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

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

PROTOCOL NUMBER: 205MS303/NCT01797965

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: 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 Who Have Completed Study 205MS301

EUDRA CT NO: 2012-003176-39

DATE: 29 September 2017
Version 5
FINAL

Supersedes previous Version 4 dated 06 March 2017.

SPONSOR SIGNATURE PAGE

Protocol 205MS303 was approved by:

[redacted], MD

4TH OCT 2017
Date

Biogen MA Inc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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

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

Biogen Australia Pty Ltd
Level 3
123 Epping Road
North Ryde, NSW 2113
Australia

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

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

2. LIST OF ABBREVIATIONS

ADAs	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ARR	annualized relapse rate
AST	aspartate aminotransferase
AUDIT-C	Alcohol Use Disorders Identification Test - Consumption Questionnaire
BDI-II	Beck Depression Inventory, Second Edition
bpm	beats per minute
BUN	blood urea nitrogen
CRF	case report form
CRO	contract research organization
DAC HYP	Daclizumab High Yield Process
DHA	Directions for Handling and Administration
EDSS	Expanded Disability Status Scale
EQ-5D	European Quality of Life, 5-dimensions
EQ-VAS	European Quality of Life, visual analog scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gd	gadolinium
GGT	gamma-glutamyltransferase
HIV	human immunodeficiency virus
HRPQ	Health Related Productivity Questionnaire
HRU	health resource utilization
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFN	interferon
IL-2	interleukin-2
IM	intramuscular
ITT	intent-to-treat
IV	intravenous
IVIg	intravenous immunoglobulin
IVMP	intravenous methylprednisolone
LFT	liver function test
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale-29
NAbs	neutralizing antibodies
NK	natural killer cells
PASAT 3	3-Second Paced Auditory Serial Addition Test

[redacted]	[redacted]
PFS	prefilled syringe
PHI	protected health information
PK	pharmacokinetic(s)
RRMS	relapsing-remitting multiple sclerosis
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
SC	subcutaneous
SDMT	Symbol Digit Modalities Test
SGOT	serum glutamic oxaloacetic transaminase; see AST
SGPT	serum glutamic pyruvic transaminase; see ALT
SNP	single nucleotide polymorphism
SUSAR	suspected unexpected serious adverse reaction
T1	MRI hypointense designation
T2	MRI hyperintense designation
T4	thyroxine
ULN	upper limit of normal
US	United States
VAS	visual analog scale

3. SYNOPSIS

This is a brief summary. For details refer to the body of the protocol.

Protocol Number:	205MS303
Protocol Title:	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 Who Have Completed Study 205MS301
Version Number:	4
Name of Study Treatment:	Daclizumab High Yield Process (DAC HYP)
Study Indication:	Relapsing-Remitting Multiple Sclerosis (RRMS)
Phase of Development:	3
Rationale for the Study:	To evaluate the long-term safety, efficacy, and immunogenicity of DAC HYP in subjects with multiple sclerosis (MS) who have completed Study 205MS301 (DECIDE), Study 205MS203 (SELECTED), or Study 205MS302 (OBSERVE).
Study Objectives and Endpoints:	**Objectives** Primary: 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. Secondary: 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 Avonex® in Study 205MS301

Exploratory:

- [redacted]

Endpoints

Primary:

- Incidence of adverse events (AEs) and serious AEs (SAEs)

Secondary:

- 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, gadolinium-enhancing (Gd+) 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 (EQ-5D) and European Quality of Life, visual analog scale (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 analog scale [VAS]) and clinician injection site assessments
- Incidence of anti-drug antibodies to DAC HYP over time
- Incidence of neutralizing antibodies to DAC HYP over time

Study Design:	Multicenter, open-label, long-term extension study
Rationale for Dose and Schedule Selection:	The DAC HYP dose and schedule were used in the pivotal Phase 3 205MS301 study and will be the treatment regimen used in the commercial setting. The same DAC HYP dose and schedule were used in Study 205MS203 and Study 205MS302.
Study Location:	Global
Number of Planned Subjects:	Approximately 1600 subjects. This includes approximately 1200 subjects who completed Study 205MS301. Additionally, approximately 400 subjects from the other ongoing DAC HYP extension studies (Study 205MS203 and Study 203MS302) will be eligible to enter Study 205MS303 at Week 144 of Study 205MS303.
Study Population:	This study will be conducted in subjects with MS currently participating in Study 205MS301 who have completed either the Week 144 Visit or the End of Study Visit (Week 96) of

	Study 205MS301 OR subjects with MS currently participating in Study 205MS203 or Study 205MS302.
Treatment Groups:	This is a single-arm study. All subjects will receive open-label treatment with DAC HYP 150 mg by a subcutaneous injection using the PFS every 4 weeks. Depending on availability and local regulations, some subjects may dose with DAC HYP using a single-use autoinjector that contains a PFS.
Duration of Treatment and Follow-up:	Subjects will participate in this study for up to approximately 5 years, or until availability of commercial product (whichever is sooner), and in accordance with applicable laws and regulations. All subjects should complete safety follow-up evaluations at 4 (End of Treatment Visit), 8, 12, 16, 20, and 24 weeks after the subject's last dose of DAC HYP.
Criteria for Evaluation:	
Efficacy:	Clinical relapse assessments, EDSS, MSFC (Timed 25-Foot Walk, Nine-Hole Peg Test with both upper extremities, PASAT 3), SDMT, and brain MRI scan with and without Gd (T2 hyperintense lesions, T1 hypointense lesions, Gd+ lesions, brain atrophy).
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]
[redacted]:	[redacted]
Safety:	Physical and neurological exams; vital signs; clinical laboratory assessments (hematology, blood chemistry, thyroid function panel, urinalysis); urine pregnancy testing; Beck Depression Inventory, Second Edition; immunogenicity assessments; Alcohol Use Disorders Identification Test - Consumption Questionnaire

	(AUDIT-C); and AE and concomitant medication monitoring will be performed in this study. Additional comprehensive hepatic testing will be required for subjects who permanently discontinue study treatment due to elevated liver function tests.
Subject Reported Assessments:	Subject assessment of MSIS-29, EQ-5D quality of life questionnaire (the EQ-5D descriptive system and the respondent's self-rated health on a vertical visual analog scale [EQ-VAS]), Treatment Satisfaction Questionnaire for Medication (before the first use of a PFS and at multiple timepoints during the study), Treatment Satisfaction Survey at selected sites (before the first and last use of an autoinjector), HRU, and HRPQ.
Statistical Methods:	Analyses will generally be descriptive in nature and will focus on data collected during Study 205MS303 only. Efficacy endpoints will be summarized for all subjects using descriptive statistics. For relevant efficacy analyses, the data may be summarized for subjects by previous treatment group (Avonex® or DAC HYP 150 mg). The adjusted ARR and number of new or newly enlarging T2 lesions will be estimated using a negative binomial regression model. The proportion of subjects with sustained progression and the proportion with a relapse will be estimated from the Kaplan-Meier curve. The incidence of AEs and changes in clinical laboratory assessments will also be summarized. An analysis by 3- or 6-month intervals may also be performed. Summary statistics for other safety, efficacy, and pharmacokinetic (PK) endpoints will be presented.
Sample Size Determination:	There is no formal sample size calculation for this study. The number of subjects in this study is determined by the number of subjects who completed Study 205MS301, Study 205MS203, or Study 205MS302, and enrolled in Study 205MS303.
Study Stopping Rules:	Biogen may terminate this study, after informing Investigators, at any time. Investigators will be notified by Biogen or designee if the study is placed on hold, completed, or closed.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS TABLES FOR STUDY 205MS303

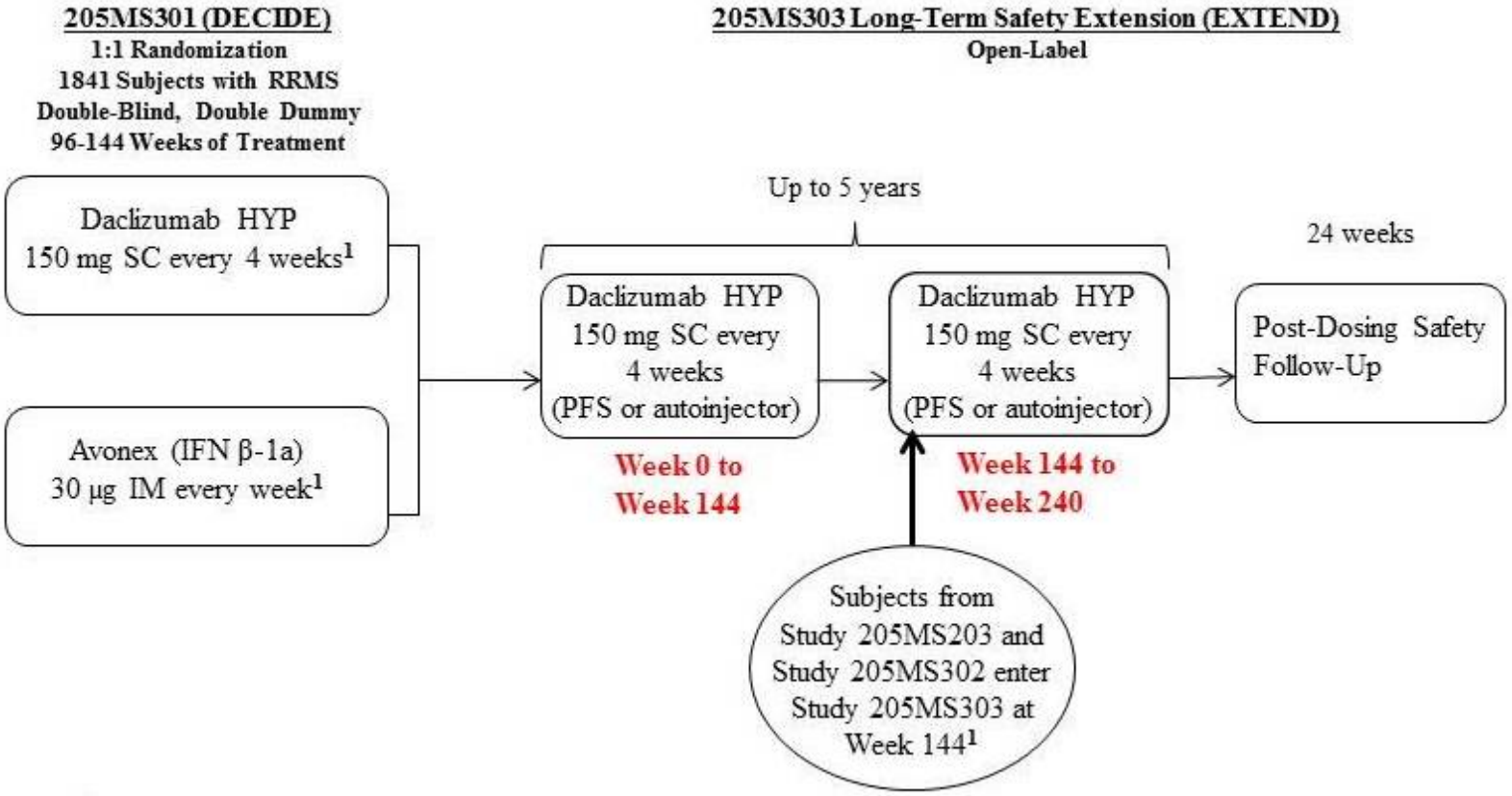
A schematic of the study design is provided in Section 4.1.

The tabulated schedule of events for this study is provided in Section 4.2.

4.1. Study Schematic

Figure 1 shows the design of Study 205MS301 and its open-label extension, Study 205MS303, in which subjects from Study 205MS203 and 205MS302 enter at Week 144.

Figure 1: Study Design



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

4.2. 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 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 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			
[redacted]	X			X	X		X			
[redacted]	X						X			
[redacted]	X			X	X		X			
[redacted]										

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
Anti-Drug Antibody Sample	X			X	X		X			
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 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 [redacted] collection in 205MS301 will be re-approached for this consent upon entry into Study 205MS303. A separate informed consent form may be used for [redacted] sample collection. Samples for [redacted] 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 as per 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 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 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]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. 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 Assessment[4]	X
Anti-Drug Antibody Sample[4]	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 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 (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 Section 14.4.3)							
Liver Function Tests at Central Laboratory[2 3]	X	X	X	X	X	X	X	X
DAC HYP Concentration Assessment				X				X
Anti-Drug Antibody Sample[4]				X				X
Urine Pregnancy Test[5]		X		X		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
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 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.
[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.
[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					X
EDSS					X
Physician Global Assessment Scale	Performed only in subjects with ongoing cutaneous AEs (see 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.
[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 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[redacted] 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[redacted] Assessments				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 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 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 Section 11.8.
[redacted]

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

Table 7: Schedule of Activities: Autoinjector Use by Subjects at Selected Sites

Note: At the Sponsor's discretion, approximately 75-100 eligible subjects from Study 205MS303 at selected sites may begin using autoinjectors on any regularly scheduled dosing day, after they have received at least 6 consecutive monthly doses of DAC HYP by prefilled syringe (PFS) in Study 205MS303. Six consecutive DAC HYP injections will be administered by the subject. Doses 1 and 4 will be supervised during clinic visits, all other doses can be given at home or the clinic. Following the use of autoinjectors, subjects should resume administration of DAC HYP using the PFS.

Note: Subjects are to continue the visit schedule and evaluations listed in Table 1 through Table 6 while they are using autoinjectors.

	Autoinjector 1[1]		Autoinjector 2 4 weeks ±4 days		Autoinjector 3 8 weeks ±4 days		Autoinjector 4[1] 12 weeks ±4 days		Autoinjector 5 16 weeks ±4 days		Autoinjector 6 20 weeks ±4 days	
Tests and Assessments	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**
Informed Consent	X[2]											
Weight	X											
Waist Circumference[3]	X											
Abdominal Fold Thickness[3]	X											
DAC HYP Administration		X		X		X		X		X		X
Injection Site Assessment		X[4]					X					
Subject Assessment of Injection Pain (VAS)[5]		X						X				
Observer Report		X						X				
Treatment Satisfaction Survey[6]	X							X				X
Patient Usability Survey[6]								X				X
DAC HYP Concentration Assessment	X						X					
Anti-Drug Antibody Sample	X						X					

[1]To be administered during a scheduled clinic visit.
[2]Subjects must provide written informed consent for autoinjector use prior to first DAC HYP dose by autoinjector.

[3]The procedure for taking this measurement is provided in the Study Reference Manual.
[4]Injection Site Assessment to be completed as soon as possible but within 10 minutes after the injection at Visit 1.
[5]VAS to be completed as soon as possible after the injection is administered but no later than 10-30 minutes post-injection.
[6]If the subject withdraws from the study or reverts to PFS use prior to receiving all 6 autoinjector doses, the subject should complete the Treatment Satisfaction Survey and the Patient Usability Survey provided for the Autoinjector 6 dosing day before returning to PFS or receiving alternative MS disease modifying therapy.

5. INTRODUCTION

5.1. Profile of Previous Experience with Daclizumab in MS

Background

DAC HYP is a humanized monoclonal IgG1 antibody specific for CD25 (α subunit of the IL-2 receptor). CD25 is expressed at low levels on resting T cells but is rapidly upregulated after T-cell activation, enabling high-affinity IL-2 signal transduction. The primary hypothesis for using DAC HYP to treat MS is to selectively inhibit activated T cells.

Anti-CD25 antibodies have multiple in vitro effects that suggest DAC HYP may directly decrease T-cell activation and proliferation. These include inhibition of IL-2 dependent lymphocyte proliferation, disruption of both IL-2 dependent and independent pathways of IFN-gamma production, and interference in CD28-dependent CD40 ligand expression. In vivo, daclizumab has been confirmed to cause expansion of $CD56^{bright}$ NK cells. This expansion has also been shown to correlate with MRI-defined therapeutic response of daclizumab in MS. $CD56^{bright}$ NK cells are believed to have an immunoregulatory function, and they have been shown to kill activated T cells through a contact-dependent mechanism. Therefore, selective inhibition of activated T cells with DAC HYP may occur through both direct and indirect mechanisms [Bielekova 2009; Bielekova 2004].

Clinical Experience With Daclizumab in Multiple Sclerosis

Initial clinical studies of daclizumab in MS were conducted with material manufactured by F. Hoffmann-La Roche, Ltd. (Roche) at their facilities in Nutley, New Jersey (DAC Nutley) [Bielekova 2004; Rose 2003; Rose 2004], and in Penzberg, Germany (DAC Penzberg) [Wynn 2010]. Study 205MS301 is conducted with DAC HYP, which is produced using a different manufacturing process than the previous versions of daclizumab. DAC HYP has characteristics that are similar to DAC Nutley and DAC Penzberg, although certain differences in physicochemical and biological characteristics have been observed (refer to the Investigator's Brochure for details).

Study 205MS201

Study 205MS201 (SELECT) was a double-blind, placebo-controlled study to evaluate the safety and efficacy of DAC HYP in subjects with RRMS that randomized 621 subjects in a 1:1:1 ratio to receive placebo, 150 mg DAC HYP, or 300 mg DAC HYP SC every 4 weeks over a 52-week treatment period. Among subjects randomized to DAC HYP (150 mg, 300 mg) versus placebo, there was a significantly lower annualized relapse rate (ARR; 0.21, 0.23 versus 0.46; $p < 0.001$), a higher proportion of relapse-free subjects (81%, 80% versus 64%; $p < 0.001$), and a trend towards improvement in the MSIS-29 physical score ($p = 0.128$ for DAC HYP 300 mg versus placebo; $p < 0.001$ for DAC HYP 150 mg versus placebo). There were significant reductions in the mean number of new or newly enlarging T2 lesions at 1 year (2.4, 1.7 versus 8.1) and in the mean number of new Gd+ lesions between Weeks 8 and 24 in a monthly MRI substudy ($n = 307$) (1.5, 1.0 versus 4.8) in the DAC HYP 150 mg and 300 mg groups versus placebo ($p < 0.001$ for all comparisons). The risk of 3-month sustained disability progression at 1 year, a

tertiary study endpoint, was reduced by 57% (p = 0.021) in the DAC HYP 150 mg group and by 43% (p = 0.091) in the DAC HYP 300 mg group.

