimate the proportion of subjects who relapsed.

Subjects without a confirmed relapse will be censored at either early withdrawal or the end of the 205MS303 Treatment period. If a subject took an alternative MS medication before the first relapse, the subject will be censored at the time of the alternative MS medication. Kaplan-Meier plots of the time to first relapse will also be presented and used to estimate the median time (and/or the 25th percentile) for all subjects combined.

7.3.3. Proportion of Subjects with Relapse in the 205MS302-303 ITT Population

The proportion of subjects who relapsed will be summarized for the 205MS302-303 ITT population in the 205MS303 Treatment period. Relapse will be defined using the same definition that was used for the annualized relapse rate endpoint. The proportion of subjects who relapsed at selected time points will be estimated. Kaplan-Meier curve of time to the first relapse during the study period will be used to estimate the proportion of subjects who relapsed. Subjects without a confirmed relapse will be censored at either early withdrawal or the end of the 205MS303 treatment period. If a subject took an alternative MS medication before the first relapse, the subject will be censored at the time of the alternative MS medication. Kaplan-Meier plots of the time to first relapse will also be presented and used to estimate the median time (and/or the 25th percentile).

7.4. Sustained 6-month Disability Progression

7.4.1. Sustained 6-month Disability Progression in the 205MS301-303 ITT Population

Time to confirmed 6-month disability progression will be summarized for the following populations and study periods:

- 205MS301-303 ITT population during the 205MS303 Treatment Period, from the date of first dose in 205MS303
- 205MS301-303 ITT population during the Combined Study Period, from the date of first dose in 205MS301

Sustained disability progression is defined as: at least a 1.0 point increase on the EDSS from baseline EDSS $\geq$1.0 that is sustained for 24 weeks, or at least a 1.5 point increase on the EDSS from

baseline EDSS = 0 that is sustained for 24 weeks. The date of the initial visit at which the minimum increase in the EDSS is met will be the date of onset of the progression. The EDSS progression is defined as confirmed when this minimum EDSS change is present on the next study visit occurring after 158 days from the initial observation.

For the Combined Study Period, progression will be calculated relative to the EDSS score at the 205MS301 baseline. For the 205MS303 Treatment Period, progression must start after the first dose in the 205MS303 study and will be calculated relative to 205MS303 baseline.

Progression will not be confirmed at a visit where a relapse is also occurring. A subject is considered to be having a relapse for at least 29 days after the start date of a protocol-defined relapse in 205MS301 or 205MS303. If a subject meets the defined criteria of sustained progression and is also having a relapse, the subject will be required to meet the defined minimum criteria at the subsequent visit.

If a subject had a tentative progression prior to the start of alternative MS medication, the appropriate EDSS evaluation performed while taking alternative MS medication will be used to assess confirmation of the progression. Death due to MS will be counted as progression. If the subject was in the midst of a tentative progression at the time of death (e.g. the EDSS evaluation prior to death is a tentative progression), the progression date will be the tentative progression start date. Otherwise, the progression date will be the date of death. If the death was not due to MS, then the subject will be censored using the same rules as for subjects who withdraw from the study.

Subjects who do not have a sustained progression based on the above rules (and have sufficient follow up data to confirm that there is no progression) will be censored. For the analyses based on either 205MS303 treatment period or the combined study period data, the censoring date will be the date of the last EDSS prior to the end date of the 205MS303 treatment period. Subjects who withdraw from the study after the baseline visit but prior to the first clinical evaluation scheduled visit will be censored at baseline.

For subjects with a tentative progression that cannot be confirmed because there are no additional EDSS assessments, the follow-up ends before a sustained progression occurs (i.e., due to the subject withdrawing from the study or due to the cutoff of data collection), or because the confirmatory assessment does not meet other criteria (i.e., the last EDSS assessment is <158 days after the tentative progression or the last EDSS assessment is at the time of a relapse), the censor date will be the date of the last EDSS assessment.

Time to confirmed disability progression will be explored using Kaplan-Meier method, with the first dose date in the corresponding study period as the start date, by the treatment group of the 205MS301 study. Kaplan-Meier method for time to disability progression will be used to estimate the proportion of subjects who experienced progression at selected time points, by treatment group of the 205MS301 study. A subject with sustained disability progression during the 205MS301 Treatment Period will still be considered at risk in the analysis for the 205MS303 Treatment Period.

Kaplan-Meier plots of the time to first progression will be presented and used to estimate the median time (and/or 25th percentile) by the previous treatment group of the 205MS301 study for each study period.

If the EDSS score is missing at the 205MS301 baseline visit, the 205MS301 screening score will be used instead for the 205MS301 baseline. If both baseline and screening scores are missing, the first available assessment will be used as the baseline EDSS score. For the 205MS303 baseline, the last available EDSS score before or on the first dose in the 205MS303 study will be used. The start date for calculation of day to progression or censoring will be the first dosing date in the corresponding period.

Imputation of subjects with tentative progression at their last assessment for (sensitivity analysis)

If a subject has a tentative progression at the last EDSS assessment and no EDSS assessments to confirm progression, the presence or absence of sustained disability progression will be imputed using a Multiple Imputation (MI) approach for the sensitivity analysis. Among subjects with at least one tentative progression, the probability of confirmation for those with a missing EDSS to confirm progression will be estimated via logistic model adjusting for treatment group of the 205MS301 study, EDSS at baseline (as a continuous variable), change in EDSS from baseline to the tentative progression and presence (or absence) of a relapse within the last 29-days of the tentative progression. For the subjects with multiple tentative progressions, the confirmed (if subject had a confirmed progression) or the last (if subject did not have any tentative progressions confirmed) tentative progression record will be retained. Based on these probability estimates, confirmed progression flags will be imputed via multiple imputations. The multiple imputations via this logistic regression model will be conducted 50 times with pre-specified random seed to generate 50 analysis datasets. Analyses will be conducted on each of the 50 data sets. Results will be combined to provide the final analysis results.