Analysis of safety data from Study 205MS201 showed that, overall, DAC HYP was well tolerated in this patient population. The most frequently reported (≥10%) adverse events (AEs) for subjects treated with DAC HYP, excluding MS relapse, were nasopharyngitis (14%), and headache and upper respiratory tract infection (10% each). In Study 205MS201, serious adverse events (SAEs) including MS relapses occurred in 26% of placebo-treated subjects and in 16% of subjects treated with DAC HYP. Excluding MS relapses, SAEs occurred in 6% of the placebo group, in 7% of the DAC HYP 150 mg group, and in 9% of the DAC HYP 300 mg group. One DAC HYP-treated subject died due to ischemic colitis following a complicated course of events. Adverse events observed more frequently in DAC HYP-treated patients included an increase in serious infections (2%), serious cutaneous events (1%), and elevations in LFTs (ALT/AST) >5× the upper limit of normal (ULN) (4%).

Upon completion of the 12-month treatment period in Study 205MS201, subjects were eligible to complete up to an additional 12 months of treatment with DAC HYP in a double-blind extension study (Study 205MS202 [SELECTION]), which was completed in 2012. Study 205MS202 also assessed the effects of DAC HYP washout in some subjects who were actively treated in Study 205MS201. Subjects completing Study 205MS202 continued long-term therapy with open-label DAC HYP in extension Study 205MS203 (SELECTED), which evaluated long-term safety and efficacy of DAC HYP monotherapy for up to an additional 144 weeks.

Study 205MS301

Study 205MS301 (DECIDE), a double-blind, randomized, parallel-group, active-controlled study testing the superiority of DAC HYP monotherapy compared to Avonex® (IFN β-1a) in preventing MS relapse, was initiated in May 2010; 1841 subjects with RRMS have been enrolled and randomized in a 1:1 ratio to receive 150 mg DAC HYP given SC every 4 weeks, or Avonex 30 mcg given IM once weekly over a 96- to 144-week treatment period. The primary endpoint was the annualized relapse rate. In this study, DAC HYP demonstrated statistically and clinically meaningful superiority to IFN β-1a, on validated clinical, radiographic, and patient-reported MS outcome measures. DAC HYP reduced the annualized relapse rate by 45% (p<0.0001) compared to IFN β-1a. DAC HYP's treatment effect on relapses was also evidenced by a 41% reduction in the risk of relapse in subjects in the DAC HYP group compared to the IFN β-1a group (p<0.0001). A reduction in the proportion of subjects relapsing was observed as early as 24 weeks after the initiation of treatment and persisted throughout the end of the study. The risk of 12-week confirmed disability progression was reduced by 16% in the DAC HYP group compared with the IFN β-1a group, a result that was not statistically significant (p=0.1575) in the primary analysis. In the pre-specified analysis of 24-week confirmed progression, disability progression was reduced by 27% (p=0.0332) in the DAC HYP group compared with the IFN β-1a group. Overall, the results of the 12-week and 24-week confirmed progression analyses were consistent with each other and supported a clinically meaningful effect of DAC HYP in preventing confirmed disability progression compared with IFN β-1a. DAC HYP reduced the number of new or newly enlarging T2 lesions at Week 96 by 54.4% (p<0.0001) compared to IFN β-1a. The magnitude of the treatment effect was consistent with the results seen on the primary endpoint of annualized relapse rate. The tertiary MRI endpoints

of T2, T1, and Gd-enhancing lesion count and volume were also consistent with the effect on new or enlarging T2 lesions and provide important confirmation of DAC HYP's ability to reduce focal and destructive areas of brain inflammation in RRMS patients. The treatment effect of DAC HYP on new or enlarging T2 lesions and other MRI endpoints was detectable by Week 24 ($p<0.0001$) and was sustained through to the Week 96 and Week 144 MRI at a similar magnitude.

In Study 205MS301, the safety profile of DAC HYP was characterized by an increased incidence of elevations of serum transaminases and serious hepatic events, cutaneous events, infections, and gastrointestinal events. The overall incidence of AEs was balanced across the 2 treatment groups (91% IFN β-1a vs. 91% DAC HYP). The majority of subjects with AEs had events that were mild to moderate in severity. The incidence of subjects with AEs that were considered severe was 14% in the DAC HYP group and 12% in the IFN β-1a group. AEs reported more frequently in the DAC HYP group than in the IFN β-1a group included nasopharyngitis, upper respiratory tract infections, influenza, oropharyngeal pain, rash, and lymphadenopathy, whereas influenza-like illness, pyrexia, chills, and hypertension were reported more frequently in the IFN β-1a group.

There was a higher incidence of SAEs in the DAC HYP group (24%) compared with the IFN β-1a group (21%). Excluding MS relapse, SAEs were reported in 10% of the IFN β-1a group and in 15% of the DAC HYP group. Five deaths were reported in the study (4 subjects in the IFN β-1a group, 1 subject in the DAC HYP group). None of the deaths were considered by the Investigators to be related to study treatment. While safety events were more common in the DAC HYP-treated subjects compared with IFN β-1a-treated subjects, the types of events were generally manageable with standard medical care, monitoring, and treatment discontinuation, as appropriate for the event. Overall, the results of the study support a positive benefit/risk profile for DAC HYP.

The PK and immunogenicity of DAC HYP 150 mg SC administered every 4 weeks using a prefilled syringe (PFS) were investigated in 26 subjects in Study 205MS302 (OBSERVE), a single-arm, open-label study that enrolled a total of 113 subjects with RRMS.

Refer to the Investigator's Brochure for additional details.

5.2. Study Rationale

This study will evaluate the long-term safety, efficacy, and immunogenicity of DAC HYP in subjects with MS who have completed Study 205MS301, Study 205MS203, or Study 205MS302. In addition, this study will assess the safety, tolerability, and efficacy of switching to DAC HYP in subjects previously on long-term treatment with interferon β-1a in Study 205MS301.

5.3. Rationale for Dose and Schedule Selection

The existing scientific and clinical experience with DAC HYP supports its further investigation in the management of MS. The DAC HYP dose and schedule in this protocol were used in the pivotal Phase 3 Study 205MS301 and will be the treatment regimen used in the commercial

setting. The same DAC HYP dose and schedule were used in Study 205MS203 and Study 205MS302.

A single-use, disposable PFS will be provided to simplify the injection process and thereby reduce the burden of administering a long-term therapy such as DAC HYP in the clinic or at home. At the Sponsor's discretion, single-use autoinjectors containing PFS may be used to administer DAC HYP in 75-100 subjects from Study 205MS303 at selected sites. Autoinjectors will be dispensed to each participating subject for use on up to 6 consecutive scheduled dosing days.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

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.

6.1.2. Secondary Objectives

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 PFS
- To assess the safety, tolerability, and efficacy of switching to DAC HYP in subjects previously on long-term treatment with interferon β-1a in Study 205MS301

6.1.3. Exploratory Objective

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoints

- Incidence of AEs and SAEs

6.2.2. Secondary Endpoints

- 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 (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 (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

7. STUDY DESIGN

7.1. Study Overview

The design of Study 205MS303 is provided in Figure 1. Approximately 1600 subjects will enroll in this study. This includes approximately 1200 subjects who completed Study 205MS301. Additionally, approximately 400 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 an 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).

7.2. Overall Study Duration and Follow-Up

The study period will consist of Baseline/Entry Visit assessments, treatment (for up to approximately 5 years), and post-treatment safety follow-up visits (from approximately 4 to 24 weeks after the last dose of DAC HYP).

7.2.1. Baseline/Entry Visit Assessments

Subjects Entering From Study 205MS301

Tests/assessments performed at the subject's last visit in Study 205MS301 and within 28 days of the subject's first dose of DAC HYP (Week 0) in Study 205MS303 may be used as the baseline for Study 205MS303; if final Study 205MS301 tests/assessments are not performed within the 28-day window, they must be repeated upon entry into Study 205MS303 and before the first dose of DAC HYP is administered.

Subjects Entering From Study 205MS203 or Study 205MS302

The Week 144 Visit of Study 205MS303 will be the Entry Visit for subjects enrolled from Study 205MS203 or Study 205MS302. 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. Central LFT testing is *mandatory* at the Entry Visit.

7.2.2. Treatment

Subjects from Study 205MS301 continuing in Study 205MS303 will receive DAC HYP treatment for up to approximately 5 years, or until availability of commercial product (whichever is sooner), under this protocol. Subjects from Study 205MS203 and Study 205MS302 entering Study 205MS303 at Week 144 will have DAC HYP treatment for up to approximately 2 years, or until availability of commercial product (whichever is sooner), under this protocol.

At the Sponsor's discretion, 75-100 subjects from Study 205MS303 at selected sites may dose with DAC HYP using a single-use autoinjector that contains a PFS on 6 consecutive scheduled dosing days (Table 7).

Eligible subjects will have clinic visits scheduled every 4 weeks for up to Week 12 in this study, followed by clinic visits scheduled every 12 weeks.

Subjects who are dosing at home must be instructed to not administer their monthly dose of DAC HYP until the study site has contacted them to authorize dosing (after the *Study Neurologist* or their backup has reviewed LFT results obtained during the previous 32 days). Subjects need to record the date and time of dosing in their diary if they are dosing at home.

A window of ±4 days applies to scheduled visits and home dosing.

7.2.3. Post-Treatment Long-Term Follow-Up

In addition to the End of Treatment Visit (Week 240), which occurs 4 weeks (±4 days) after the subject's last dose of DAC HYP, subjects are to return to the study site for follow-up visits at 8, 12, 16, 20, and 24 weeks (±10 days) after the last dose of DAC HYP.

7.3. Study Stopping Rules

Biogen may terminate this study, after informing Investigators, at any time. Investigators will be notified by Biogen or designee if the study is placed on hold, completed, or closed.

7.4. End of Study

The End of Study is last subject, last visit for final collection of data.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the 205MS303 Baseline/Entry Visit or at the timepoint specified in the individual eligibility criterion listed (Note: Week 0/Day 1 is the Baseline Visit in Study 205MS303 for 205MS301 subjects. Week 144 is the Entry Visit in Study 205MS303 for 205MS203 and 205MS302 subjects):

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
2. Must be a subject currently participating in Study 205MS301 who has completed either the Week 144 Visit or the End of Study Visit (Week 96) of Study 205MS301 OR subject currently participating in Study 205MS203 or Study 205MS302.
3. Women of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 4 months after their last dose of study treatment.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the Study 205MS303 Baseline/Entry Visit or at the timepoint specified in the individual criterion listed (Note: Week 0/Day 1 is the Baseline Visit in Study 205MS303 for 205MS301 subjects. Week 144 is the Entry Visit in Study 205MS303 for 205MS203 and 205MS302 subjects):

Medical History

1. Any subject who permanently discontinued study treatment in Study 205MS301, Study 205MS203, or Study 205MS302 prior to the end of the study treatment period, or had an early termination in those studies OR any subject who has completed all the safety follow-up visits after Week 144 of Study 205MS303 per the original protocol.

   Note: Subjects for whom dosing was temporarily suspended in Study 205MS301, Study 205MS203, or Study 205MS302 are not excluded from participation in this extension study if the criteria for resuming DAC HYP treatment under the parent study protocol have been met at the time of enrollment into Study 205MS303.
2. Any significant change in the subject's medical history that would preclude administration of DAC HYP, including laboratory tests or a current clinically significant condition that, in the opinion of the Investigator, would have excluded the subject's participation in Study 205MS301, Study 205MS203, or Study 205MS302. The Investigator must re-review the subject's medical fitness for participation and consider any factors that would preclude treatment in Study 205MS303, including:

- History of any significant cardiac, endocrine, hematological, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurological (other than MS), and/or other major disease (e.g., malignancy) that would preclude administration of DAC HYP.
- Clinically significant laboratory abnormalities (hematology and blood chemistry) from the most recently available test in the parent study, as determined by the Investigator. Laboratory findings mandating discontinuation of study treatment as defined in parent study protocol are exclusionary.

3. Other medical reasons that, in the opinion of the Investigator and/or Biogen, make the subject unsuitable for enrollment.

Treatment History

4. Treatment with any prohibited concomitant medication during the parent study, as described in Section 11.5 of this protocol.

   Note: Subjects who start an approved, open-label IFN β preparation after completion of dosing in Study 205MS301 are not excluded, but IFN β treatment must be discontinued before the first dose of DAC HYP in Study 205MS303 is given.

Miscellaneous

5. Female subjects who are currently pregnant or breastfeeding, or considering becoming pregnant while in the study.
6. History of drug or alcohol abuse (as defined by the Investigator) at any time after the start of Study 205MS303 or any of the parent studies.
7. Unwillingness or inability to comply with the requirements of the protocol, including the presence of any condition (physical, mental, or social) that is likely to affect the subject's ability to comply with the protocol.

9. ENROLLMENT AND REGISTRATION PROCEDURES

9.1. Enrollment and Screening

Subjects must be consented before any procedures are performed. At the time of consent, the subject will be enrolled into the study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the enrollment log. Any test/assessment done at the subject's last visit in the parent studies and within 28 days of the subject's first dose in Study 205MS303 will be used as the baseline for Study 205MS303 and does not need to be repeated at entry into Study 205MS303 (Note: Central LFT testing is mandatory at the Week 144 Entry Visit for subjects rolling over from Study 205MS203 and Study 205MS302 into Study 205MS303). Testing required at the Baseline/Entry Visit that is done outside the 28-day window must be repeated upon entry into 205MS303.

9.2. Registration of Subjects

Subjects should be registered in the study after the Investigator has verified that they are eligible per the criteria in Section 8.1 and Section 8.2 and all baseline assessments have been performed. No subject may begin treatment prior to enrollment and registration.

As confirmation, the Investigator will be provided with written verification of the subject's registration by mail or fax.

Refer to the Study Reference Manual for details on registration.

10. STUDY TREATMENT MANAGEMENT

Study treatment (PFS or autoinjectors) must be stored in a secure location. Accountability for study treatment is the responsibility of the Investigator. Study treatment must only be dispensed by a Pharmacist or medically qualified staff, and stored in a secure, monitored, locked location in accordance with the conditions specified in current prescribing information or the Directions for Handling and Administration (DHA) included in the Study Reference Manual.

Study treatment is to be dispensed only to subjects enrolled in this study. Once treatment is dispensed to a subject, it can only be used by that subject.

10.1. DAC HYP

Prefilled Syringe

DAC HYP is supplied as a liquid in a 1-mL BD-staked PFS with a 29 gauge × ½ inch needle, comprising 150 mg/mL DAC HYP plus excipient materials (sodium succinate, sodium chloride, and polysorbate 80). At a minimum, the study treatment label will include a study reference code, drug identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. Depending on country requirements, the Investigator's name may also appear on the label. DAC HYP must not be used after the expiration date unless a written notification of an expiration date extension is provided by Biogen.

Autoinjector

The DAC HYP PFS is assembled inside a single-use, disposable autoinjector device.

The autoinjector label will include the DAC HYP product code "BIIB019," conditions for storage, Sponsor, and a caution statement. Depending on country requirements, the Investigator's name may also appear on the label. DAC HYP must not be used after the expiration date unless a written notification of an expiration date extension is provided by Biogen.

10.2. DAC HYP Preparation

Each DAC HYP PFS or autoinjector contains only one dose and is intended for SINGLE USE INJECTION ONLY. Any drug that remains in the PFS after injection must not be used for another dose or another subject.

After Week 12, subjects may choose to administer their DAC HYP dose at home, either by administering the injection themselves or by a designated caregiver. The subject or designated caregiver will be trained by clinic staff on the correct PFS injection technique prior to initiating at-home DAC HYP dosing.

Autoinjectors may be provided to selected sites and will be supplied injection-ready. Study personnel or subjects at these sites do not need to insert the PFS into the device. Study site personnel will receive appropriate autoinjector training from a Sponsor-designated trainer prior to initiation of autoinjector use.

10.3. DAC HYP Accountability

The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), any amount returned by subject, and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all PFS and autoinjectors, both used and unused, must be saved for study treatment accountability. At the end of the study, a final reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed or returned to Biogen.

A written explanation will be provided for any discrepancies. After reconciliation, the Investigator must destroy or return to Biogen all unused study treatment PFS and autoinjectors as instructed by Biogen.

If any study treatment supplies are to be destroyed at the site, the Principal Investigator(s) must obtain prior approval by Biogen. The Principal Investigator(s) must notify Biogen, in writing, of the method, date, and location of destruction.

11. TREATMENT OF SUBJECTS

Biogen will provide DAC HYP (PFS or autoinjectors) to all study sites.

Refer to Section 10 (Study Treatment Management) for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

11.1. Study Treatment Schedule and Administration

All subjects will receive one DAC HYP 150 mg SC injection every 4 weeks.