7.4.2. Sustained 6-month Disability Progression in the 205MS203-303 ITT Population

Time to confirmed 6-month disability progression will be summarized for the 205MS203-303 ITT population in the 205MS303 Treatment period. For the 205MS303 Treatment Period, progression will be calculated relative to the EDSS score at the 205MS303 baseline. Subjects who do not have a sustained progression will be censored on the date of the last EDSS prior to the end date of the 205MS303 treatment period. For subjects with a tentative progression that cannot be confirmed because there are no additional EDSS assessments, the follow-up ends before a sustained progression occurs (i.e., due to the subject withdrawing from the study or due to the cutoff of data collection), or because the confirmatory assessment does not meet other criteria (i.e., the last EDSS assessment is <158 days after the tentative progression or the last EDSS assessment is at the time of a relapse), the censor date will be the date of the last EDSS assessment. Due to the limited number of subjects, no imputation will be conducted for subjects with tentative progression in the 205MS203-303 ITT population.

Time to confirmed disability progression will be explored using Kaplan-Meier method, with the first dose date in the 205MS303 Treatment period as the start date for all subjects combined. Kaplan-Meier method for time to disability progression will be used to estimate the proportion of subjects who experienced progression at selected time points for all subjects combined.

7.4.3. Sustained 6-month Disability Progression in the 205MS302-303 ITT Population

Time to confirmed 6-month disability progression will be summarized for the 205MS302-303 ITT population during the 205MS303 Treatment Period. Time to confirmed disability progression will be explored using Kaplan-Meier method, with the first dose date in the corresponding study period as the start date. Kaplan-Meier method for time to disability progression will be used to estimate the proportion of subjects who experienced progression at selected time points. Kaplan-Meier plots of the time to first progression will be presented and used to estimate the median time (and/or 25th percentile). Due to the limit number of subjects, no imputation will be conducted for subjects with tentative progression in the 205MS302-303 ITT population.

7.5. MSIS-29

Scoring algorithm described in Hobart J, Lamping et al. (2001) will be used to calculate the MSIS-29 Physical Impact and Psychological Impact scores. Physical score will be based on the responses from items 1-20, while psychological score is based on items 21-29. Missing scores will not be imputed. MSIS-29 physical score data obtained after subjects take alternative medication for MS during the study will be set to missing.

For the 205MS301-303 ITT population, the actual values for MSIS-29 physical score, MSIS-29 psychological score, their change from 205MS303 baseline, and the proportion of subjects with a >= 7.5 worsening in MSIS-29 physical score from the 205MS303 baseline will be summarized by 205MS301 treatment group in the Combined Study Period (by study visit in 205MS303 study).

Note that MSIS-29 is not collected for patients enrolled from the 205MS203 or 205MS302 study to the 205MS303 study.

7.6. MRI Endpoints

7.6.1. MRI Endpoints Analyses for the 205MS301-303 ITT Population

MRI is measured on all subjects in the 205MS301 and 205MS303 studies. Observed MRI data measured after subjects started alternative MS medications will be excluded. The following MRI parameters will be analyzed in the 205MS301-303 ITT population:

- The total number of new or newly enlarging T2 hyperintense lesions relative to the 205MS301 baseline
- The total number of new or newly enlarging T2 hyperintense lesions relative to the 205MS303 baseline
- The total number of new T1 hypointense lesions relative to the 205MS301 baseline
- The total number of new T1 hypointense lesions relative to the 205MS303 baseline
- The total number of Gd-enhancing lesions at 205MS301 study and 205MS303 study

- The total volume of T2 hyperintense lesions
- The volume of new or newly enlarging T2 hyperintense lesions compared to the 205MS301 baseline
- The volume of new or newly enlarging T2 hyperintense lesions compared to the 205MS303 baseline
- The volume of new T1 hypointense lesions compared to the 205MS301 baseline
- The volume of new T1 hypointense lesions compared to the 205MS303 baseline
- Percent Brain Volume Change (PBVC) relative to the 205MS301 baseline
- Percent Brain Volume Change (PBVC) relative to the 205MS303 baseline

Baseline:

Records up to 28 days after the first dose in 205MS301 may be used as the 205MS301 baseline assessments; If there are multiple records for the 205MS301 baseline, then the observation closest to the first dose will be selected (if tied, then the record prior to dosing will be defined as baseline). For the 205MS301 Week 96 MRI assessment, records collected up to 28 days after 205MS303 extension trial first dose will be included.

For the baseline assessment in 205MS303, the baseline MRI obtained in 205MS303 will be used as the baseline if it was obtained up to 28 days after the first dose in 205MS303. If a subject did not have a baseline MRI assessment in 205MS303, then the last assessment obtained during 205MS301 will be used at the baseline assessment for the total number of Gd-enhancing lesions and the total volume of T2 hyperintense lesions.

The total number of T2 lesions at 205MS303 baseline will be calculated by summing the 205MS301 baseline number of T2 lesions and the number of new or newly enlarging lesions since the previous visit at 205MS301 Week 24, 205MS301 Week 96, 205MS301 Week 144 (if available) and 205MS303 Baseline (if available). The same algorithm will be applied to the total number of T1 lesions and the total volume of T1 lesions at 205MS303 baseline.

Data obtained after alternative MS medication will be set to missing. Missing data will not be imputed.

The total number of new or newly enlarging T2 hyperintense lesions

The number of new or newly-enlarging T2 hyperintense lesions relative to the 205MS301 baseline will be analyzed for Week 24 and Week 96 of the 205MS301 study. The number of new or newly-enlarging T2 hyperintense lesions relative to the 205MS303 baseline will be analyzed for Weeks 48, 96, 144, 192, and 240 (if available) of the 205MS303 study.

A negative binomial regression model will be used to analyze the observed new or newly enlarging T2 lesions. The model for the analysis relative to the 205MS301 baseline will be adjusted for the following characteristics at the 205MS301 baseline: volume of T2 hyperintense lesions, history of prior IFN β use and baseline age (age ≤ 35 versus age >35). The model for the analysis relative to

the 205MS303 baseline will be adjusted for the following characteristics: the volume of T2 hyperintense lesions at the 205MS303 baseline, history of prior IFN β use at the 205MS301 baseline, and baseline age (age ≤ 35 versus age >35) at the 205MS303 baseline.

The total number of new T1 hypointense lesions

The total number of new T1 hyperintense lesions relative to the 205MS301 baseline and the 205MS303 baseline will be analyzed using the same methodology as for the analysis new or newly-enlarging T2 hyperintense lesions. The estimated number of lesions will be evaluated using negative binomial regression, adjusted for the history of prior IFN β use at the 205MS301 baseline, age (age ≤ 35 versus age >35) at the corresponding baseline, and volume of T1 hypointense lesions at the corresponding baseline.

Number of Gd-Enhancing Lesions

The total number of Gd-enhancing lesions will be tabulated for the following visits of the 205MS301 study: Baseline, Week 24, Week 96 and Week 144, and for the following visits of the 205MS303 study: Baseline, Weeks 48, 96, 144, 192, and 240 (if available). Summary statistics by the 205MS301 treatment group will also be provided.

The total volume of T2 hyperintense lesions

Summary statistics for the total volume of T2 hyperintense lesions and its change from 205MS301 baseline, by 205MS301 treatment group, will be provided for Week 24, Week 96 and Week 144 of the 205MS301 study. Similar analysis will be performed for Weeks 48, 96, 144, 192, and 240 (if available) of the 205MS303 study (with change from the 205MS303 baseline).

Volume of new or newly enlarging T2 hyperintense lesions

Summary statistics for the volume of new or newly enlarging T2 hyperintense lesions, by 205MS301 treatment group, will be provided for the following visits of the 205MS301 study: Week 24, Week 96 and Week 144, and for the following visits of the 205MS303 study: Baseline, Weeks 48, 96, 144, 192, and 240 (if available).

Volume of new T1 hypointense lesions

The criteria and analysis for this endpoint will be the same as used for the volume of new or newly enlarging T2 hyperintense lesions.

Percent Brain Volume Change (PBVC)

Summary statistics for the (annualized) Percent Brain Volume Change (PBVC) relative to either the 205MS301 baseline or the 205MS303 baseline, by 205MS301 treatment group, will be provided for the Weeks 48, 96, 144, 192, and 240 (if available) of the 205MS303 study.

7.6.2. MRI Endpoints Analyses for the 205MS203-303 ITT Population

For the 205MS203-303 ITT population, MRI was not collected at 205MS303 baseline, and most of the subjects only have one MRI visit in the 205MS303 study. By visit summary will be presented for selected parameters including the total number of Gd-enhancing lesions, and the total volume of T2 hyperintense lesions. Note that due to the timing of implementation of protocol version 4, there is very limited data available for other MRI parameters and therefore these will not be summarized.

7.6.3. MRI Endpoints Analyses for the 205MS302-303 ITT Population

For the 205MS302-303 ITT population, MRI was not collected at 205MS303 baseline, and most of the subjects only have one MRI visit in the 205MS303 study. By visit summary will be presented for the selected parameters, including the total number of Gd-enhancing lesions, and the total volume of T2 hyperintense lesions. Note that due to the timing of implementation of protocol version 4, there is very limited data available for other MRI parameters and therefore these will not be summarized.

7.7. EDSS

7.7.1. EDSS in the 205MS301-303 ITT Population

For the 205MS301-303 ITT population, the EDSS score with change from 205MS303 baseline will be summarized by 205MS301 treatment group in the 205MS303 Treatment Period (by study visit in 205MS303 study).

7.7.2. EDSS in the 205MS203-303 ITT Population

For the 205MS203-303 ITT population, the EDSS score with change from 205MS303 baseline will be summarized in the 205MS303 Treatment Period (by study visit in 205MS303 study) for all subjects together.

7.7.3. EDSS in the 205MS302-303 ITT Population

For the 205MS302-303 ITT population, the EDSS score with change from 205MS303 baseline with change from 205MS303 baseline will be summarized by study visit in 205MS303 for all subjects together.

7.8. EQ-5D

The EQ-5D is a generic health-related quality of life (QoL) instrument which has been extensively validated. There are two components to the EQ-5D used in this protocol, a Health State Profile and a Visual Analog Scale (VAS). With the Health State Profile, patients record their level of current health for five domains comprising a health profile: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A score of 1, 2, or 3 are possible responses for each of the five questions in the Health State Profile (1=no problems, 2=some problem, 3=severe problems). With the Visual Analogue Scale (VAS), patients are asked to rate their current health on a 20 cm scale from 0 to 100

where 0 represents “worst imaginable health state” and 100 represents “best imaginable health state”. The EQ-5D summary index score will be computed from the Health State Profile using MVH A1 Tariff (Dolan, 1997). Missing values will not be imputed. The EQ-5D summary index score data obtained after subjects take alternative medication for MS during the study will be set to missing.

7.8.1. EQ-5D in the 205MS301-303 ITT Population

For the 205MS301-303 ITT population, the EQ-5D Health State Profile scores, the EQ-VAS scores with change from 205MS303 baseline, and the summary index scores with change from 205MS303 baseline will be summarized for the 205MS301-303 ITT population by 205MS301 treatment group and by study visit in 205MS303.