DAC HYP will be administered by clinic staff at the monthly visits for the first 12 weeks of this study. After Week 12, administration of DAC HYP may occur in the clinic or at home (by the subject or by a designated caregiver) depending on subject preference. The subject or designated caregiver will be trained by clinic staff on the correct injection technique prior to initiating at-home DAC HYP dosing. **Subjects who are dosing at home must be instructed to not administer their monthly dose of DAC HYP until the study site has contacted them to authorize dosing. A window of ±4 days applies to home dosing.**

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. Study personnel should promptly inform the subject whether the monthly dose of DAC HYP should be administered or whether study treatment is to be withheld based on the dosing criteria defined in Section 11.7.2. Study personnel will document this communication with the subject. Subjects should administer DAC HYP as soon as permission has been given as per the dosing schedule. Subjects need to record the date and time of dosing in their diary if they are dosing at home.

11.2. Placebo or Reference Product Agents

Not applicable.

11.3. Treatment Precautions

Anaphylactic-like and hypersensitivity reactions following administration of proteins such as DAC HYP can occur. DAC HYP will be administered in the clinic under observation by qualified medical personnel for the first 12 weeks of this study. Subjects will be educated by the *Study Neurologist* or their back-up on the signs and symptoms of hypersensitivity reactions and instructed to contact the site if they experience any acute or delayed reactions post injection.

11.4. Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by study site staff.

After Week 12, subjects who choose to administer their DAC HYP dose at home will record treatment in a dosing diary. The diary will be reviewed periodically by study site staff and the Clinical Monitor throughout the study. Subjects who choose at-home administration will return used PFS or autoinjectors to the clinic at their scheduled clinic visits.

11.5. Concomitant Therapy

A concomitant therapy is any drug or substance administered from the Baseline/Entry Visit until completion of the study. A concomitant procedure is defined as any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed from the time the subject is enrolled in the study until the subject's final clinic visit.

11.5.1. Concomitant Therapies That are Prohibited

Concomitant treatment with any of the following is not allowed during the study, unless approved by the Biogen Medical Director(s) or the Advisory Committee, or as otherwise described in this protocol:

- Any alternative disease modifying MS drug treatment such as chronic immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to: IFN-β, IFN-α, glatiramer acetate, cyclophosphamide, methotrexate, mycophenolate mofetil, mitoxantrone, cyclosporine, azathioprine, or related products).
- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications.
- Any monoclonal antibodies other than DAC HYP.
- Intravenous immunoglobulin (IVIg), plasmapheresis or cytapheresis, total lymphoid irradiation, or T-cell or T-cell receptor vaccination.
- Any systemic steroid therapy including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IV methylprednisolone (IVMP), except for protocol-defined treatment of relapses as described in Section 14.6 or for limited, acute treatment of general medical conditions as per the discretion of *Study Neurologist*. Steroids that are administered by non-systemic routes (e.g., topical, inhaled) are allowed.
- Antineoplastic or chemotherapeutic agents, including, but not limited to, cyclophosphamide, methotrexate, azathioprine, cladribine, cytarabine, or flutamide.
- Valproic acid, carbamazepine, lamotrigine, or phenytoin. Subjects who have been taking **1** of these medications at a stable dose for at least 6 consecutive months may continue to receive the medication and may continue study treatment under this protocol. However, if any of these medications must be initiated or dose escalated, study treatment must be permanently discontinued as described in Section 11.8.

  Subjects who have been treated with any of these medications (which have not been approved by the Biogen Medical Director[s]) for fewer than 6 consecutive months, or who take more than 1 of these medications, or who have had dose escalations within the past 6 months must do 1 of the following:

  - Discontinue the medication (any agent used for <6 consecutive months must be discontinued). Subjects may use an alternative medication allowed by the protocol, if needed.
  - Subjects taking more than 1 agent must reduce to ≤1 agent (any agent that is continued must have been taken for at least 6 consecutive months).
  - In the case of dose escalation, revert to a previous dose that had been used for at least 6 months.
  - Permanently discontinue study treatment.
- Isoniazid, propylthiouracil, or nimesulide. Subjects who currently take any of these medications must either change to an alternative medication allowed by the protocol or permanently discontinue study treatment.

Subjects who receive any of these restricted medications may be required to permanently discontinue study treatment as outlined in Section 11.8. Subjects who permanently discontinue study treatment will be allowed to receive IVMP as treatment for MS relapse while they are participating in the study, as described in Section 11.8.

11.5.2. Concomitant Therapies That Require Precaution

Caution should be used when administering drugs of known hepatotoxic potential, including non-prescription products, concomitantly with DAC HYP. Patients should be observed for signs and symptoms of hepatic dysfunction, particularly when DAC HYP is used concomitantly with other potentially hepatotoxic medicinal products. Use of the following medications is strongly discouraged during the study:

- Herbal or dietary supplements.
- Agents that have established risks of hepatotoxicity or serious rash according to labeling information (examples include, but are not limited to, amoxicillin/clavulanate, clarithromycin, ketoconazole, minocycline, nitrofurantoin, trimethoprim/sulfamethoxazole, diclofenac, sulfasalazine, amiodarone, methyldopa, nefazodone, halothane, and tizanidine). Alternatives to these therapies should be used whenever possible.

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue is not restricted, but should be optimized as early as possible in an attempt to maintain consistent treatment for the duration of the study. Symptomatic therapies for spasticity that have established risks of hepatotoxicity are strongly discouraged for use during the study. Initiation of Fampridine-SR after enrollment is permitted, including when it is used in the acute management of protocol-defined relapse (as described in Section 14.6).

11.5.3. Concomitant Therapy Guidelines

Subjects should be instructed not to start taking any new medications, including non-prescribed medications, unless they have received permission from the Investigator. The use of live vaccines in humans concurrently treated with daclizumab has not been explored; therefore live vaccines should not be administered to MS subjects who are being treated with DAC HYP.

The use of concomitant therapies or procedures defined in this section must be recorded on the subject's case report form (CRF), according to instructions for CRF completion (Note: concomitant therapies in the parent study that continued at Study 205MS303 entry must be recorded on the CRF). AEs related to administration of these therapies or procedures must be documented on the appropriate CRF. For subjects who prematurely discontinue study treatment, all concomitant medications should be recorded throughout the remainder of the subject's participation in the study.

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If DAC HYP is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

11.7. Treatment Schedule Modifications

Subjects who experience a significant change in their medical status (e.g., neurological worsening/suspected MS relapse, possible injection-site reaction, infection, cutaneous AE, fever, abdominal pain, persistent diarrhea, jaundice, nausea, vomiting, pruritus) must contact the *Study Neurologist* as soon as possible and no more than 48 hours after symptom onset. The subject should then be evaluated by the *Study Neurologist* within no more than 72 hours for physical and neurological assessments and further treatment recommendations if appropriate. These subjects should not administer additional DAC HYP until they have been evaluated by the *Study Neurologist* or their backup.

Unscheduled PK/[redacted] Visit (Table 6) can be performed in subjects who have evidence of significant changes in their medical conditions (as assessed by the Investigator). This visit must be approved by the Biogen Medical Director in advance.

Additional treatment considerations for specific events are described below.

11.7.1. Infections

Subjects who have evidence of a clinically significant infection will be instructed to notify the *Study Neurologist* or their backup within 48 hours of onset, and scheduled dosing of DAC HYP may be withheld. If the subject's infection resolves within 2 weeks of the scheduled DAC HYP dose, the subject may receive the previously scheduled dose of DAC HYP at that time. If the infection has not resolved within the 2 weeks, dosing of DAC HYP will remain suspended, and the subject will miss dosing until the infection is resolved.

11.7.2. Elevated Liver Function Tests

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, and must be within the protocol-required limits shown below (LFT procedures are described in Section 14.4.3).

If a subject develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark

urine), promptly measure serum transaminases and interrupt or discontinue treatment with DAC HYP, as appropriate.

Table 8 summarizes how subjects with elevated LFTs will be managed during the study.

11.7.2.1. ALT/SGPT or AST/SGOT >3 to ≤5×ULN

In subjects with alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) or aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) >3 to ≤5×ULN and total bilirubin ≤2×ULN, the following should be performed:

- Study treatment *must be temporarily suspended*.
- LFT elevation should be confirmed as soon as possible but no later than 1 week by a repeat test performed at the central laboratory.
- Tests are repeated weekly until both ALT/SGPT and AST/SGOT are <2×ULN.
- After a temporary suspension, dosing of DAC HYP may be resumed when ALT/SGPT and AST/SGOT are <2×ULN provided that the criteria for permanent discontinuation have not been met (see Section 11.8).

In subjects with ALT/SGPT or AST/SGOT >3 to ≤5×ULN and total bilirubin >2×ULN, the following should be performed:

- Study treatment must be withheld.
- LFT elevation should be confirmed as soon as possible but no later than 1 week by a repeat test performed at the central laboratory.
- If the elevation is confirmed on repeat testing, study treatment *must be permanently discontinued*. Otherwise, follow the guidelines in Section 11.7.2.4.

In addition to these conditions, study treatment must be temporarily suspended and managed per the guidelines in Section 11.7.2.4 if a subject develops any other clinically significant hepatic condition in the opinion of the Investigator, including jaundice.

11.7.2.2. ALT/SGPT or AST/SGOT >5×ULN

In subjects with an ALT/SGPT or AST/SGOT >5×ULN, regardless of total bilirubin level, the following should be performed:

- Study treatment must be withheld.
- LFT elevation should be confirmed as soon as possible but no later than 1 week by a repeat test performed at the central laboratory.
- If the elevation of >5×ULN is confirmed on repeat testing, study treatment *must be permanently discontinued*. Otherwise, follow the guidelines in Section 11.7.2.4.

11.7.2.3. Second Temporary Suspension Due to Elevated LFTs

If a subject has treatment suspended for an LFT elevation and has also had a prior treatment suspension for an LFT elevation during DAC HYP use, DAC HYP must be permanently

discontinued unless an alternative explanation for the LFT elevation unrelated to DAC HYP use is clearly identified by the Investigator.

11.7.2.4. Management Guidelines Following Temporary Suspension or Permanent Discontinuation

All subjects with elevated LFTs **(ALT/SGPT or AST/SGOT >3×ULN)** should be managed per the guidelines below.

- Study treatment must be temporarily suspended and LFT elevation should be confirmed as soon as possible but no later than 1 week by a repeat test performed at the central laboratory. In cases where LFTs cannot be performed via the central laboratory, repeat LFT results from a local laboratory can be used for confirmation.
- After a temporary suspension, dosing of DAC HYP may be resumed when ALT/SGPT and AST/SGOT are <2×ULN provided that the criteria for permanent discontinuation have not been met (see Section 11.8).
- For subjects that have had DAC HYP treatment suspended for >8 weeks due to elevated LFTs, Investigators should consider whether subjects should permanently discontinue treatment with DAC HYP in order to allow treatment with another disease-modifying therapy and minimize the risk of return of MS disease activity. Such decisions are at the discretion of the Investigators and their assessment of risks and benefits.
- All subsequent testing after a temporary treatment suspension or permanent discontinuation is required to be performed centrally *at least weekly* until the LFT elevation is <2×ULN.
- Monitoring of LFT elevations will occur for up to 6 months after the last DAC HYP dose has been administered. If after 6 months the LFT remains elevated at ≥2×ULN, the Investigator or health care professional should continue to monitor the LFT as clinically appropriate; any relevant follow-up data should be reported to the Sponsor as a spontaneous report.
- A careful review of all concomitant medications must be documented. The Investigator should consider discontinuation of all potential hepatotoxic medications. All recently started or non-essential concomitant medications should be suspended until the LFT elevation is <2×ULN.
- An Unscheduled Hepatic Assessment Visit as soon as possible but within 1 week should be performed in the event of permanent discontinuation due to elevated LFTs (see Table 6).
- Subjects should be referred to a hepatic specialist if medically indicated. In consultation with the hepatic specialist, a full evaluation of alternative causes of liver injury should be performed. Additional hepatic studies should be performed according to local standard of care. The central laboratory may be utilized for additional hepatic testing per Investigator request. If testing for viral hepatitis is negative, LFT elevations are not improving, DAC HYP is suspected as the cause of

the LFT elevation, and there are no known contraindications for corticosteroids, then, in continued consultation with the hepatic specialist, empiric treatment with systemic corticosteroids should be considered.

Table 8: Summary of Management of Subjects With Elevated Liver Function Tests

Total Bilirubin	Serum Transaminases		
	ALT/SGPT or AST/SGOT >3 to ≤5×ULN	**ALT/SGPT or AST/SGOT >5×ULN**	**Second Temporary Suspension Due to Elevated ALT/SGPT or AST/SGOT**
≤2×ULN	Temporarily suspend dosing[1] Weekly LFT until both ALT/SGPT and AST/SGOT are <2×ULN	Withhold dosing[2] Repeat test as soon as possible but no later than 1 week after the elevation If confirmed, permanently discontinue study treatment. Otherwise, follow the guidelines in Section 11.7.2.4.	Withhold dosing[2] Repeat test as soon as possible but no later than 1 week after the elevation If confirmed, permanently discontinue study treatment. Otherwise, follow the guidelines in Section 11.7.2.4.
>2×ULN	Withhold dosing[2] Repeat test as soon as possible but no later than 1 week after the elevation If confirmed, permanently discontinue study treatment. Otherwise, follow the guidelines in Section 11.7.2.4.	As above	As above

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFT = liver function test; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal.

[1] Subjects should be managed according to the following guidelines: LFT elevation should be confirmed as soon as possible but no later than 1 week; LFT is required to be performed *at least weekly* until the LFT elevation is <2×ULN; dosing of DAC HYP may be resumed when ALT/SGPT, AST/SGOT, and bilirubin are <2×ULN, provided that the criteria for permanent discontinuation have not been met; a careful review of all concomitant medications must be documented; and if treatment is permanently discontinued, subjects should be referred to a hepatic specialist if medically indicated.

[2] Subjects should be managed according to the following guidelines: LFT elevation should be confirmed as soon as possible but no later than 1 week; LFT is required to be performed *at least weekly* until the LFT elevation is <2×ULN; an Unscheduled Hepatic Assessment Visit is performed as soon as possible but within 1 week of the elevation; a careful review of all concomitant medications must be documented; and if treatment is permanently discontinued, subjects should be referred to a hepatic specialist if medically indicated.

11.7.3. Cutaneous Events

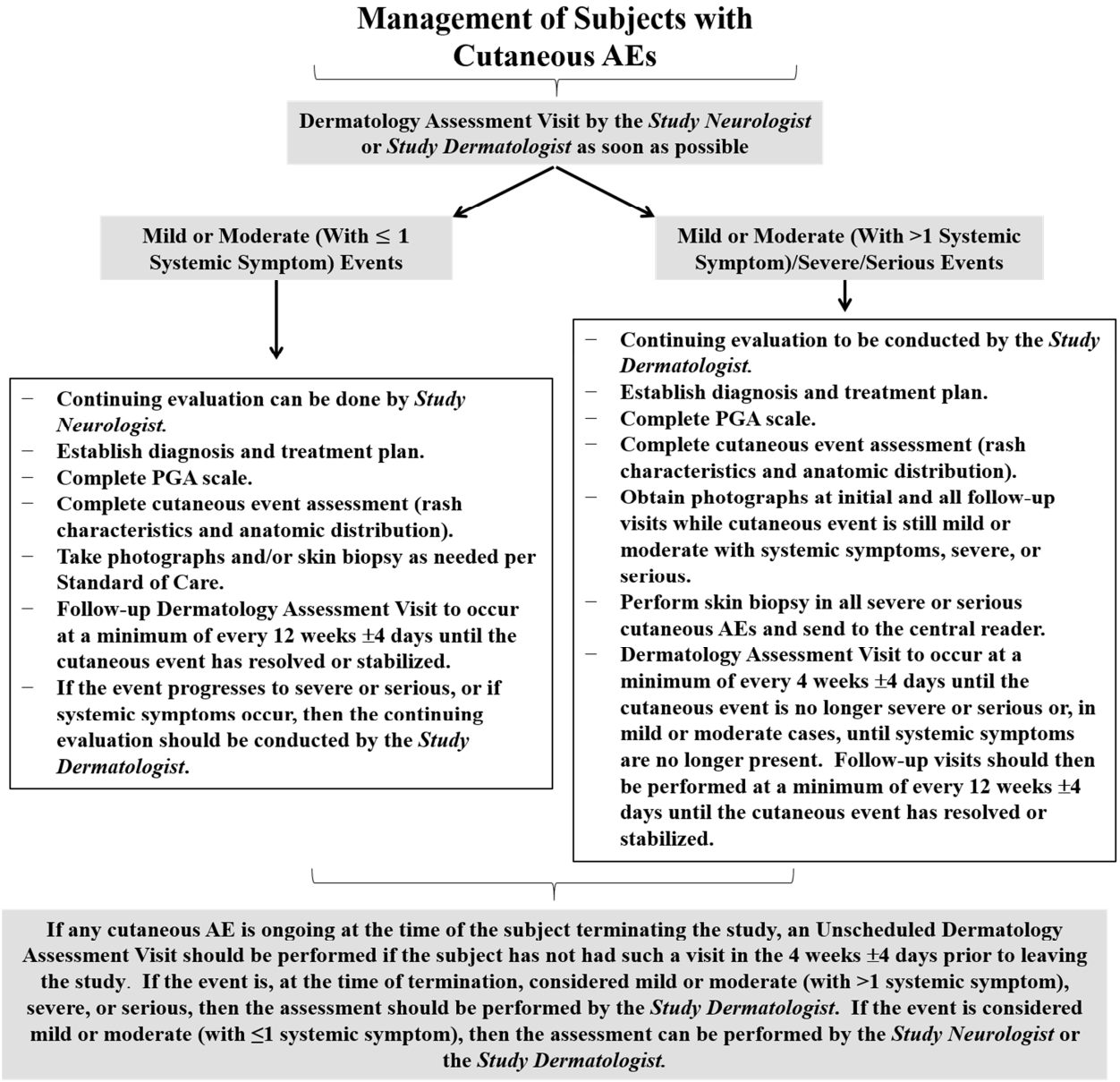
Subjects participating in Study 205MS303 who develop a mild or moderate cutaneous AE that is not associated with more than 1 systemic symptom or sign do not need to be evaluated by the *Study Dermatologist*; the *Study Neurologist* can complete the Unscheduled Dermatology

Assessment Visit as soon as possible. In such cases, the *Study Neurologist* should complete the Physician's Global Assessment Scale form. Any subject participating in Study 205MS303 who develops 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) needs to be evaluated by the *Study Dermatologist* at an Unscheduled Dermatology Assessment Visit as soon as possible. Systemic symptoms associated with a mild or moderate cutaneous AE that would require evaluation by a dermatologist may include, but are not limited to, fever, hematological abnormalities, abnormalities of internal organs (as may be detected by renal and liver function tests), and lymphadenopathy.