7.8.2. EQ-5D in the 205MS203-303 ITT Population

For the 205MS203-303 ITT population, the EQ-5D Health State Profile scores, the EQ-VAS scores with change from 205MS303 baseline, and the summary index scores with change from 205MS303 baseline will be summarized for all subjects combined in the205MS303 Treatment Period (by study visit in 205MS303 study).

7.8.3. EQ-5D in the 205MS302-303 ITT Population

For the 205MS302-303 ITT population, the EQ-5D Health State Profile scores, the EQ-VAS scores with change from 205MS303 baseline, and the summary index scores with change from 205MS303 baseline will be summarized by study visit in 205MS303.

7.9. Health Resource Utilization (HRU)

7.9.1. HRU in the 205MS301-303 ITT Population

For the 205MS301-303 ITT population, the total number of unscheduled site visits per collection time will be summarized separately for MS-related and non-MS related visits. Summaries will be presented by 205MS301 treatment group in the 205MS301 Treatment Period and the 205MS303 Treatment period. The annualized rate of unscheduled site visits will be calculated as the total number of unscheduled visits collected on Patient Health Care Treatment CRF page, divided by the total number of years.

7.9.2. HRU in the 205MS203-303 ITT Population

For the 205MS203-303 ITT population, the total number of unscheduled site visits per collection time will be summarized separately for MS-related and non-MS related visits. Summaries will be presented for all subjects combined in the 205MS303 Treatment period. The annualized rate of unscheduled site visits will be calculated as the total number of unscheduled visits collected on Patient Health Care Treatment CRF page, divided by the total number of years.

7.9.3. HRU in the 205MS302-303 ITT Population

For the 205MS302-303 ITT population, the total number of unscheduled site visits per collection time will be summarized separately for MS-related and non-MS related visits. The annualized rate of unscheduled site visits will be calculated as the total number of unscheduled visits collected on Patient Health Care Treatment CRF page, divided by the total number of years.

7.10. Health Related Productivity Questionnaire (HRPQ)

7.10.1. HRPQ in the 205MS301-303 ITT Population

For the 205MS301-303 ITT population, responses to the HRPQ will be summarized by 205MS301 treatment group in the 205MS303 Treatment Period.

7.10.2. HRPQ in the 205MS203-303 ITT Population

For the 205MS203-303 ITT population, responses to the HRPQ will be summarized in the 205MS303 Treatment Period.

7.10.3. HRPQ in the 205MS302-303 ITT Population

For the 205MS302-303 ITT population, responses to the HRPQ will be summarized in the 205MS303 Treatment Period.

7.11. Symbol Digit Modalities Test (SDMT)

For the 205MS301-303 ITT population, SDMT actual value and change from 205MS301 baseline will be summarized by 205MS301 treatment group in the Combined Study Period (by study visit in 205MS301 and 205MS303 studies). Additionally, proportion of patients with ≥3 points or ≥4 points increase from 205MS301 baseline, and proportion of patients with ≥3 points or ≥4 points decrease from 205MS301 baseline will be summarized by 205MS301 treatment group in the Combined Study Period (see also, Benedict et. al 2017). Similar analyses will be done for the 205MS303 treatment period with changes from 205MS303 baseline. Note that in the 205MS303 study, SDMT is only collected for subjects in 205MS301-303 ITT population starting from week 144 in the study.

SDMT is not collected for patients enrolled from the 205MS203 or 205MS302 study to the 205MS303 study.

7.12. 3 Second Paced Auditory Serial Addition Test (PASAT3)

For the 205MS301-303 ITT population, PASAT3 actual value and change from 205MS301 baseline will be summarized by 205MS301 treatment group in the Combined Study Period (by study visit in 205MS301 and 205MS303 studies). Similar analyses will be done for the 205MS303 treatment period with changes from 205MS303 baseline.

Note that PASAT3 is not collected for patients enrolled from the 205MS203 or 205MS302 study to the 205MS303 study.

7.13. Proportion of subjects who are free from disease activity

Subjects were considered free of disease activity if they were without clinical or radiological activity. Clinical activity included an assessment of relapses and of disease progression, and radiological activity included an assessment of Gd+ lesions and new or enlarging T2 lesions.
For the 205MS301-303 ITT population, proportion of subjects who are free from disease activity in the 205MS303 treatment period will be summarized by 205MS301 treatment group.

8. Safety Data

8.1. Summary of Safety Analyses

As shown in Table 11, safety analyses will be performed over the 205MS303 Treatment period for the 205MS301-303 safety population, the 205MS203-303 safety population, and the 205MS302-303 safety population, respectively. For the 205MS301-303 safety population, results will be summarized by treatment group in the 205MS301 study and for all subjects combined. For the 205MS203-303 safety population, results will be summarized for all subjects combined. For the 205MS302-303 safety population, results will be summarized for all subjects combined. Sections below include more details about these analyses.

Table 11: Summary of populations for safety analyses over the 205MS303 Treatment Period

Population	Statistical Methods
205MS301-303 safety population	AEs, AEs of special interest, lab data, and vital signs will be descriptively summarized by treatment group in the 205MS301 study, and for all subjects combined.
205MS203-303 safety population	AEs, AEs of special interest, lab data, and vital signs will be descriptively summarized for all subjects combined.
205MS302-303 safety population	AEs, AEs of special interest, lab data, and vital signs will be descriptively summarized for all subjects combined.

8.2. Clinical Adverse Events

All treatment-emergent events in 205MS303 study will be included in the evaluation of safety. A treatment emergent event is defined as any event that either occurs or worsens in severity after the first dose of DAC HYP treatment in 205MS303 study. Events starting after permanent discontinuation of study drug will be included provided the start date was within 180 days of the last dose. Unless explicitly stated otherwise, analyses of adverse events will be limited to treatment emergent events in the 205MS303 study. If treatment emergence cannot be determined due to incomplete or partial start and/or end dates, the event will be considered to be 205MS303 treatment emergent.

Adverse events will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA) version 16.1. In general, the incidence of treatment emergent adverse events will be presented by system organ class (SOC) and preferred terms (PT) but other classifications may be used.

The number and percentage of subjects with at least one event, at least one severe event and at least one study-drug related event will be presented. The incidence of adverse events classified by the appropriate system organ class and preferred terms will be summarized by severity and overall. If a patient experiences an event more than once with varying severity during the study, he/she will be counted only once with the maximum severity within each system organ class/preferred term. Events leading to study withdrawal and/or treatment discontinuation will be summarized.

In general, for the 205MS301-303 safety population, adverse events will be summarized by treatment group in the 205MS301 study and for all subjects combined. For the 205MS203-303 safety population, adverse events will be summarized for all subjects combined. For the 205MS302-303 safety population, adverse events will be summarized for all subjects combined.

Any deaths that occurred during the study will be listed and relevant information including timing of the death relative to study treatment, concomitant medications, the investigator assessment of the cause of death will be provided.

8.3. Adverse Events of Interest

The following groups of adverse events are of special interest due to potential mechanism of action, therapeutic class, or prior clinical experience with DAC HYP. The groups of interest, and the MedDRA-based or other criteria utilized to determine the events falling into each group are described in the following table.

Table 12: Adverse Events of Special Interest

	Group	Criteria	Summary by
1.	Infections and serious infections	SOC of Infections and Infestations	PT and seriousness
2.	Serious skin reactions	SOC of Skin and Subcutaneous Tissue Disorders; SMQ for Severe cutaneous adverse reactions (SMQ) [narrow terms only]	PT
3.	Hepatic events	Sublevel SMQ of Drug Related Hepatic Disorders – Comprehensive Search under the SMQ of Hepatic Disorders	SOC/PT
4.	Colitis	HLT of Colitis (Excl Infective), primary or secondary pathway	PT
5.	Autoimmune haemolytic anaemia	SMQ Haemolytic disorders	PT

6.	Lymphadenopathy	Customized search of the following PTs: abdominal lymphadenopathy, adenoiditis, angiolymphoid hyperplasia with eosinophilia, autoimmune lymphoproliferative syndrome, Castleman's disease, hilar lymphadenopathy, histiocytic necrotising lymphadenitis, lymph node pain, lymph node palpable, lymphadenitis, lymphadenocyst, lymphadenopathy, lymphadenopathy mediastinal, lymphatic disorder, lymphoid tissue hyperplasia, lymphoproliferative disorder, lymphoproliferative disorder in remission, myeloproliferative neoplasm, paratracheal lymphadenopathy, persistent generalised lymphadenopathy, PFAPA syndrome, retroperitoneal lymphadenopathy	SOC/PT
7.	Depression and suicide	SMQ of Depression and Suicide/Self Injury	PT
8.	Malignancies	Sublevel SMQ of Malignant or Unspecified Tumours under the SMQ of Malignancies, then confirmed as malignancies following medical review.	PT
9.	Hypersensitivity	SMQ of Hypersensitivity (narrow search terms)	SOC/PT
10	Anaphylactic reactions	SMQ of Anaphylactic Reactions (narrow search terms) SAEs within 24 hours after dosing	PT
11	Angioedema	SMQ of Angioedema (narrow search terms)	PT
12	Opportunistic infections	Customized search including selected preferred terms	PT
13	Lymphopenia	PTs: Lymphopenia; lymphocyte count abnormal; Lymphocyte count decreased; B-lymphocyte count decreased, Leukopenia, Differential white blood cell count abnormal; Lymphocyte percentage decreased, Lymphocyte percentage abnormal	SOC/PT per severity
14	Immune mediated disorders	HLGT of Autoimmune Disorders, primary or secondary pathway, plus the additional 1 PT of Coombs Negative Hemolytic Anemia, minus the 2 PT of Multiple Sclerosis and Optic Neuritis	SOC/PT
15	Sarcoidosis	High Level Term: Acute and chronic sarcoidosis and the Preferred Term of Heerfordts syndrome	PT

The incidence of adverse events in each group will be summarized for the 205MS301-303 safety population, the 205MS203-303 safety population, and the 205MS302-303 safety population, respectively; where appropriate, the analysis will be repeated for serious events.

8.4. Additional Efficacy and Safety Endpoints

Additional efficacy and safety endpoints described in this section will be analyzed for the 205MS301-205MS303 study.

8.4.1. Beck Depression Inventory Score

Depression scores will be calculated according to the BDI-II manual, Second Edition. Subjects with a total score of 18 or higher will be considered as positive for depression. For the 205MS301-303 safety population, BDI-II scores, their change from DAC HYP Baseline, and the proportion of subjects positive for depression will be summarized by visit in the 205MS303 study. If there are more than 2 responses for the same question, the response with the highest (worst) rating will be used in the analysis.

Note that Beck depression inventory score is not collected for patients enrolled from 205MS203 or 205MS302 study to the 205MS303 study.

8.4.2. Treatment Satisfaction Questionnaire for Medication

Summary statistics for the treatment satisfaction questionnaire for medication, by 205MS301 treatment group, will be provided for baseline and post-baseline visits of the 205MS303 study for the 205MS301-303 ITT population. The responses to the questionnaire may be grouped properly.

Note that treatment satisfaction questionnaire for medication is not collected for patients enrolled from 205MS203 or 205MS302 study to the 205MS303 study.

8.4.3. MSFC Score

There are 3 components to the MSFC:

(1) the average scores from the 4 trials on the 9-hole peg test (9HPT) (the 2 trials for each hand are averaged, converted to the reciprocals of the mean times for each hand and then the 2 reciprocals are averaged);

(2) the average scores of the 2 Timed 25-Foot Walk trials;

(3) the number correct on the Paced Auditory Serial Addition (PASAT) 3 test.