If the *Study Neurologist* sees the subject prior to the *Study Dermatologist*, the *Study Neurologist* should, if possible, assess the cutaneous AE prior to the subject seeing the *Study Dermatologist*. The information from the assessment by the *Study Neurologist* will be captured in addition to the information from the assessment by the *Study Dermatologist*. If the cutaneous AE is assessed by the *Study Dermatologist* as a mild or moderate cutaneous AE not associated with more than 1 systemic symptom or sign, any follow-up visits can be conducted by the *Study Neurologist*.

A flowchart is presented in Figure 2 to summarize how these subjects will be managed during the study.

Figure 2: Flowchart for Management of Subjects With Cutaneous AEs



AE = adverse event; PGA = Physician's Global Assessment.

Photographs can be taken by the *Study Neurologist* or designee at these visits for mild or moderate cutaneous AEs that are associated with more than 1 systemic symptom or sign, severe cutaneous AEs (with or without systemic symptoms or signs), or serious cutaneous AEs (with or without systemic symptoms or signs) if they have not been taken by the *Study Dermatologist* (see Section 4.2). The subjects will be asked for their consent to having their dermatological photographs used for educational purposes, if required.

Skin biopsy must be performed in subjects with severe or serious cutaneous AEs (with or without systemic symptoms or signs) at the Unscheduled Dermatology Assessment Visit, unless medically contraindicated.

Skin biopsies from study subjects with severe or serious cutaneous AEs (with or without systemic symptoms or signs) will be sent to a centralized laboratory for evaluation. Results of the skin biopsy will be provided back to the *Study Dermatologist* as soon as possible with a copy sent to the sponsor. Skin biopsy may also be locally evaluated per the discretion of the *Study Dermatologist*.

If the cutaneous AE is suspected to be an allergic or hypersensitivity reaction to study treatment, study treatment must be suspended until consultation with the *Study Dermatologist.* Under the consultation of the *Study Dermatologist*, the subject should also withhold all other non-essential medications, including protocol-required medications (as appropriate), and non-prescription drugs and supplements, at least until the cutaneous event has resolved. The decision to permanently discontinue study treatment should be made by the Investigator in consultation with the *Study Dermatologist*. If an allergic or hypersensitivity reaction to study treatment is confirmed, study treatment must be permanently discontinued.

11.7.4. Gastrointestinal Events of Inflammatory Colitis

For any subject participating in Study 205MS303 who develops symptoms of inflammatory colitis (e.g., persistent diarrhea and abdominal cramps, blood in the stool, and fever), treatment with DAC HYP should be stopped and the subject should be referred to a specialist. Some subjects with mild colitis who require DAC HYP therapy may be able to continue the study treatment if the benefit-risk profile is considered positive per Investigator's assessment and the subject's informed decision.

11.7.5. Lymphadenopathy or Lymphadenitis Events

Any subject participating in Study 205MS303 who develops clinically significant lymphadenopathy or lymphadenitis should be referred to a specialist. Additional diagnostic tests, such as imaging, blood tests, and/or biopsy, should be performed according to the local standard of care.

When diagnostic tests are performed, the results may be requested for internal safety review and, when available, biopsy materials will be sent to a centralized laboratory for evaluation. The results of the central laboratory biopsy report will be provided back to the *Study Neurologist* as soon as possible, with a copy sent to the Sponsor.

Study treatment may continue or be resumed after a temporary suspension in cases of uncomplicated lymphadenopathy if the benefit-risk profile is considered positive per the Investigator’s assessment and the subject’s informed decision. Subjects who discontinued study treatment for any reason while presenting with ongoing lymphadenopathy or lymphadenitis should be followed until the lymphadenopathy or lymphadenitis has stabilized or resolved or the study has terminated, whichever comes first.

11.8. Discontinuation of Study Treatment

A subject *must* permanently discontinue DAC HYP for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.5.4.
- The subject experiences a hypersensitivity or suspected allergic reaction (e.g., anaphylaxis and anaphylactoid reactions) to study treatment.
- The subject develops a chronic viral infection (e.g., hepatitis C, HIV).
- The subject develops elevated LFTs that meet any of the following criteria:
  - ALT/SGPT or AST/SGOT >5×ULN that is confirmed by a repeat test performed within 1 week
  - ALT/SGPT or AST/SGOT >3×ULN with concomitant elevation of total bilirubin >2×ULN that is confirmed by a repeat test performed within 1 week
  - If a subject has treatment suspended for an LFT elevation and has also had a prior treatment suspension for an LFT elevation during DAC HYP use, DAC HYP must be permanently discontinued unless an alternative explanation for the LFT elevation unrelated to DAC HYP use is clearly identified by the Investigator.
- The subject experiences a cutaneous AE, which the Investigator (in consultation with the *Study Dermatologist*) considers to be a generalized allergic or hypersensitivity reaction to study treatment (see Section 11.7.3).
- The subject experiences inflammatory colitis, except in subjects with mild colitis who require DAC HYP therapy and have a positive benefit-risk profile per Investigator's assessment and the subject's informed decision (see Section 11.7.4).
- The subject requires treatment with any of the disallowed concomitant medications, unless approval is given by the Biogen Medical Director(s) or Advisory Committee. Note: IVMP for treatment of a protocol-defined relapse is allowed as detailed in the protocol (see Section 11.5). Treatment with valproic acid, carbamazepine, lamotrigine, or phenytoin is only allowed under the conditions detailed in the protocol.
- The subject experiences a medical emergency that necessitates permanent discontinuation of treatment.
- The subject desires to discontinue treatment under this protocol.
- At the discretion of the Investigator for medical reasons or for non-compliance.
- Upon confirmatory tests 1 month apart, the subject's hematology results are as follows in the absence of an identified reversible cause by the Investigator (e.g., infection):
  - white blood cell count is <2500 cells/μL, or
  - lymphocyte count is <800 cells/μL, or

  - platelet count is <75,000 cells/μL

    Subjects who meet the above criteria must have study treatment withheld until hematology retest results are available.

- The subject experiences severe depression and/or suicidal ideation. Severe depression is defined as any episode that requires hospitalization, or at the discretion of the Investigator.

Subjects who permanently discontinue DAC HYP treatment should complete all post-treatment safety follow-up evaluations (see Section 14.10).

Subjects who permanently discontinue study treatment may be treated with alternative approved MS therapies according to local practices, and should remain in the study and complete safety follow-up evaluations as described in Section 4.2 and Section 13. However, subjects who desire to discontinue participation in this study or are unwilling or unable to comply with the protocol should be withdrawn from the study and complete an Early Termination Visit. As noted in Table 6 (Footnote 3) and Section 11.9, subjects terminating treatment with an ongoing cutaneous AE require an Unscheduled Dermatology Assessment Visit prior to leaving the study if the subject has not had such a visit in the 4 weeks±4 days prior to leaving the study. If the event is, at the time of termination, 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), then the assessment should be performed by the *Study Dermatologist*. If the event is considered mild or moderate and is not associated with more than 1 systemic symptom or sign, then the assessment can be performed by the *Study Neurologist* or the *Study Dermatologist*.

The reason(s) for discontinuation of treatment must be recorded in the subject's CRF.

11.9. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.

Subjects who withdraw from the study should complete the End of Treatment Visit assessments as described in Section 14.10 (subjects should be encouraged to complete all other post-treatment safety follow-up visits). The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

For subjects with an ongoing mild or moderate cutaneous AE that is associated with more than 1 systemic symptom or sign, severe cutaneous AE (with or without systemic symptoms or signs), or serious cutaneous AE (with or without systemic symptoms or signs), the *Study Dermatologist* should perform an Unscheduled Dermatology Assessment Visit if this visit has not been performed in the 4 weeks±4 days prior to leaving the study (see Section 11.7.3). If the event is considered mild or moderate and is not associated with more than 1 systemic symptom or sign, then the assessment can be performed by the *Study Neurologist* or the *Study Dermatologist.*

12. EFFICACY, DAC HYP CONCENTRATION, AND [redacted] ASSESSMENTS

12.1. Clinical Efficacy Assessments

The following clinical tests/assessments will be performed to assess the efficacy of DAC HYP:

- Relapse Assessment: Subjects who suspect they are experiencing new symptoms or worsening symptoms need to contact the *Study Neurologist* within 48 hours of the onset of the symptoms.
- Refer also to Section 14.6 Unscheduled Relapse Assessment Visit for additional details.
- EDSS [Kurtzke 1983]: Review of EDSS procedures will be performed prior to study start as necessary for training purposes.
- MSFC [Fischer 1999]: Timed 25-Foot Walk, 9HPT with both upper extremities, and PASAT 3
- SDMT: Data will be collected only from subjects enrolled from Study 205MS301, and test performance data will be collected beginning in Week 144 and every 24 weeks thereafter.
- PASAT 3: This test will be performed separately from the MSFC beginning in Week 144 and every 24 weeks thereafter. Data will be collected only from subjects enrolled from Study 205MS301.
- Brain MRI scan with and without Gd (T2 hyperintense lesions, T1 hypointense lesions, Gd+ lesions, brain atrophy).
- Subjects will complete the following questionnaires at various timepoints specified in Section 4.2:
  - EQ-5D quality of life questionnaire (the EQ-5D descriptive system and the EQ-VAS)
  - MSIS-29 (29-item physical and psychological assessment)
  - HRU (hospitalizations, emergency room visits, and unscheduled neurologist visits)
  - Treatment Satisfaction Questionnaire for Medication (with PFS use) or Treatment Satisfaction Survey (with autoinjector use)
  - HRPQ (productivity questionnaire)

Refer to Section 4.2 for the timing of assessments.

12.2. Pharmacokinetic Assessments

Blood samples 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]

Unscheduled PK/[redacted] Visits

Whole blood samples will be collected at Unscheduled PK/[redacted] Visits for potential determination of DAC HYP serum concentrations 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.

Refer to Section 4.2 for the timing of sample collection.

12.3. [redacted]

[redacted]

PK/[redacted]

PK/[redacted]

12.4. [redacted]

[redacted]

13. SAFETY ASSESSMENTS

13.1. Clinical Safety Assessments

The following clinical assessments will be performed to determine the safety profile of DAC HYP:

- Medical history
- Physical and neurological examination
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate (subjects must remain in the same body position quietly for 5 minutes prior to having their pulse and blood pressure taken)
- Weight
- Concomitant therapy and procedure recording
- AE and SAE recording
- Beck Depression Inventory, Second Edition (BDI-II)
- Immunogenicity assessments
- Alcohol Use Disorders Identification Test - Consumption Questionnaire (AUDIT-C)

See Section 4.2 for the timing of assessments.

13.2. Laboratory Safety Assessments

The following laboratory tests will be performed to assess the safety profile of DAC HYP:

- Hematology: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell count, white blood cell count (with differential), and platelet count
- Blood chemistry: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT/SGPT AST/SGOT, lactate dehydrogenase, gamma glutamyl transferase, blood urea nitrogen (BUN), creatinine, and bicarbonate
- Comprehensive hepatic panel (only required for subjects who permanently discontinue dosing due to elevated LFTs as defined in Section 11.7.2). Testing will include screening for the following:
  - hepatitis A, B, C, and E
  - other viral infections: Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV-6), varicella zoster virus (VZV), herpes simplex virus (HSV), and Parvovirus B19
  - gamma-globulins, including IgG levels

  - autoantibodies: antinuclear antibody (ANA), anti-smooth muscle antibody (anti-SM), anti-liver/kidney microsome-1 antibody (anti-LKM1), antimitochondrial antibody (AMA), and anti-soluble liver antigen (SLA)

  Additional testing may be performed based on results of the above testing or the subject's clinical history. Additional hepatic assessments should be performed according to local standard of care.

- Thyroid function panel, including TSH and T4
- Urinalysis: protein, blood, glucose, ketones, nitrite, leukocytes, pH, specific gravity by dipstick and microscopy
- Urine pregnancy testing
- Skin biopsy (only required for subjects who experience cutaneous AEs reported as serious or severe as defined in Section 11.7.3)

Refer to Section 4.2 for the timing of assessments.

13.3. Study-Specific Safety Assessments

Blood serum collection for binding and neutralizing anti-drug antibody testing will be performed. Note: When necessary, samples drawn for one purpose (e.g., immunogenicity) may be used to meet another protocol-defined objective (e.g., DAC HYP concentration assessment).

14. SCHEDULE OF EVENTS

14.1. Overview

A written, signed Informed Consent Form (ICF) and all authorizations required by local law (e.g., Protected Health Information [PHI] in North America) must be obtained prior to performing any tests or assessments under this protocol.

For subjects entering from Study 205MS301, tests/assessments performed at the subject's last visit in Study 205MS301 and within 28 days of the subject's first dose of DAC HYP (Week 0) in Study 205MS303 may be used as baseline data for Study 205MS303; if final Study 205MS301 tests/assessments are not performed within the 28-day window, they must be repeated upon entry into Study 205MS303 and before the first dose of DAC HYP is administered.

Week 144 Visit of Study 205MS303 will be the Entry Visit for subjects enrolled from Study 205MS203 or Study 205MS302. 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; test/assessments performed >28 days before the Entry Visit must be repeated at the Entry Visit. Central LFT testing is *mandatory* at Entry Visit.

Clinic visits will occur once every 4 weeks for the first 12 weeks, then every 12 weeks thereafter.

On a dosing day, all tests and assessments must be performed prior to DAC HYP administration. When DAC HYP administration and MRI evaluation are required at the same visit, the MRI scan should be performed prior to DAC HYP administration (Note: MRI scan can be performed up to 4 days prior to the visit).

Before a monthly dose of DAC HYP is given, LFT results (ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only) from prior testing performed within the previous 32 days must be reviewed by the *Study Neurologist* or their backup, and must be within the protocol-required limits.

After Week 12, subjects will have the option of administering DAC HYP at home following Investigator review of monthly pre-dose LFT results. Subjects who are not able to administer their own dose or prefer not to administer their own dose of DAC HYP will be given the option to choose another individual (caregiver) to administer their treatment at home or to have their treatment administered by staff at the study site.

Follow-up visits will take place at 4 (End of Treatment Visit), 8, 12, 16, 20, and 24 weeks after each subject's last dose of DAC HYP. Unscheduled Relapse Assessment Visits (if necessary) should be scheduled within 72 hours of the onset of any new neurological symptoms that may indicate neurological worsening or possible clinical relapse. Unscheduled Hepatic Assessment Visits (if necessary) should be scheduled as soon as possible (but within 1 week) following discontinuation of study treatment due to elevated LFTs. Unscheduled Dermatology Assessment Visits will be performed as per Section 11.7.3.

Unscheduled PK/[redacted] Visits should be scheduled as soon as possible following significant changes in subjects' medical conditions, as assessed by the Investigator. This visit must be approved by the Biogen Medical Director in advance.

14.2. Site Personnel

For each subject, the Principal Investigator will designate the following study site personnel:

- A primary *Study Neurologist* and backup neurologist
- A primary and backup *Nurse* (or Study Coordinator)
- A primary and backup *Examining Technician*
- An *MRI Technician*
- A *Pharmacist* (or authorized designee)
- A *Study Dermatologist*

The *Study Neurologist* must have a minimum of 2 years of neurology specialty training and anticipate at least a 3-year commitment to the study, or be approved by the study Advisory Committee. The *Study Neurologists* may designate another neurologist at the center who meets the same qualifications to perform the EDSS assessments and other neurologic assessment during the trial. Whenever possible, the EDSS and other neurologic assessments should be performed by the same examiner who performed these assessments in the parent study.

The primary *Study Neurologist* will be responsible for:

- Management of the routine neurological care of the subject
- Assessment (including assignment of causality) and treatment of AEs and MS relapses
- Obtaining an EDSS score based on a detailed neurological examination at the scheduled timepoints required in the protocol, and at every Unscheduled Relapse Assessment Visit
- Review of selected hematology and all blood chemistry results from the central laboratory
- Assessment of LFT results, as detailed in Section 11.7.2
- Monitoring and follow-up of any abnormal hepatic tests
- Referral of subjects to a dermatologist if that subject experiences 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) as described in Section 11.7.3
- Performing Dermatology Assessments and Physician Global Assessment Scale in subjects with mild or moderate cutaneous AEs (not associated with more than 1 systemic symptom or sign), as detailed in Section 11.7.3

- Assessment of injection sites, as detailed in Table 7

Hematology and blood chemistry data will be sent to the investigational sites to aid in management of the subject.