The MSFC z-score is calculated by creating z-scores for each component of the MSFC, as explained below, and averaging them to create an overall composite score, i.e.,

MSFC z-score = $(Z_{25\text{-foot-walk}} + Z_{9HPT} + Z_{PASAT3})/3$, where Z_{xxx} refers to Z-scores.

A z-score represents the number of standard deviations a subject's test result is higher (z >0) or lower (z <0) than the average test result (z = 0) of the reference population.

Calculation for Raw and Z-score for each component

The following describes the scoring, rules for missing value imputation for each component.

Timed 25-Foot Walk Z-score Calculation

The Z-score is calculated as in the following formula:

$$Z_{25\text{-foot-walk}} = (-1) * \frac{((t_1 + t_2)/2) - MEAN(reference)}{SD(reference)},$$

where t_1 and t_2 are the time (in seconds) from the two trials, and the mean (reference) and SD (reference) are the mean and standard deviation respectively, of baseline values for the reference population. For scores to be comparable with scores in 205MS301, the same reference population is used. Baseline values for the reference population are the values at the 205MS301 baseline for the reference population (205MS301 ITT population). The same is applicable to 9HPT and PASAT 3 Z-scores.

Timed 25-Foot Walk Raw Score Calculation

The row score is calculated as in the following formula:

$$R_{25\text{-foot-walk}} = (t_1 + t_2)/2,$$

where t_1 and t_2 are the time (in seconds) from the two trials.

Missing Value Handling for Timed 25-Foot Walk

For missing baseline and post-baseline values, if a subject is missing only one trial for any post-baseline visit, then the score from the non-missing trial will be used to calculate both the Z-score and Raw score, unless the reason for the missing score is due to MS related physical limitation or other physical limitations. If reason is due to one of the reasons listed above, the score for that specific trial will be back-calculated using the Z-score value of -13.7 (see formula below), and then the average of the two trials will be taken. The steps outlined above will remain the same.

If both scores from the two trials are missing for any post-baseline visit due to MS related physical limitation or other physical limitations, (based on the missing data algorithm suggested by the MSFC algorithm) the subject will be given a Z-score of -13.7 for the Timed 25-Foot walk. The Row-score will be back-calculated using the following formula:

$$R_{25\text{-foot-walk}} = MEAN(reference) + 13.7*SD(reference).$$

9HPT Z-score Calculation

Z-score for the 9HPT is calculated as in the following formula:

$$Z_{9HPT} = \frac{((\frac{1}{(t_{11}+t_{12})/2} + \frac{1}{(t_{21}+t_{22})/2})/2) - MEAN(reference)}{SD(reference)},$$

where t_{11}, t_{12}, t_{21}, t_{22} are the time (in seconds) taken to complete for dominant hand trial 1, dominant hand trial 2, non-dominant hand trial 1, and non-dominant hand trial 2, respectively. The mean (reference) and SD (reference) are the mean and standard deviation, respectively, of reference population's baseline score.

9HPT Raw Score Calculation

Raw-score for the 9HPT is calculated as in the following formula:

$$R_{9HPT} = ((t_{11}+t_{12})/2 + (t_{11}+t_{12})/2)/2$$

where t_{11}, t_{12}, t_{21}, t_{22} are the time (in seconds) taken to complete for dominant hand trial 1, dominant hand trial 2, non-dominant hand trial 1, and non-dominant hand trial 2, respectively.

Missing Values for 9-hole Peg Test

For missing baseline and post-baseline values, if a subject is missing only one trial for any post-baseline visit (for either dominant or non-dominant hand), then the score from the non-missing trial will be used to calculate both scores, unless the reason for the missing score is due to MS related physical limitation or other physical limitations. If reason is due to one of the reasons listed above, the score for that specific trial will be imputed with a raw score value of 777, and then the average of the two trials will be taken. The steps outlined above will remain the same.

The missing data algorithm suggested by the MSFC manual will be used to impute missing values. If both scores from either hands are missing for any post-baseline visit, due to MS related physical limitation or other physical limitations, then the subject will be given a Row-score using a value of 777. The Z-score will be calculated with the following formula:

$$Z_{9HPT} = \frac{\frac{1}{777} - MEAN(reference)}{SD(reference)},$$

PASAT 3 Z-score Calculation

For the PASAT 3, the z-score for each subject at each time-point will be created by subtracting the reference population's baseline mean score on the PASAT 3 from the subject's PASAT 3 score and dividing by the baseline SD on the PASAT 3 of the reference population, i.e.

$$Z_{PASAT3} = \frac{\text{PASAT 3 raw score} - MEAN(reference)}{SD(reference)},$$

and PASAT 3 raw score = # of items correct.

Missing Values

For missing post-baseline values, if a subject is missing the PASAT 3 score due to MS disease limitations, then a score of 0 will be imputed as the *raw score*. Missing baseline values will not be imputed.

For the 205MS301-303 ITT population, actual value, change and percentage change from the 205MS301 baseline in the MSFC z-scores as well as for each individual MSFC component z-scores will be summarized by 205MS301 treatment group in Combined Study Period (by study visit in 205MS301 and 205MS303 studies). Similarly, for the 205MS301-303 ITT population, the MSFC z-scores as well as for each individual MSFC component z-scores with change from 205MS303 baseline will be summarized by 205MS301 treatment group in the 205MS303 Treatment Period (by study visit in 205MS303 study).

8.5. Laboratory Data

Analyses of laboratory assessments will be performed on subjects in each of the safety population utilizing the following rule: post-baseline data will include measurements occurring after the first DAC HYP dose date and during the 205MS303 Treatment Period. For subjects who were randomized to IFN β-1a in the 205MS301 study, this means that post-baseline data includes measurements occurring after the first DAC HYP dose date in the 205MS303 study. For subjects randomized to DAC HYP in the 205MS301 study, this means that post-baseline data includes measurements occurring during the 205MS303 studies on or after the first DAC HYP dose date in 205MS303. For subjects transitioned from the 205MS203 study or the 205MS302 study, this means that post-baseline data includes measurements occurring during the 205MS303 studies on or after the first DAC HYP dose date in 205MS303.

The following laboratory parameters will be included in the aforementioned analyses:

- Hematology:
  - White blood cell (WBC) parameters (as absolute values and as percentage of WBC): basophils, eosinophils, lymphocytes, monocytes, and segmented neutrophils
  - other hematology parameters: hematocrit, hemoglobin, Mean Corpuscular Hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelets, red blood cell (RBC) count, WBC

- Blood chemistry:
  - liver function tests (LFTs): alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) and total bilirubin.
  - renal function tests and electrolytes: blood urea nitrogen (BUN), creatinine, bicarbonate, chloride, potassium and sodium.
  - thyroid function tests: total T4, and thyroid stimulating hormone (TSH).

- Urinalysis:
  - quantitative urinalysis parameters: pH and specific gravity
  - categorical urinalysis parameters: color and clarity, blood, glucose, leukocyte esterase, ketones, nitrite and protein.

Shifts to abnormally high or abnormally low values for quantitative parameters: Any subject with a non-high DAC HYP baseline (whether low, normal or unknown) will be counted in the risk set for shifts to high. Similarly, any subject with a non-low DAC HYP baseline result will be counted in the risk set for shifts to low. Shifts tables to the most extreme value in the 205MS303 Treatment Period (highest for shifts to high, lowest for shifts to low) will be conducted. The rationale for using the most extreme values or worst value is that should a treatment affect a laboratory value, that value could be affected at different times for different subjects. Therefore, the analyses present the most extreme values for each subject over time. For the 205MS301-303 safety population, the shift tables will be presented by previous treatment group of the 205MS301 study and for all subjects combined. For the 205MS203-303 safety population and 205MS302-303 safety population, the shift tables will be presented for all subjects combined within each of the safety population.

Shifts to abnormal values for categorical parameters: Any subject with a non-abnormal DAC HYP baseline (whether normal or unknown) will be counted in the risk set for shifts to abnormal. For the 205MS301-303 safety population, shifts from baseline to the most extreme post-baseline value will be presented by previous treatment group of the 205MS301 study and for all subjects combined. For the 205MS203-303 safety population and the 205MS302-303 safety population, the shift tables will be presented for all subjects combined within each of the safety population.

Descriptive summary statistics over time in the 205MS303 Treatment Period for quantitative parameters, of actual values, change from DAC HYP baseline (and when appropriate, percent change from baseline). These statistics may be displayed as figures. Time points analyzed will be based on protocol scheduled assessments and availability of data. Visit windows will be used to select the laboratory result used for each time point in the summary.

The number and percent of subjects with potentially clinically significant hematology laboratory abnormalities will be provided. The criteria of the potentially significant hematology laboratory abnormalities are provided below. Listing of lymphocytes for subjects with severe and prolonged lymphopenia defined as post DAC baseline lymphocytes <0.5x10^9 cells/L consecutively for at least 6 months will be provided.

For the baseline thyroid function test parameters, descriptive summary statistics of actual values will be given. For urinalysis parameters, actual values will be listed.

Table 13: Criteria for Potentially Clinically Significant Hematology Abnormalities

Test	Criteria
White blood cell count (10^9 cells/L)	<3.0; >=16.0
Lymphocytes (10^9 cells/L)	<0.8; <0.5; >12.0
Segmented neutrophils (10^9 cells/L)	<=1.0; <1.5; >=12.0
Red blood cell count (10^12 cells/L)	<=3.3; >=6.8
Hemoglobin (g/L)	<=100
Platelets (10^9 cells/L)	<=100; >=600

In addition, summary of baseline and worst post-baseline laboratory values categorized based on CTC (common toxicity criteria) grade, will also be presented for selected parameters of interest. The data may also be presented in graphs. The criteria for CTC grade for hematology parameters are provided below.

Table 14: Severity Grades for Hematology

Test	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (g/L)	[100, LLN)	[80, 100)	[65, 80)	<65
Lymphocytes (10^9 cells/L)	[0.8, LLN)	[0.5, 0.8)	[0.2, 0.5)	<0.2
Platelets (10^9 cells/L)	[75, LLN)	[50, 75)	[25, 50)	<25
Segmented neutrophils (10^9 cells/L)	[1.5, LLN)	[1.0, 1.5)	[0.5, 1.0)	<0.5
White blood cell count (10^9 cells/L)	[3.0, LLN)	[2.0, 3.0)	[1.0, 2.0)	<1.0

Additional Analyses of Liver Function Tests

For LFTs Alkaline phosphatase, ALT, AST, GGT and total bilirubin, additional categories will be defined to present baseline and post-baseline values (see table below). The incidence of ALT and/or AST elevations >3X ULN by concurrently elevated bilirubin will also be summarized. [redacted]

Table 15: Severity Grades for LFTs

Test	Grade 1	Grade 2	Grade 3		Grade 4
ALT	(1.0, 3.0)	[3.0, 5.0]	(5.0, 10.0]	(10.0, 20.0]	> 20.0
AST	(1.0, 3.0)	[3.0, 5.0]	(5.0, 10.0]	(10.0, 20.0]	> 20.0

Test	Grade 1	Grade 2	Grade 3	Grade 4
Alkaline phosphatase	(1.0, 2.5]	(2.5, 5.0]	(5.0, 20.0]	> 20.0
GGT	(1.0, 2.5]	(2.5, 5.0]	(5.0, 20.0]	> 20.0
Total bilirubin	(1.0, 1.5]	(1.5, 3.0]	(3.0, 10.0]	> 10.0

Grades determined by multiples of ULN. Grade 3 ALT and AST results will be subdivided as shown.