The primary *Nurse* or Study Coordinator will be responsible for:

- Assisting the *Study Neurologist* in subject management, including the treatment of AEs, the treatment and assessment of disease relapses, and the recording of AEs and concomitant medications
- Monitoring the EDSS scores and informing the *Study Neurologist* if a subject experiences at least a 1.0-point increase on the EDSS 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
- Administering the patient-reported questionnaires (BDI-II, MSIS-29, EQ-5D), HRU, and subject assessment of injection pain (VAS)
- Collection of blood samples and obtaining vital signs
- Study treatment administration/dispensation/accountability

To ensure consistency across sites, *Examining Technicians* must undergo a standardized training session prior to enrollment of subjects at their site. All sites should attempt to maintain the same *Examining Technician* throughout the study. If an *Examining Technician* has to be replaced, the new *Examining Technician* must undergo a training session. It is not necessary for the *Examining Technician* to be a healthcare professional as long as he/she is qualified, in the opinion of the Principal Investigator, to administer the MSFC (Note: MSFC was administered in this study only until Week 48; therefore, the role of the *Examining Technician* ended after that).

The *MRI Technician* will be responsible for:

- Performing a brain MRI scan with and without Gd at all protocol-required timepoints. Study-specific MRI scan procedures and protocols, which will be provided prior to study start, must be followed.

The *Pharmacist* (or authorized designee) will be responsible for:

- Storage, distribution, and accountability of study treatment.

The *Study Dermatologist* will be responsible for:

- Performing Cutaneous Assessments and Physician Global Assessment Scale in subjects with 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), as detailed in Section 11.7.3
- Documenting cutaneous events, as per the protocol.
- Taking photograph(s) of the affected body areas, as required.
- Performing a skin biopsy, as required.

- Evaluating, treating, and managing mild or moderate cutaneous AEs that are associated with more than 1 systemic symptom or sign, severe cutaneous AEs (with or without systemic symptoms or signs), or serious cutaneous AEs (with or without systemic symptoms or signs), as described in Section 11.7.3.

14.3. Subject Management

The following restrictions apply to all subjects enrolled into this study:

- Subjects must follow the restrictions for concomitant medications and procedures described in Section 11.5.
- Contraception requirements are to be followed as described in Section 15.5.3.
- Whenever possible, a subject should undergo protocol-required tests and assessments at the same time of day throughout the study.
- Subjects should not donate blood until 4 months after their last dose of DAC HYP.
- Subjects should not receive live or live-attenuated vaccines during DAC HYP treatment or for at least 6 months after treatment with DAC HYP.

14.4. Special Instructions for Tests and Assessments

Note: Information about the tests and assessments to be performed in this study is also provided in Section 12 and Section 13, and in the Study Reference Manual.

14.4.1. Rescreening

Subjects who are not eligible for participation at baseline due to a temporary condition (e.g., acute infection) are allowed to be rescreened once the condition has resolved, provided they are rescreened and enrolled within 6 months of completing Study 205MS301, Study 205MS203, or Study 205MS302.

14.4.2. Pregnancy Testing

- Pregnancy testing is only required for women of childbearing potential. A urine pregnancy test is to be performed at the Baseline/Entry Visit and at other timepoints designated in Section 4.2 Schedule of Events. Study treatment will be immediately discontinued if the subject has a positive pregnancy test at any time during the study.
- Results from all urine pregnancy tests must be reviewed by the study site prior to dosing and must be negative.

14.4.3. Liver Function Test Assessments Prior to DAC HYP Dosing

Before a monthly dose of DAC HYP is given, LFT results from prior testing performed within the previous 32 days must be reviewed by the *Study Neurologist* or their backup, and must be within protocol-required limits as described in Section 11.7.2.

LFTs can be performed as follows:

- Samples for LFTs must be drawn prior to administration of the monthly DAC HYP dose. These samples may be tested either locally inside or outside of the clinic (e.g., at a local laboratory or by visiting nurses) or at the central laboratory at the discretion of the Investigator and the results can then be used to determine whether dosing should continue or be suspended at the monthly dosing timepoint (see Section 11.1).
- 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).
- If the subject is administering DAC HYP injections at home, site personnel must contact the subject after review of prior LFT results performed within the previous 32 days to authorize the monthly injection, or if LFT results warrant, to instruct the subject to withhold their injection.
- LFTs following a treatment suspension must be performed through the central laboratory until the LFT abnormality is <2×ULN. In cases where LFTs cannot be performed via central laboratory, repeat LFT results from local laboratory can be used for confirmation.

14.4.4. Other Assessments

- Vital signs include systolic and diastolic blood pressure, pulse, and body temperature, and should be measured pre-dose. The subject must rest quietly for 5 minutes prior to blood pressure and pulse measurements. Weight will be collected at Baseline/Entry Visit and at the time of first autoinjector use at selected sites.
- The MSIS-29 must be administered prior to the subject's visit with the *Study Neurologist*.
- Subject assessment of injection pain using a VAS should be completed as soon as possible after the injection is administered but no later than 10 to 30 minutes post-injection.
- The first 4 DAC HYP injections (i.e., Weeks 0 through 12) must be given in the clinic. The first of these injections must be given by study personnel. At subsequent visits, subjects and/or caregivers will be instructed on DAC HYP self-administration and may administer their scheduled dose under staff supervision. After the subject completes the required in-clinic injections (i.e., after Week 12), DAC HYP may be dispensed to subjects for at-home administration if the subject chooses. If necessary, drug dispensation may occur at monthly intervals.
- Additional visits to assess elevated LFTs, cutaneous events, or PK/[redacted] markers may be required as described in Section 11.7.

14.5. Definition of MS Relapse and Disability Progression

14.5.1. MS Relapse

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** or their backup. The subject must have objective signs on the examination confirming the event.

*When possible subjects should be evaluated by the same neurologist assigned to them in the parent study.

New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse. New or recurrent neurological symptoms that occur less than 30 days following the onset of a protocol-defined relapse should be considered part of the same relapse. Management of MS relapse is described in Section 14.6.

14.5.2. Disability Progression

Disability progression can only be confirmed from the EDSS scores obtained according to the protocol-defined schedule of assessments at regular visits, and is defined as one of the following:

- at least a 1.0-point increase on the EDSS 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

14.6. Management of MS Relapse

Subjects who experience new or worsening neurological symptoms must contact the *Nurse* or *Study Neurologist* or their backup within 48 hours after the onset of symptoms. A standardized Suspected Relapse Questionnaire will be completed to determine the necessity of an Unscheduled Relapse Assessment Visit.

If required, the subject will then be evaluated in person by the *Study Neurologist* not more than 72 hours after the onset of the symptoms. At the Unscheduled Relapse Assessment Visit, the *Study Neurologist* is to perform a relapse assessment and obtain an EDSS score. New objective findings on neurological examination performed by the *Study Neurologist** are required to determine if a suspected protocol-defined relapse has occurred. Treatment of an acute relapse event with intravenous methylprednisolone (IVMP) [or equivalent] may proceed at the discretion of the *Study Neurologist* after the examination and will not affect the subject's eligibility to continue in the study.

*When possible subjects should be evaluated by the same neurologist assigned to them in the parent study.

Subjects who prematurely discontinue study treatment should complete safety follow-up evaluations (see Section 4.2 and Section 13).

Subjects who permanently discontinue DAC HYP treatment should complete the visit schedule described in Section 11.8.

14.7. Cutaneous Events

Subjects who experience 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) must be referred to and evaluated and managed by the *Study Dermatologist* as per Section 11.7.3. An Unscheduled Dermatology Assessment Visit will be performed, at which time a photograph will be taken, whenever a subject experiences 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), per Table 6. 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.

If a generalized allergic or hypersensitivity reaction to study treatment is confirmed, study treatment must be permanently discontinued as per Section 11.8.

14.8. Unscheduled Hepatic Assessment Visit

The following tests/assessments will be performed as soon as possible (but within 1 week) after discontinuation of study treatment for subjects who are required to discontinue dosing due to elevated LFTs as described in Table 6 and Section 11.8.

- Physical examination and vital signs
- Comprehensive hepatic panel
- Recording of concomitant therapy
- Monitor and record AE/SAEs
- Protocol compliance and DAC HYP accountability
- LFTs (ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only)

14.9. Lymphadenopathy and Lymphadenitis Events

Subjects who experience a clinically significant event of lymphadenopathy or lymphadenitis should be referred to a specialist as per Section 11.7.5.

Interruption or discontinuation of DAC HYP treatment due to events of lymphadenopathy or lymphadenitis is a clinical decision that should take the overall benefit-risk assessment of therapy into consideration. Subjects who discontinued study treatment for any reason while presenting with ongoing lymphadenopathy or lymphadenitis should be followed until the lymphadenopathy or lymphadenitis has stabilized or resolved or the study has terminated, whichever comes first.

14.10. Post-Treatment Safety Follow-Up Visit Schedule for All Subjects

All subjects should complete the following schedule of safety follow-up visits after their last dose of DAC HYP:

- End of Treatment Visit (i.e., the assessments required at Week 240). For subjects who prematurely discontinue study treatment before Week 240, these assessments should be performed 4 weeks (±4 days) after the subject's last dose of DAC HYP.
- Post-treatment safety follow-up visits at 8, 12, 16, 20, and 24 weeks after the subject's last dose. The details of these visits are shown in Table 5.

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 from Week 156 Visit in Study 205MS303 (see Table 4) as long as they meet the eligibility criteria (Section 8).

15. SAFETY DEFINITIONS, MONITORING, AND REPORTING

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

At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Serious Pretreatment Event

A serious pretreatment event is any event that meets the criteria for SAE reporting (as defined in Section 15.1.3) and occurs after the subject signs the ICF, but before administration of study treatment.

15.1.2. Adverse Event

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

15.1.3. Serious Adverse Event

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

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

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.

15.2. Monitoring and Recording Events

15.2.1. Serious Pretreatment Events

A serious pretreatment event experienced by the subject after signing and dating the ICF but before administration of study treatment is to be recorded on the SAE Form and faxed to the contract research organization (CRO) within 24 hours of the study site staff becoming aware of the event (see Section 15.2.5).

15.2.2. Adverse Events

Any AE experienced by the subject between the time of signing the ICF and subject's final visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

15.2.3. Serious Adverse Events

Any SAE experienced by the subject between the time of the first dose of study treatment and subject's final visit is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to the CRO.

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

Subjects will be followed for all SAEs until the subject's final visit. Thereafter, the event should only be recorded if the Investigator considers it related to study treatment.

15.2.4. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.3.
- The relationship of the event to study treatment as defined in Section 15.3.1.
- The severity of the event as defined in Section 15.3.2.

15.2.5. Immediate Reporting of Serious Adverse Events

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

Reporting Information for SAEs

Any Serious Event that occurs between the time the subject has signed informed consent and subject's final visit must be reported to the CRO within 24 hours of the study site staff becoming aware of the event. **Thereafter, the event should only be recorded if the Investigator considers it related to study treatment**.

A report pertaining to an event that occurs between the time the subject has signed informed consent and subject's final visit ***must be submitted*** to the CRO regardless of the following:

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

To report initial or follow-up information on a Serious Event, fax a completed SAE form to the following:

North America: [redacted]
Latin America: [redacted]
Europe and Asia Pacific: [redacted]

(Country-specific fax numbers are provided in the Study Reference Guide.)

15.2.5.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate CRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen SABR or designee.

15.3. Safety Classifications

15.3.1. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

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

15.3.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.3.3. Expectedness of Events

Expectedness of all AEs will be determined according to the Investigator's Brochure.

15.4. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the

Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.

- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

15.5. Procedures for Handling Special Situations

15.5.1. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed to the CRO within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded in the CRF; dosing information is recorded on a CRF.

15.5.2. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator or designee should contact the CRO Medical Monitor at one of the following phone numbers:

North America (USA and Canada): [redacted]

Latin America: [redacted]

Europe and Asia Pacific: [redacted]

15.5.3. Contraception Requirements

All women of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 4 months after their last dose of study treatment.

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

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy

For the purposes of the study, effective contraception is defined as follows:

For females:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with spermicide; diaphragm, sponge, cervical cap)

- True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

15.5.4. Pregnancy

Subjects should not become pregnant during the study. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report the pregnancy by faxing the appropriate form to Pharmacovigilance at the CRO within 24 hours of the study site staff becoming aware of the pregnancy (refer to Section 15.2.5 for reporting information). The Investigator or study site staff must report the outcome of the pregnancy to Pharmacovigilance at the CRO.

Please note that congenital abnormalities/birth defects in the offspring of male or female subjects should be reported when conception occurred during the study treatment period.

15.5.5. Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Biogen Safety and Benefit-Risk Management (SABR) will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

15.6. Investigator Responsibilities

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow-up on the outcome of the pregnancy.
- Complete an SAE form for each serious event and fax it to the CRO within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the CRO within 24 hours of the study site staff becoming aware of new information.
- Complete an Adverse Event of Special Interest form for each transaminase elevation, hepatic event, and cutaneous event as described in the protocol and fax it to the CRO as soon as possible following the study site staff becoming aware of the event.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.

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

15.7. Biogen Responsibilities

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor or designee is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

16.1. Description of Objectives

See Section 6.1, Objectives.

16.2. Description of Endpoints

See Section 6.2, Endpoints.

16.3. Demography and Baseline Disease Characteristics

Demographic data collected at baseline will be summarized (i.e., age, gender, ethnicity, and weight). Medical history and baseline characteristic data (e.g., EDSS, number of relapses in the previous study, MRI endpoints) will also be summarized.

16.4. Safety and Efficacy

16.4.1. Analysis Population

Study 205MS303 Safety Population

The safety population will include all subjects who received at least 1 dose of DAC HYP in Study 205MS303. All safety analyses will be completed on the safety population.

Study 205MS303 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who received at least 1 dose of DAC HYP in Study 205MS303. This population will be utilized for the efficacy analyses.

Study 205MS301 and Study205MS303 Intent-to-Treat population

This population will include all subjects randomized to DAC HYP or Avonex in Study 205MS301 and received at least one dose of DAC HYP in Study 205MS303.

16.4.2. General Methods of Analysis

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include the number of subjects with data, mean, standard deviation, median, and range. Categorical endpoints will include the number of subjects with data and the percentage in each category.

Analyses will generally be descriptive in nature and will focus on data collected during Study 205MS303 only. However, for relevant efficacy analyses, the data may be summarized by previous treatment group (Avonex or DAC HYP). Also, statistical comparisons may be made between efficacy in Study 205MS301 and efficacy in Study 205MS303 among subjects previously randomized to Avonex in Study 205MS301.

All statistical tests will be 2-sided with an overall Type I error of 5%. Adjustments for multiple comparisons will not be considered.

16.4.3. Primary Endpoints Analysis

Clinical Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. All treatment-emergent events will be included in the evaluation of safety. Treatment emergent includes any event that either occurs or worsens in severity after the onset of study treatment. Overall incidence of treatment-emergent events will be summarized; in addition, summaries by severity and by relationship to study treatment will be provided. The summary tables will include incidence estimates for the overall system organ class as well as for preferred terms within each system organ class. In order to assess whether the incidence of events changes over time, the incidence of key events may also be summarized by time period (e.g., 6-month time intervals).

16.4.4. Other Safety Endpoint Analyses

Unless otherwise specified, the baseline measurement for safety assessments such as laboratory values and vital signs was the measurement acquired on the day of the first receipt of DAC HYP. The first receipt of dosing of DAC HYP could be either Study 205MS303 (for subjects who received Avonex in Study 205MS301) or the parent studies (i.e., Study 205MS301, Study 205MS203, or Study 205MS302) for all other subjects.

Laboratory Data

Changes in laboratory values will be summarized using shift tables. Shift tables will include hematology, LFTs, kidney function tests, electrolytes, and other blood chemistry tests. Shifts will be presented from baseline of DAC HYP treatment (the last measurement acquired before or on the day of the first receipt of DAC HYP, e.g., Study 205MS303 baseline for subjects randomized to Avonex in Study 205MS301 and Study 205MS301 baseline for subjects randomized to DAC HYP 150 mg in Study 205MS301). Summaries of worst post-baseline laboratory values by clinically relevant categories may also be presented for selected parameters of interest by treatment group. For example, for LFT (alkaline phosphatase, ALT, AST, GGT, and total bilirubin), categories may be defined based on cutoff values relative to the ULN.

Vital Signs

Vital signs collected will be examined to determine the incidence of clinically relevant abnormalities. These abnormalities are described in Table 9. For the purpose of the shifts from baseline, the baseline evaluation at the start of DAC HYP treatment will be used.

For each vital sign, the number of subjects evaluated and the number and percentage of subjects with the defined abnormality at any time post dosing will be presented by treatment group.

Table 9: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C or an increase from baseline of ≥1°C
Pulse	>120 beats per minute (bpm) or an increase from baseline of 20 bpm <50 bpm or a decrease from baseline of >20 bpm
Systolic Blood Pressure	>180 mmHg or an increase from baseline of >40 mmHg <90 mmHg or a decrease from baseline of >30 mmHg
Diastolic Blood Pressure	>105 mmHg or an increase from baseline of >30 mmHg <50 mmHg or a decrease from baseline of >20 mmHg

Physical Examination

The physical examination findings will be summarized.

16.4.5. Efficacy Endpoints Analyses

Annualized Relapse Rate

Relapses will be summarized over the follow-up period in Study 205MS303. For subjects in Study 205MS301 and Study 205MS303 ITT population, relapses may be summarized over the combined study period (Studies 205MS301 and 205MS303).

A negative binomial regression model will be used to estimate the adjusted ARR.