Plots of concurrent and non-concurrent peak bilirubin versus peak ALT or AST will be presented, as multiples of ULN on the log scale. Incidence of subjects experiencing total bilirubin at or above 2xULN and ALT or AST above 3xULN (either concurrent) will be summarized.

8.6. Subgroup analysis

Subgroup analysis, based on the DAC HYP baseline characteristics or usage of potential hepatotoxic medication, will be performed for the following selected safety endpoints for each of the three safety populations (the 205MS301-303 safety population, the 205MS203-303 safety population, and the 205MS302-303 safety population), over the 205MS303 Treatment Period.

Selected safety endpoints:

- Adverse event
- Serious adverse event
- Hepatic adverse event
- Serious hepatic adverse event
- Liver function test

The following DAC HYP baseline characteristics or usage of potential hepatotoxic medication are used to define subgroups if applicable:

- Age at DAC HYP baseline (age <50 versus age >=50)
- Pre-existing liver conditions at DAC baseline based on hepatic medical history report
- Taking potential hepatotoxic medication

For the potential hepatotoxic medication subgroup analysis, patients will be categorized as either without taking potential hepatotoxic medication or taking potential hepatotoxic medication. For patients taking potential hepatotoxic medications, they will be further categorized as either initiating first potentially hepatotoxic medication while on DAC HYP treatment or initiating first potentially hepatotoxic medication prior to DAC HYP treatment. Note that the list of potential hepatotoxic medications is defined and agreed by SABR prior to database lock.

Incidence of adverse events and serious adverse events will be summarized by DAC baseline age subgroup, and by system organ class and preferred term.

Summaries of hepatic events, as defined as an AE of special interest in Table 12, will be provided by subgroup for pre-existing liver conditions subgroup and potential hepatotoxic medication subgroup, respectively. In addition, incidence of hepatic events and serious hepatic events will be summarized by system organ class and preferred term for each of the subgroups of pre-existing liver conditions and potential hepatoxic medication.

Summaries of maximum liver function test values will be provided by subgroup for both the pre-existing liver conditions subgroup and the potential hepatotoxic medication subgroup.

8.7. Vital Signs

Vital signs collected in the 205MS303 study will be examined to determine the incidence of clinically relevant abnormalities. For each of the safety population, the number and percentage of subjects with clinically relevant post-DAC HYP baseline abnormalities in the 205MS303 study will be summarized. The definitions of abnormalities are provided in Table 16. For the purpose of determining shifts, DAC HYP baseline will be used. Summary statistics for actual values and change from DAC HYP baseline will also be presented.

For the 205MS301-303 safety population, the summary tables will be presented by previous treatment group of the 205MS301 study, and for all subjects combined. For the 205MS203-303 safety population and the 205MS302-303 safety population, the summary tables will be presented for all subjects combined within each safety population.

Table 16: Criteria to determine clinically relevant abnormalities in vital signs

Vital Sign	Shift	Criteria for Abnormalities
Temperature (°C)	Increase	>38°C and increase from baseline of at least 1°C
Pulse (bpm)	Increase	>120 beats per minute (bpm) if ≤120 bpm at baseline, or increase from baseline of more than 20 bpm
	Decrease	<50 bpm if ≥50 bpm at baseline, or decrease from baseline of more than 20 bpm
Systolic blood pressure (mmHg)	Increase	>180 mmHg if ≤180 mmHg at baseline, or increase from baseline of more than 40 mmHg
	Decrease	<90 mmHg if ≥90 mmHg at baseline, or decrease from baseline of more than 30 mmHg
Diastolic blood pressure (mmHg)	Increase	>105 mmHg if ≤105 mmHg at baseline, or increase from baseline of more than 30 mmHg;
	Decrease	<50 mmHg if ≥50 mmHg at baseline, or decrease from baseline of more than 20 mmHg

8.8. Physical Examination

A listing of subjects with change from normal to abnormal status in physical examination at any time during the 205MS303 study will be presented for each of the safety population.

8.9. Immunogenicity Data

Immunogenicity to daclizumab (i.e., anti-drug antibodies (ADAs) that bind to Daclizumab) will be assessed on all subjects in 205MS303 with available data. Positive samples will be further tested for neutralizing antibodies using a specific neutralizing antibody (NAb) assay. Results will be tabulated by nominal visit and overall.

For the 205MS301-303 safety population, the summary tables will be presented by previous treatment group of the 205MS301 study, and for all subjects combined. For the 205MS203-303 safety population and the 205MS302-303 safety population, the summary tables will be presented for all subjects combined within each safety population.

[redacted]

9. Pharmacokinetics and Pharmacodynamics

9.1. Pharmacokinetics

Blood serum will be collected at selected timepoints throughout the study to determine DAC HYP serum concentrations in order to monitor the drug trough level and [redacted]. Listings of DAC HYP plasma concentrations by subject will be presented for each of the safety population.

9.2. Pharmacodynamics

[redacted]

10. Sample Size Justification

There is no formal sample size calculation for the main study. The number of subjects in the 205MS303 study is determined by the number of subjects who completed studies 205MS301, 205MS203 and 205MS302 and who were eligible to and chose to enroll in study 205MS303.

11. References

Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain*, 2001 May; 124(Pt 5): 962-973.

Dolan P Modeling Valuations for EuroQol Health States. *Medical Care*, 1997, 11: 1095-1108.

Benedict RH, Cohan S, Lynch SG, Riester K, Wang P, Castro-Borrero W, Elkins J, Sabatella G. Improved cognitive outcomes in patients with relapsing–remitting multiple sclerosis treated with daclizumab beta: Results from the DECIDE study. *Multiple Sclerosis Journal*. 2017 May 1:1352458517707345.