Proportion of Subjects with a Relapse

The proportion of subjects relapsed will be estimated using a Kaplan-Meier curve.

Disability Progression

Sustained disability progression is defined as at least a 1.0 point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 24 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS <1.0 that is sustained for 24 weeks. The proportion of subjects with progression will be summarized using a Kaplan-Meier curve. In addition, summary statistics for EDSS and for the change from baseline in EDSS will be presented by visit, and for subjects who participated in Study 205MS301, by previous treatment group.

MSFC

Changes in the MSFC z-score will be summarized by study visit, and for subjects who participated in Study 205MS301, by previous treatment group. For subjects in Study 205MS301 and Study 205MS303 ITT population, MSFC z-score may be summarized over the combined study period (Studies 205MS301 and 205MS303). Details on the calculations of the z-score for each component will be described in the statistical analysis plan.

SDMT

Changes in the SDMT scores will be summarized by study visit and by previous treatment group in Study 205MS301. Change in the SDMT scores over the combined study period (Studies 205MS301 and 205MS303) will be calculated using the Study 205MS301 baseline visit

as baseline. Change in the SDMT score over the Study 205MS303 study period will be calculated using the last SDMT measurement in Study 205MS301 as baseline.

PASAT 3

Changes in the PASAT 3 scores will be summarized by study visit and by previous treatment group in Study 205MS301. Change in the PASAT 3 scores over the combined study period (Studies 205MS301 and 205MS303) will be calculated using the Study 205MS301 baseline visit as baseline. Change in the PASAT 3 score over the Study 205MS303 study period will be calculated using the Week 0/baseline visit as baseline.

MRI Endpoints

MRI endpoints will be summarized with descriptive statistics both as a continuous variable and categorically. Over time summaries and summaries by previous treatment group (Avonex or DAC HYP 150 mg) may also be provided. A negative binomial regression model will be used for the analysis of new or newly enlarging T2 lesions. The change in volume of lesions will be analyzed using an analysis of covariance.

Quality of Life Outcomes

Actual scores and change from baseline in quality of life endpoints will be summarized by visit.

Pharmacokinetics

The population for DAC HYP concentration analyses will include all subjects who received at least 1 dose of study medication and who have at least 1 sample available for analysis.

Serum concentration levels will be summarized with descriptive statistics by visit.

Antigenicity/Immunogenicity Data

Immunogenicity (i.e., ADAs to DAC HYP) will be assessed on subjects. Positive samples will be further tested for NAbs to DAC HYP using a specific NAb assay. Results will be tabulated by time period and overall.

16.5. Interim Analyses

No formal interim analyses are planned for this study. However, analyses may be performed prior to the end of the study at the discretion of the Sponsor.

16.6. Sample Size Considerations

There is no formal sample size calculation. The number of subjects in this study is determined by the number of subjects who completed Study 205MS301, Study 205MS203, or Study 205MS302.

17. ETHICAL REQUIREMENTS

Biogen and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

17.1. Declaration of Helsinki

The Investigator and Biogen must adhere to the principles set forth by the Declaration of Helsinki dated October 2008.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor may submit documents on behalf of the study sites in countries other than the US as applicable.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

It is the responsibility of the Principal Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

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

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

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

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including Baseline/Entry Visit tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all subjects participating in a clinical study conducted by Biogen.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including Baseline/Entry Visit tests and assessments.

Each consent form should contain an authorization allowing the Principal Investigator(s) and Biogen to use and disclose PHI (i.e., subject-identifiable health information) in compliance with local law.

The signed consent form will be retained with the study records.

17.4. Subject Data Protection

Prior to any testing under this protocol, including Baseline/Entry Visit tests and assessments, candidates must also provide all authorizations required by local law (e.g., PHI authorization in North America).

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws.

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not enroll any subjects prior to completion of a study initiation visit, conducted by Biogen or designee. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Principal Investigator(s) must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the course of the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the study site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

Biogen will be responsible for all administrative aspects of this study including, but not limited to, study initiation, monitoring, management of AEs, and data management.

19.1. External Contract Organizations

19.1.1. Contract Research Organization

The CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Electronic or Remote Data Capture

Subject information will be captured and managed by study sites on electronic CRFs via a remote data capturing system.

19.1.3. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by Biogen to analyze all hematology, blood chemistry, and urine samples collected for this study.

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).

19.1.4. Central Facility for Independent Assessment of Biopsy Samples

A central laboratory service has been selected by Biogen to coordinate the collection and distribution of biopsy samples. A central assessor has been selected to subsequently analyze skin biopsies or lymph node biopsies (as applicable).

19.1.5. Central Facility for Other Assessments

MRI Reading Center

All scheduled MRI scans with and without Gd will be evaluated at a central MRI reading center. All study sites will be required to send a test scan to the MRI Reading Center for evaluation in order to ensure that the site's scanning techniques are appropriate. This review will take place before the study site is permitted to enroll any subjects into the study.

Original MRI images are to be sent to the MRI Reading Center for review (MRI shipping instructions will be provided prior to the start of enrollment at each site).

Additional and more detailed MRI scans with and without Gd procedures and instructions are included in the study MRI manual (to be provided under separate cover prior to start of the study).

19.2. Study Committees

19.2.1. Advisory Committee

The Advisory Committee from parent Study 205MS301 will oversee the administrative progress and provide scientific and medical direction for this study while Study 205MS301 is ongoing. Advisory Committee will monitor subject accrual and compliance with the protocol at individual study sites. The Advisory Committee will determine whether the study should be stopped or amended for reasons other than safety.

Members of the Advisory Committee will include the Medical Director, Clinical Trial Manager, and Project Statistician from Biogen (and/or their designees), and participating Investigators. Biogen will designate one of the participating Investigators to be the Chairperson of the Advisory Committee.

19.2.2. Internal Safety Monitoring Committee

An internal Safety Monitoring Committee will be formed to review interim safety data on an ongoing basis. Investigational sites will be notified of any relevant safety findings that may jeopardize subject safety.

19.3. Changes to Final Study Protocol

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

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

In the event of a protocol modification, the subject consent form may require similar modifications (see Section 17.2 and Section 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator

must notify Biogen of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate one of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors, including, but not limited to, the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by Biogen.

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

20. REFERENCES

Bielekova B, Howard T, Packer AN, et al. Effect of anti-CD25 antibody daclizumab in the inhibition of inflammation and stabilization of disease progression in multiple sclerosis. Arch Neurol. 2009;66(4):483-9.

Bielekova B, Richert N, Howard T, et al. Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta. Proc Natl Acad Sci U S A. 2004;101(23):8705-8.

Fischer JS, LaRocca NG, Miller DM, et al. Recent developments in the assessment of quality of life in multiple sclerosis (MS). Mult Scler. 1999;5(4):251-9.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52. Epub 1983/11/01.

Rose JW. Treatment of Multiple Sclerosis with a Humanized Monoclonal Antibody Specific for IL-2 Receptor Chain. Neurology. 2003;60(Suppl 1):A478-9.

Rose JW, Watt HE, White AT, et al. Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. Ann Neurol. 2004;56(6):864-7.

Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol. 2010;9(4):381-90.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "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 Who Have Completed Study 205MS301" and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

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

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

PROTOCOL NUMBER: 205MS303

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: 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 Who Have Completed Study 205MS301

EUDRA CT NO: 2012-003176-39

DATE: 06 March 2017
Version 4
FINAL

SPONSOR SIGNATURE PAGE

Protocol 205MS303 was approved by:

[redacted], MD

08 MAR 2017
Date

[redacted]
Biogen MA Inc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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

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

Biogen Australia Pty Ltd
Level 3
123 Epping Road
North Ryde, NSW 2113
Australia

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

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

2. LIST OF ABBREVIATIONS

ADAs	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ARR	annualized relapse rate
AST	aspartate aminotransferase
AUDIT-C	Alcohol Use Disorders Identification Test - Consumption Questionnaire
BDI-II	Beck Depression Inventory, Second Edition
bpm	beats per minute
BUN	blood urea nitrogen
CRF	case report form
CRO	contract research organization
DAC HYP	Daclizumab High Yield Process
DHA	Directions for Handling and Administration
EDSS	Expanded Disability Status Scale
EQ-5D	European Quality of Life, 5-dimensions
EQ-VAS	European Quality of Life, visual analog scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gd	gadolinium
GGT	gamma-glutamyltransferase
HIV	human immunodeficiency virus
HRPQ	Health Related Productivity Questionnaire
HRU	health resource utilization
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFN	interferon
IL-2	interleukin-2
IM	intramuscular
ITT	intent-to-treat
IV	intravenous
IVIg	intravenous immunoglobulin
IVMP	intravenous methylprednisolone
LFT	liver function test
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale-29
NAbs	neutralizing antibodies
NK	natural killer cells

PASAT 3	3-Second Paced Auditory Serial Addition Test
[redacted]	[redacted]
PFS	prefilled syringe
PHI	protected health information
PK	pharmacokinetic(s)
RRMS	relapsing-remitting multiple sclerosis
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
SC	subcutaneous
SDMT	Symbol Digit Modalities Test
SGOT	serum glutamic oxaloacetic transaminase; see AST
SGPT	serum glutamic pyruvic transaminase; see ALT
SNP	single nucleotide polymorphism
SUSAR	suspected unexpected serious adverse reaction
T1	MRI hypointense designation
T2	MRI hyperintense designation
T4	thyroxine
ULN	upper limit of normal
US	United States
VAS	visual analog scale

3. SYNOPSIS

This is a brief summary. For details refer to the body of the protocol.

Protocol Number:	205MS303
Protocol Title:	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 Who Have Completed Study 205MS301
Version Number:	4
Name of Study Treatment:	Daclizumab High Yield Process (DAC HYP)
Study Indication:	Relapsing-Remitting Multiple Sclerosis (RRMS)
Phase of Development:	3
Rationale for the Study:	To evaluate the long-term safety, efficacy, and immunogenicity of DAC HYP in subjects with multiple sclerosis (MS) who have completed Study 205MS301 (DECIDE), Study 205MS203 (SELECTED), or Study 205MS302 (OBSERVE).
Study Objectives and Endpoints:	**Objectives** Primary: 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. Secondary: 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 Avonex® in Study 205MS301

Exploratory:

- [redacted]

Endpoints

Primary:

- Incidence of adverse events (AEs) and serious AEs (SAEs)

Secondary:

- 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, gadolinium-enhancing (Gd+) 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 (EQ-5D) and European Quality of Life, visual analog scale (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 analog scale [VAS]) and clinician injection site assessments
- Incidence of anti-drug antibodies to DAC HYP over time
- Incidence of neutralizing antibodies to DAC HYP over time

Study Design:	Multicenter, open-label, long-term extension study
Rationale for Dose and Schedule Selection:	The DAC HYP dose and schedule were used in the pivotal Phase 3 205MS301 study and will be the treatment regimen used in the commercial setting. The same DAC HYP dose and schedule were used in Study 205MS203 and Study 205MS302.
Study Location:	Global
Number of Planned Subjects:	Approximately 1600 subjects. This includes approximately 1200 subjects who completed Study 205MS301. Additionally, approximately 400 subjects from the other ongoing DAC HYP extension studies (Study 205MS203 and Study 203MS302) will be eligible to enter Study 205MS303 at Week 144 of Study 205MS303.

Study Population:	This study will be conducted in subjects with MS currently participating in Study 205MS301 who have completed either the Week 144 Visit or the End of Study Visit (Week 96) of Study 205MS301 OR subjects with MS currently participating in Study 205MS203 or Study 205MS302.
Treatment Groups:	This is a single-arm study. All subjects will receive open-label treatment with DAC HYP 150 mg by a subcutaneous injection using the PFS every 4 weeks. Depending on availability and local regulations, some subjects may dose with DAC HYP using a single-use autoinjector that contains a PFS.
Duration of Treatment and Follow-up:	Subjects will participate in this study for up to approximately 5 years, or until availability of commercial product (whichever is sooner), and in accordance with applicable laws and regulations. All subjects should complete safety follow-up evaluations at 8, 12, 16, and 24 weeks after the subject's last dose of DAC HYP.
Criteria for Evaluation:	
Efficacy:	Clinical relapse assessments, EDSS, MSFC (Timed 25-Foot Walk, Nine-Hole Peg Test with both upper extremities, PASAT 3), SDMT, and brain MRI scan with and without Gd (T2 hyperintense lesions, T1 hypointense lesions, Gd+ lesions, brain atrophy).
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].
[redacted]	[redacted]
Safety:	Physical and neurological exams; vital signs; clinical laboratory assessments (hematology, blood chemistry,

	thyroid function panel [including thyroid-stimulating hormone and T4], urinalysis); urine pregnancy testing; Beck Depression Inventory, Second Edition; immunogenicity assessments; Alcohol Use Disorders Identification Test - Consumption Questionnaire (AUDIT-C); and AE and concomitant medication monitoring will be performed in this study. Additional comprehensive hepatic testing will be required for subjects who permanently discontinue study treatment due to elevated liver function tests.
Subject Reported Assessments:	Subject assessment of MSIS-29, EQ-5D quality of life questionnaire (the EQ-5D descriptive system and the respondent's self-rated health on a vertical visual analog scale [EQ-VAS]), Treatment Satisfaction Questionnaire for Medication (before the first use of a PFS and at multiple timepoints during the study), Treatment Satisfaction Survey at selected sites (before the first and last use of an autoinjector), HRU, and HRPQ.
Statistical Methods:	Analyses will generally be descriptive in nature and will focus on data collected during Study 205MS303 only. Efficacy endpoints will be summarized for all subjects using descriptive statistics. For relevant efficacy analyses, the data may be summarized for subjects by previous treatment group (Avonex® or DAC HYP 150 mg). The adjusted ARR and number of new or newly enlarging T2 lesions will be estimated using a negative binomial regression model. The proportion of subjects with sustained progression and the proportion with a relapse will be estimated from the Kaplan-Meier curve. The incidence of AEs and changes in clinical laboratory assessments will also be summarized. An analysis by 3- or 6-month intervals may also be performed. Summary statistics for other safety, efficacy, and pharmacokinetic (PK) endpoints will be presented.
Sample Size Determination:	There is no formal sample size calculation for this study. The number of subjects in this study is determined by the number of subjects who completed Study 205MS301, Study 205MS203, or Study 205MS302, and enrolled in Study 205MS303.

Study Stopping Rules:	Biogen may terminate this study, after informing Investigators, at any time. Investigators will be notified by Biogen or designee if the study is placed on hold, completed, or closed.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS TABLES FOR STUDY 205MS303

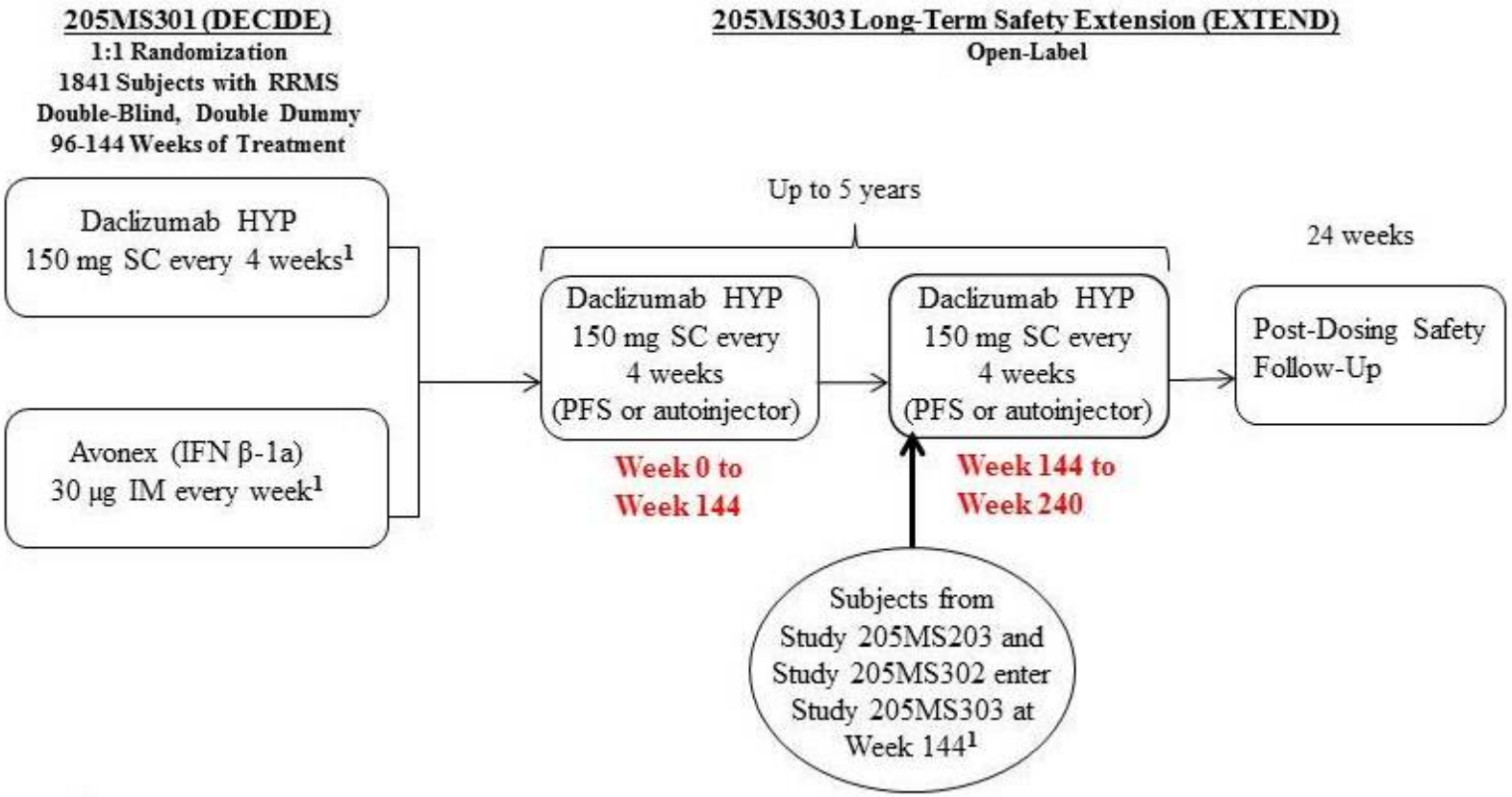
A schematic of the study design is provided in Section 4.1.

The tabulated schedule of events for this study is provided in Section 4.2.

4.1. Study Schematic

Figure 1 shows the design of Study 205MS301 and its open-label extension, Study 205MS303, in which subjects from Study 205MS203 and 205MS302 enter at Week 144.

Figure 1: Study Design



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

4.2. 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 for abnormal liver function tests (LFTs), LFTs must be re-evaluated as specified in 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 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			
[redacted]	X			X	X		X			
[redacted]	X						X			
[redacted]	X			X	X		X			
[redacted]										

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
Anti-Drug Antibody Sample	X			X	X		X			
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 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]
Subjects who did not consent to [redacted] collection in 205MS301 will be re-approached for this consent upon entry into Study 205MS303. A separate informed consent form may be used for [redacted] collection. Samples for [redacted] 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 for abnormal LFTs, LFTs must be re-evaluated as per 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 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 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. 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 Assessment[4]	X
Anti-Drug Antibody Sample[4]	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 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 (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 Section 14.4.3)							
Liver Function Tests at Central Laboratory[2 3]	X	X	X	X	X	X	X	X
DAC HYP Concentration Assessment[4]				X				X
Anti-Drug Antibody Sample[4]				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 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 not necessary for the Early Termination visit.
[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.
[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 (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
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 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.
[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 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[redacted] 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[redacted] Assessments				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 1 or more systemic symptoms or signs 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 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 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 Section 11.8.

[redacted]

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

Table 7: Schedule of Activities: Autoinjector Use by Subjects at Selected Sites

Note: At the Sponsor's discretion, approximately 75-100 eligible subjects from Study 205MS303 at selected sites may begin using autoinjectors on any regularly scheduled dosing day, after they have received at least 6 consecutive monthly doses of DAC HYP by prefilled syringe (PFS) in Study 205MS303. Six consecutive DAC HYP injections will be administered by the subject. Doses 1 and 4 will be supervised during clinic visits, all other doses can be given at home or the clinic. Following the use of autoinjectors, subjects should resume administration of DAC HYP using the PFS.

Note: Subjects are to continue the visit schedule and evaluations listed in Table 1 through Table 6 while they are using autoinjectors.

	Autoinjector 1[1]		Autoinjector 2 4 weeks ±4 days		Autoinjector 3 8 weeks ±4 days		Autoinjector 4[1] 12 weeks ±4 days		Autoinjector 5 16 weeks ±4 days		Autoinjector 6 20 weeks ±4 days	
Tests and Assessments	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**
Informed Consent	X[2]											
Weight	X											
Waist Circumference[3]	X											
Abdominal Fold Thickness[3]	X											
DAC HYP Administration		X		X		X		X		X		X
Injection Site Assessment		X[4]					X					
Subject Assessment of Injection Pain (VAS)[5]		X						X				
Observer Report		X						X				
Treatment Satisfaction Survey[6]	X							X				X
Patient Usability Survey[6]								X				X
DAC HYP Concentration Assessment	X						X					
Anti-Drug Antibody Sample	X						X					

[1]To be administered during a scheduled clinic visit.

[2]Subjects must provide written informed consent for autoinjector use prior to first DAC HYP dose by autoinjector.
[3]The procedure for taking this measurement is provided in the Study Reference Manual.
[4]Injection Site Assessment to be completed as soon as possible but within 10 minutes after the injection at Visit 1.
[5]VAS to be completed as soon as possible after the injection is administered, but no later than 10-30 minutes post-injection.
[6]If the subject withdraws from the study or reverts to PFS use prior to receiving all 6 autoinjector doses, the subject should complete the Treatment Satisfaction Survey and the Patient Usability Survey provided for the Autoinjector 6 dosing day before returning to PFS or receiving alternative MS disease modifying therapy.

5. INTRODUCTION

5.1. Profile of Previous Experience with Daclizumab in MS

Background

DAC HYP is a humanized monoclonal IgG1 antibody specific for CD25 (α subunit of the IL-2 receptor). CD25 is expressed at low levels on resting T cells but is rapidly upregulated after T-cell activation, enabling high-affinity IL-2 signal transduction. The primary hypothesis for using DAC HYP to treat MS is to selectively inhibit activated T cells.

Anti-CD25 antibodies have multiple in vitro effects that suggest DAC HYP may directly decrease T-cell activation and proliferation. These include inhibition of IL-2 dependent lymphocyte proliferation, disruption of both IL-2 dependent and independent pathways of IFN-gamma production, and interference in CD28-dependent CD40 ligand expression. In vivo, daclizumab has been confirmed to cause expansion of $CD56^{bright}$ NK cells. This expansion has also been shown to correlate with MRI-defined therapeutic response of daclizumab in MS. $CD56^{bright}$ NK cells are believed to have an immunoregulatory function, and they have been shown to kill activated T cells through a contact-dependent mechanism. Therefore, selective inhibition of activated T cells with DAC HYP may occur through both direct and indirect mechanisms [Bielekova 2009; Bielekova 2004].

Clinical Experience With Daclizumab in Multiple Sclerosis

Initial clinical studies of daclizumab in MS were conducted with material manufactured by F. Hoffmann-La Roche, Ltd. (Roche) at their facilities in Nutley, New Jersey (DAC Nutley) [Bielekova 2004; Rose 2003; Rose 2004], and in Penzberg, Germany (DAC Penzberg) [Wynn 2010]. Study 205MS301 is conducted with DAC HYP, which is produced using a different manufacturing process than the previous versions of daclizumab. DAC HYP has characteristics that are similar to DAC Nutley and DAC Penzberg, although certain differences in physicochemical and biological characteristics have been observed (refer to the Investigator's Brochure for details).

Study 205MS201

Study 205MS201 (SELECT) was a double-blind, placebo-controlled study to evaluate the safety and efficacy of DAC HYP in subjects with RRMS that randomized 621 subjects in a 1:1:1 ratio to receive placebo, 150 mg DAC HYP, or 300 mg DAC HYP SC every 4 weeks over a 52-week treatment period. Among subjects randomized to DAC HYP (150 mg, 300 mg) versus placebo, there was a significantly lower annualized relapse rate (ARR; 0.21, 0.23 versus 0.46; $p < 0.001$), a higher proportion of relapse-free subjects (81%, 80% versus 64%; $p < 0.001$), and a trend towards improvement in the MSIS-29 physical score ($p = 0.128$ for DAC HYP 300 mg versus placebo; $p < 0.001$ for DAC HYP 150 mg versus placebo). There were significant reductions in the mean number of new or newly enlarging T2 lesions at 1 year (2.4, 1.7 versus 8.1) and in the mean number of new Gd+ lesions between Weeks 8 and 24 in a monthly MRI substudy ($n = 307$) (1.5, 1.0 versus 4.8) in the DAC HYP 150 mg and 300 mg groups versus placebo

($p < 0.001$ for all comparisons). The risk of 3-month sustained disability progression at 1 year, a tertiary study endpoint, was reduced by 57% ($p = 0.021$) in the DAC HYP 150 mg group and by 43% ($p = 0.091$) in the DAC HYP 300 mg group.

Analysis of safety data from Study 205MS201 showed that, overall, DAC HYP was well tolerated in this patient population. The most frequently reported (≥10%) adverse events (AEs) for subjects treated with DAC HYP, excluding MS relapse, were nasopharyngitis (14%), and headache and upper respiratory tract infection (10% each). In Study 205MS201, serious adverse events (SAEs) including MS relapses occurred in 26% of placebo-treated subjects and in 16% of subjects treated with DAC HYP. Excluding MS relapses, SAEs occurred in 6% of the placebo group, in 7% of the DAC HYP 150 mg group, and in 9% of the DAC HYP 300 mg group. One DAC HYP-treated subject died due to ischemic colitis following a complicated course of events. Adverse events observed more frequently in DAC HYP-treated patients included an increase in serious infections (2%), serious cutaneous events (1%), and elevations in LFTs (ALT/AST) >5× ULN (4%).

Upon completion of the 12-month treatment period in Study 205MS201, subjects were eligible to complete up to an additional 12 months of treatment with DAC HYP in a double-blind extension study (Study 205MS202 [SELECTION]), which was completed in 2012. Study 205MS202 also assessed the effects of DAC HYP washout in some subjects who were actively treated in Study 205MS201. Subjects completing Study 205MS202 continued long-term therapy with open-label DAC HYP in extension Study 205MS203 (SELECTED), which evaluated long-term safety and efficacy of DAC HYP monotherapy for up to an additional 144 weeks.

Study 205MS301

Study 205MS301 (DECIDE), a double-blind, randomized, parallel-group, active-controlled study testing the superiority of DAC HYP monotherapy compared to Avonex® (IFN β-1a) in preventing MS relapse, was initiated in May 2010; 1841 subjects with RRMS have been enrolled and randomized in a 1:1 ratio to receive 150 mg DAC HYP given SC every 4 weeks, or Avonex 30 mcg given IM once weekly over a 96- to 144-week treatment period. The primary endpoint was the annualized relapse rate. In this study, DAC HYP demonstrated statistically and clinically meaningful superiority to IFN β-1a, on validated clinical, radiographic, and patient-reported MS outcome measures. DAC HYP reduced the annualized relapse rate by 45% ($p<0.0001$) compared to IFN β-1a. DAC HYP's treatment effect on relapses was also evidenced by a 41% reduction in the risk of relapse in subjects in the DAC HYP group compared to the IFN β-1a group ($p<0.0001$). A reduction in the proportion of subjects relapsing was observed as early as 24 weeks after the initiation of treatment and persisted throughout the end of the study. The risk of 12-week confirmed disability progression was reduced by 16% in the DAC HYP group compared with the IFN β-1a group, a result that was not statistically significant ($p=0.1575$) in the primary analysis. In the pre-specified analysis of 24-week confirmed progression, disability progression was reduced by 27% ($p=0.0332$) in the DAC HYP group compared with the IFN β-1a group. Overall, the results of the 12-week and 24-week confirmed progression analyses were consistent with each other and supported a clinically meaningful effect of DAC HYP in preventing confirmed disability progression compared with IFN β-1a. DAC HYP reduced the number of new or newly enlarging T2 lesions at Week 96 by 54.4% ($p<0.0001$) compared to IFN β-1a. The magnitude of the treatment effect was consistent with

the results seen on the primary endpoint of annualized relapse rate. The tertiary MRI endpoints of T2, T1, and Gd-enhancing lesion count and volume were also consistent with the effect on new or enlarging T2 lesions and provide important confirmation of DAC HYP's ability to reduce focal and destructive areas of brain inflammation in RRMS patients. The treatment effect of DAC HYP on new or enlarging T2 lesions and other MRI endpoints was detectable by Week 24 ($p<0.0001$) and was sustained through to the Week 96 and Week 144 MRI at a similar magnitude.

In Study 205MS301, the safety profile of DAC HYP was characterized by an increased incidence of elevations of serum transaminases and serious hepatic events, cutaneous events, infections, and gastrointestinal events. The overall incidence of AEs was balanced across the 2 treatment groups (91% IFN β-1a vs. 91% DAC HYP). The majority of subjects with AEs had events that were mild to moderate in severity. The incidence of subjects with AEs that were considered severe was 14% in the DAC HYP group and 12% in the IFN β-1a group. AEs reported more frequently in the DAC HYP group than in the IFN β-1a group included nasopharyngitis, upper respiratory tract infections, influenza, oropharyngeal pain, rash, and lymphadenopathy, whereas influenza-like illness, pyrexia, chills, and hypertension were reported more frequently in the IFN β-1a group.

There was a higher incidence of SAEs in the DAC HYP group (24%) compared with the IFN β-1a group (21%). Excluding MS relapse, SAEs were reported in 10% of the IFN β-1a group and in 15% of the DAC HYP group. Five deaths were reported in the study (4 subjects in the IFN β-1a group, 1 subject in the DAC HYP group). None of the deaths were considered by the Investigators to be related to study treatment. While safety events were more common in the DAC HYP-treated subjects compared with IFN β-1a-treated subjects, the types of events were generally manageable with standard medical care, monitoring, and treatment discontinuation, as appropriate for the event. Overall, the results of the study support a positive benefit/risk profile for DAC HYP.

The PK and immunogenicity of DAC HYP 150 mg SC administered every 4 weeks using a prefilled syringe (PFS) were investigated in 26 subjects in Study 205MS302 (OBSERVE), a single-arm, open-label study that enrolled a total of 113 subjects with RRMS.

Refer to the Investigator's Brochure for additional details.

5.2. Study Rationale

This study will evaluate the long-term safety, efficacy, and immunogenicity of DAC HYP in subjects with MS who have completed Study 205MS301, Study 205MS203, or Study 205MS302. In addition, this study will assess the safety, tolerability, and efficacy of switching to DAC HYP in subjects previously on long-term treatment with interferon β-1a in Study 205MS301.

5.3. Rationale for Dose and Schedule Selection

The existing scientific and clinical experience with DAC HYP supports its further investigation in the management of MS. The DAC HYP dose and schedule in this protocol were used in the pivotal Phase 3 Study 205MS301 and will be the treatment regimen used in the commercial

setting. The same DAC HYP dose and schedule were used in Study 205MS203 and Study 205MS302.

A single-use, disposable PFS will be provided to simplify the injection process and thereby reduce the burden of administering a long-term therapy such as DAC HYP in the clinic or at home. At the Sponsor's discretion, single-use autoinjectors containing PFS may be used to administer DAC HYP in 75-100 subjects from Study 205MS303 at selected sites. Autoinjectors will be dispensed to each participating subject for use on up to 6 consecutive scheduled dosing days.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

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.

6.1.2. Secondary Objectives

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 PFS
- To assess the safety, tolerability, and efficacy of switching to DAC HYP in subjects previously on long-term treatment with interferon β-1a in Study 205MS301

6.1.3. Exploratory Objective

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoints

- Incidence of AEs and SAEs

6.2.2. Secondary Endpoints

- 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 (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 (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

7. STUDY DESIGN

7.1. Study Overview

The design of Study 205MS303 is provided in Figure 1. Approximately 1600 subjects will enroll in this study. This includes approximately 1200 subjects who completed Study 205MS301. Additionally, approximately 400 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 an 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).

7.2. Overall Study Duration and Follow-Up

The study period will consist of Baseline/Entry Visit assessments, treatment (for up to approximately 5 years), and post-treatment safety follow-up visits (from approximately 4 to 24 weeks after the last dose of DAC HYP).

7.2.1. Baseline/Entry Visit Assessments

Subjects Entering From Study 205MS301

Tests/assessments performed at the subject's last visit in Study 205MS301 and within 28 days of the subject's first dose of DAC HYP (Week 0) in Study 205MS303 may be used as the baseline for Study 205MS303; if final Study 205MS301 tests/assessments are not performed within the 28-day window, they must be repeated upon entry into Study 205MS303 and before the first dose of DAC HYP is administered.

Subjects Entering From Study 205MS203 or Study 205MS302

The Week 144 Visit of Study 205MS303 will be the Entry Visit for subjects enrolled from Study 205MS203 or Study 205MS302. 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. Central LFT testing is *mandatory* at the Entry Visit.

7.2.2. Treatment

Subjects from Study 205MS301 continuing in Study 205MS303 will receive DAC HYP treatment for up to approximately 5 years, or until availability of commercial product (whichever is sooner), under this protocol. Subjects from Study 205MS203 and Study 205MS302 entering Study 205MS303 at Week 144 will have DAC HYP treatment for up to approximately 2 years, or until availability of commercial product (whichever is sooner), under this protocol.

At the Sponsor's discretion, 75-100 subjects from Study 205MS303 at selected sites may dose with DAC HYP using a single-use autoinjector that contains a PFS on 6 consecutive scheduled dosing days (Table 7).

Eligible subjects will have clinic visits scheduled every 4 weeks for up to Week 12 in this study, followed by clinic visits scheduled every 12 weeks.

Subjects who are dosing at home must be instructed to not administer their monthly dose of DAC HYP until the study site has contacted them to authorize dosing (after the *Study Neurologist* or their backup has reviewed LFT results obtained during the previous 32 days). Subjects need to record the date and time of dosing in their diary if they are dosing at home.

A window of ±4 days applies to scheduled visits and home dosing.

7.2.3. Post-Treatment Long-Term Follow-Up

Subjects are to return to the study site for follow-up visits at 8, 12, 16, and 24 weeks (±10 days) after the last dose of DAC HYP.

7.3. Study Stopping Rules

Biogen may terminate this study, after informing Investigators, at any time. Investigators will be notified by Biogen or designee if the study is placed on hold, completed, or closed.

7.4. End of Study

The End of Study is last subject, last visit for final collection of data.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the 205MS303 Baseline/Entry Visit or at the timepoint specified in the individual eligibility criterion listed (Note: Week 0/Day 1 is the Baseline Visit in Study 205MS303 for 205MS301 subjects. Week 144 is the Entry Visit in Study 205MS303 for 205MS203 and 205MS302 subjects):

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
2. Must be a subject currently participating in Study 205MS301 who has completed either the Week 144 Visit or the End of Study Visit (Week 96) of Study 205MS301 OR subject currently participating in Study 205MS203 or Study 205MS302.
3. Women of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 4 months after their last dose of study treatment.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the Study 205MS303 Baseline/Entry Visit or at the timepoint specified in the individual criterion listed (Note: Week 0/Day 1 is the Baseline Visit in Study 205MS303 for 205MS301 subjects. Week 144 is the Entry Visit in Study 205MS303 for 205MS203 and 205MS302 subjects):

Medical History

1. Any subject who permanently discontinued study treatment in Study 205MS301, Study 205MS203, or Study 205MS302 prior to the end of the study treatment period, or had an early termination in those studies OR any subject who has completed all the safety follow-up visits after Week 144 of Study 205MS303 per the original protocol.

   Note: Subjects for whom dosing was temporarily suspended in Study 205MS301, Study 205MS203, or Study 205MS302 are not excluded from participation in this extension study if the criteria for resuming DAC HYP treatment under the parent study protocol have been met at the time of enrollment into Study 205MS303.
2. Any significant change in the subject's medical history that would preclude administration of DAC HYP, including laboratory tests or a current clinically significant condition that, in the opinion of the Investigator, would have excluded the subject's participation in Study 205MS301, Study 205MS203, or Study 205MS302. The Investigator must re-review the subject's medical fitness for participation and consider any factors that would preclude treatment in Study 205MS303, including:

- History of any significant cardiac, endocrine, hematological, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurological (other than MS), and/or other major disease (e.g., malignancy) that would preclude administration of DAC HYP.
- Clinically significant laboratory abnormalities (hematology and blood chemistry) from the most recently available test in the parent study, as determined by the Investigator. Laboratory findings mandating discontinuation of study treatment as defined in parent study protocol are exclusionary.

3. Other medical reasons that, in the opinion of the Investigator and/or Biogen, make the subject unsuitable for enrollment.

Treatment History

4. Treatment with any prohibited concomitant medication during the parent study, as described in Section 11.5 of this protocol.

   Note: Subjects who start an approved, open-label IFN β preparation after completion of dosing in Study 205MS301 are not excluded, but IFN β treatment must be discontinued before the first dose of DAC HYP in Study 205MS303 is given.

Miscellaneous

5. Female subjects who are currently pregnant or breastfeeding, or considering becoming pregnant while in the study.
6. History of drug or alcohol abuse (as defined by the Investigator) at any time after the start of Study 205MS303 or any of the parent studies.
7. Unwillingness or inability to comply with the requirements of the protocol, including the presence of any condition (physical, mental, or social) that is likely to affect the subject's ability to comply with the protocol.

9. ENROLLMENT AND REGISTRATION PROCEDURES

9.1. Enrollment and Screening

Subjects must be consented before any procedures are performed. At the time of consent, the subject will be enrolled into the study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the enrollment log. Any test/assessment done at the subject's last visit in the parent studies and within 28 days of the subject's first dose in Study 205MS303 will be used as the baseline for Study 205MS303 and does not need to be repeated at entry into Study 205MS303 (Note: Central LFT testing is mandatory at the Week 144 Entry Visit for subjects rolling over from Study 205MS203 and Study 205MS302 into Study 205MS303). Testing required at the Baseline/Entry Visit that is done outside the 28-day window must be repeated upon entry into 205MS303.

9.2. Registration of Subjects

Subjects should be registered in the study after the Investigator has verified that they are eligible per the criteria in Section 8.1 and Section 8.2 and all baseline assessments have been performed. No subject may begin treatment prior to enrollment and registration.

As confirmation, the Investigator will be provided with written verification of the subject's registration by mail or fax.

Refer to the Study Reference Manual for details on registration.

10. STUDY TREATMENT MANAGEMENT

Study treatment (PFS or autoinjectors) must be stored in a secure location. Accountability for study treatment is the responsibility of the Investigator. Study treatment must only be dispensed by a Pharmacist or medically qualified staff, and stored in a secure, monitored, locked location in accordance with the conditions specified in current prescribing information or the Directions for Handling and Administration (DHA) included in the Study Reference Manual.

Study treatment is to be dispensed only to subjects enrolled in this study. Once treatment is dispensed to a subject, it can only be used by that subject.

10.1. DAC HYP

Prefilled Syringe

DAC HYP is supplied as a liquid in a 1-mL BD-staked PFS with a 29 gauge × ½ inch needle, comprising 150 mg/mL DAC HYP plus excipient materials (sodium succinate, sodium chloride, and polysorbate 80). At a minimum, the study treatment label will include a study reference code, drug identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. Depending on country requirements, the Investigator's name may also appear on the label. DAC HYP must not be used after the expiration date unless a written notification of an expiration date extension is provided by Biogen.

Autoinjector

The DAC HYP PFS is assembled inside a single-use, disposable autoinjector device.

The autoinjector label will include the DAC HYP product code "BIIB019," conditions for storage, Sponsor, and a caution statement. Depending on country requirements, the Investigator's name may also appear on the label. DAC HYP must not be used after the expiration date unless a written notification of an expiration date extension is provided by Biogen.

10.2. DAC HYP Preparation

Each DAC HYP PFS or autoinjector contains only one dose and is intended for SINGLE USE INJECTION ONLY. Any drug that remains in the PFS after injection must not be used for another dose or another subject.

After Week 12, subjects may choose to administer their DAC HYP dose at home, either by administering the injection themselves or by a designated caregiver. The subject or designated caregiver will be trained by clinic staff on the correct PFS injection technique prior to initiating at-home DAC HYP dosing.

Autoinjectors may be provided to selected sites and will be supplied injection-ready. Study personnel or subjects at these sites do not need to insert the PFS into the device. Study site personnel will receive appropriate autoinjector training from a Sponsor-designated trainer prior to initiation of autoinjector use.

10.3. DAC HYP Accountability

The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), any amount returned by subject, and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all PFS and autoinjectors, both used and unused, must be saved for study treatment accountability. At the end of the study, a final reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed or returned to Biogen.

A written explanation will be provided for any discrepancies. After reconciliation, the Investigator must destroy or return to Biogen all unused study treatment PFS and autoinjectors as instructed by Biogen.

If any study treatment supplies are to be destroyed at the site, the Principal Investigator(s) must obtain prior approval by Biogen. The Principal Investigator(s) must notify Biogen, in writing, of the method, date, and location of destruction.

11. TREATMENT OF SUBJECTS

Biogen will provide DAC HYP (PFS or autoinjectors) to all study sites.

Refer to Section 10 (Study Treatment Management) for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

11.1. Study Treatment Schedule and Administration

All subjects will receive one DAC HYP 150 mg SC injection every 4 weeks.

DAC HYP will be administered by clinic staff at the monthly visits for the first 12 weeks of this study. After Week 12, administration of DAC HYP may occur in the clinic or at home (by the subject or by a designated caregiver) depending on subject preference. The subject or designated caregiver will be trained by clinic staff on the correct injection technique prior to initiating at-home DAC HYP dosing. **Subjects who are dosing at home must be instructed to not administer their monthly dose of DAC HYP until the study site has contacted them to authorize dosing. A window of ±4 days applies to home dosing.**

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. Study personnel should promptly inform the subject whether the monthly dose of DAC HYP should be administered or whether study treatment is to be withheld based on the dosing criteria defined in Section 11.7.2. Study personnel will document this communication with the subject. Subjects should administer DAC HYP as soon as permission has been given as per the dosing schedule. Subjects need to record the date and time of dosing in their diary if they are dosing at home.

11.2. Placebo or Reference Product Agents

Not applicable.

11.3. Treatment Precautions

Anaphylactic-like and hypersensitivity reactions following administration of proteins such as DAC HYP can occur. DAC HYP will be administered in the clinic under observation by qualified medical personnel for the first 12 weeks of this study. Subjects will be educated by the *Study Neurologist* or their back-up on the signs and symptoms of hypersensitivity reactions and instructed to contact the site if they experience any acute or delayed reactions post injection.

11.4. Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by study site staff.

After Week 12, subjects who choose to administer their DAC HYP dose at home will record treatment in a dosing diary. The diary will be reviewed periodically by study site staff and the Clinical Monitor throughout the study. Subjects who choose at-home administration will return used PFS or autoinjectors to the clinic at their scheduled clinic visits.

11.5. Concomitant Therapy

A concomitant therapy is any drug or substance administered from the Baseline/Entry Visit until completion of the study. A concomitant procedure is defined as any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed from the time the subject is enrolled in the study until the subject's final clinic visit.

Concomitant treatment with any of the following is not allowed during the study, unless approved by the Biogen Medical Director(s) or the Advisory Committee, or as otherwise described in this protocol:

- Any alternative disease modifying MS drug treatment such as chronic immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to: IFN-β, IFN-α, glatiramer acetate, cyclophosphamide, methotrexate, mycophenolate mofetil, mitoxantrone, cyclosporine, azathioprine, or related products).
- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications.
- Any monoclonal antibodies other than DAC HYP.
- Intravenous immunoglobulin (IVIg), plasmapheresis or cytapheresis, total lymphoid irradiation, or T-cell or T-cell receptor vaccination.
- Any systemic steroid therapy including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IV methylprednisolone (IVMP), except for protocol-defined treatment of relapses as described in Section 14.6 or for limited, acute treatment of general medical conditions as per the discretion of *Study Neurologist*. Steroids that are administered by non-systemic routes (e.g., topical, inhaled) are allowed.
- Antineoplastic or chemotherapeutic agents, including, but not limited to, cyclophosphamide, methotrexate, azathioprine, cladribine, cytarabine, or flutamide.
- Valproic acid, carbamazepine, lamotrigine, or phenytoin. Subjects who have been taking **1** of these medications at a stable dose for at least 6 consecutive months may continue to receive the medication and may continue study treatment under this protocol. However, if any of these medications must be initiated or dose escalated, study treatment must be permanently discontinued as described in Section 11.8.

  Subjects who have been treated with any of these medications (which have not been approved by the Biogen Medical Director[s]) for fewer than 6 consecutive months, or who take more than 1 of these medications, or who have had dose escalations within the past 6 months must do 1 of the following:

  – Discontinue the medication (any agent used for <6 consecutive months must be discontinued). Subjects may use an alternative medication allowed by the protocol, if needed.

  - Subjects taking more than 1 agent must reduce to ≤1 agent (any agent that is continued must have been taken for at least 6 consecutive months).
  - In the case of dose escalation, revert to a previous dose that had been used for at least 6 months.
  - Permanently discontinue study treatment.
- Isoniazid, propylthiouracil, or nimesulide. Subjects who currently take any of these medications must either change to an alternative medication allowed by the protocol or permanently discontinue study treatment.

Subjects who receive any of these restricted medications may be required to permanently discontinue study treatment as outlined in Section 11.8. Subjects who permanently discontinue study treatment will be allowed to receive IVMP as treatment for MS relapse while they are participating in the study, as described in Section 11.8.

Use of the following medications is strongly discouraged during the study:

- Herbal or dietary supplements.
- Agents that have established risks of hepatotoxicity or serious rash according to labeling information (examples include, but are not limited to, amoxicillin/clavulanate, clarithromycin, ketoconazole, minocycline, nitrofurantoin, trimethoprim/sulfamethoxazole, diclofenac, sulfasalazine, amiodarone, methyldopa, nefazodone, and halothane). Alternatives to these therapies should be used whenever possible.

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue is not restricted, but should be optimized as early as possible in an attempt to maintain consistent treatment for the duration of the study. Initiation of Fampridine-SR after enrollment is permitted, including when it is used in the acute management of protocol-defined relapse (as described in Section 14.6).

Subjects should be instructed not to start taking any new medications, including non-prescribed medications, unless they have received permission from the Investigator. The use of live vaccines in humans concurrently treated with daclizumab has not been explored; therefore live vaccines should not be administered to MS subjects who are being treated with DAC HYP.

The use of concomitant therapies or procedures defined in this section must be recorded on the subject's case report form (CRF), according to instructions for CRF completion (Note: concomitant therapies in the parent study that continued at Study 205MS303 entry must be recorded on the CRF). AEs related to administration of these therapies or procedures must be documented on the appropriate CRF. For subjects who prematurely discontinue study treatment, all concomitant medications should be recorded throughout the remainder of the subject's participation in the study.

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If DAC HYP is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

11.7. Treatment Schedule Modifications

Subjects who experience a significant change in their medical status (e.g., neurological worsening/suspected MS relapse, possible injection-site reaction, infection, cutaneous AE, fever, abdominal pain, persistent diarrhea, jaundice, nausea, vomiting, pruritus) must contact the *Study Neurologist* as soon as possible and no more than 48 hours after symptom onset. The subject should then be evaluated by the *Study Neurologist* within no more than 72 hours for physical and neurological assessments and further treatment recommendations if appropriate. These subjects should not administer additional DAC HYP until they have been evaluated by the *Study Neurologist* or their backup.

Unscheduled PK/[redacted] Visit (Table 6) can be performed in subjects who have evidence of significant changes in their medical conditions (as assessed by the Investigator). This visit must be approved by the Biogen Medical Director in advance.

Additional treatment considerations for specific events are described below.

11.7.1. Infections

Subjects who have evidence of a clinically significant infection will be instructed to notify the *Study Neurologist* or their backup within 48 hours of onset, and scheduled dosing of DAC HYP may be withheld. If the subject's infection resolves within 2 weeks of the scheduled DAC HYP dose, the subject may receive the previously scheduled dose of DAC HYP at that time. If the infection has not resolved within the 2 weeks, dosing of DAC HYP will remain suspended, and the subject will miss dosing until the infection is resolved.

11.7.2. Elevated Liver Function Tests

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, and must be within the protocol-required limits shown below (LFT procedures are described in Section 14.4.3).

Study treatment *must be temporarily suspended* if a subject develops any of the following:

- ALT/SGPT or AST/SGOT >3×ULN
- any other clinically significant hepatic condition in the opinion of the Investigator including jaundice

Note: For subjects who present with jaundice, an LFT *must* be performed as soon as possible.

After a suspension, dosing of DAC HYP may be resumed when ALT/SGPT and AST/SGOT are <2×ULN provided that the criteria for permanent discontinuation have not been met (see Section 11.8).

Study treatment *must be permanently discontinued* if a subject develops any of the following:

- ALT/SGPT or AST/SGOT elevation >8×ULN that is confirmed by a repeat test (preferably within 24 hours)
- ALT/SGPT or AST/SGOT >5×ULN for more than 2 weeks

- ALT/SGPT or AST/SGOT >3×ULN with concomitant elevation of total bilirubin >2×ULN
- If a subject has treatment suspended for an LFT elevation and has also had a prior treatment suspension for an LFT elevation during DAC HYP use, DAC HYP must be permanently discontinued unless an alternative explanation for the LFT elevation unrelated to DAC HYP use is clearly identified by the Investigator.

All subjects with elevated LFTs (**ALT/SGPT or AST/SGOT >3×ULN**) should be managed per the guidelines below.

- Study treatment must be temporarily suspended and LFT elevation should be confirmed as soon as possible but no later than a week by a repeat test performed at the central laboratory. In cases where LFTs cannot be performed via the central laboratory, repeat LFT results from local laboratory can be used for confirmation.
- All subsequent testing after a treatment suspension or discontinuation is required to be performed centrally *at least weekly* until the LFT elevation has resolved.
- In subjects with treatment suspension or discontinuation, DAC HYP treatment may resume if a laboratory error is documented upon repeat testing OR when ALT/SGPT and AST/SGOT are <2×ULN provided that the criteria for permanent discontinuation have not been met (see Section 11.8).
- A careful review of all concomitant medications must be documented. The Investigator should consider discontinuation of all potential hepatotoxic medications. All recently started or non-essential concomitant medications should be suspended until the LFT elevation has resolved.
- An Unscheduled Hepatic Assessment Visit as soon as possible but within 7 days should be performed in the event of permanent discontinuation due to elevated LFTs (see Table 6).
- Subjects should be referred to a hepatic specialist if medically indicated.
- The LFT elevation that led to treatment discontinuation should continue to be monitored until LFT elevation has resolved.
- For subjects with initial **ALT/SGPT or AST/SGOT >3×ULN and concomitant elevation of total bilirubin >2×ULN**:
    - *Permanently discontinue* DAC HYP and monitor until the LFT elevation has resolved.
- For subjects with initial **ALT/SGPT or AST/SGOT >5×ULN but ≤8×ULN**:
    - *Suspend dosing* and confirm as soon as possible but no later than a week.
    - For subjects with ALT/SGPT or AST/SGOT >5×ULN for more than 2 weeks:
        - *Permanently discontinue* DAC HYP and monitor until the LFT elevation has resolved.

- For subjects with **ALT/SGPT or AST/SGOT >8×ULN**:
    - *Suspend dosing* and confirm by a repeat test (preferably within 24 hours).
        - **If AST/SGOT >8×ULN in repeat test**: *Permanently discontinue* DAC HYP and monitor until the LFT elevation has resolved.
- For subjects with **ALT/SGPT or AST/SGOT >10×ULN not resolving for more than 2 weeks**:
    - *In consultation with the hepatic specialist*, a full evaluation of alternative causes of liver injury should be performed, and if testing for viral hepatitis is negative, LFT elevations are not improving, DAC HYP is suspected as the cause of the LFT elevation, and there are no known contraindications for corticosteroids, then, in continued consultation with the hepatic specialist, empiric treatment with systemic corticosteroids should be considered.

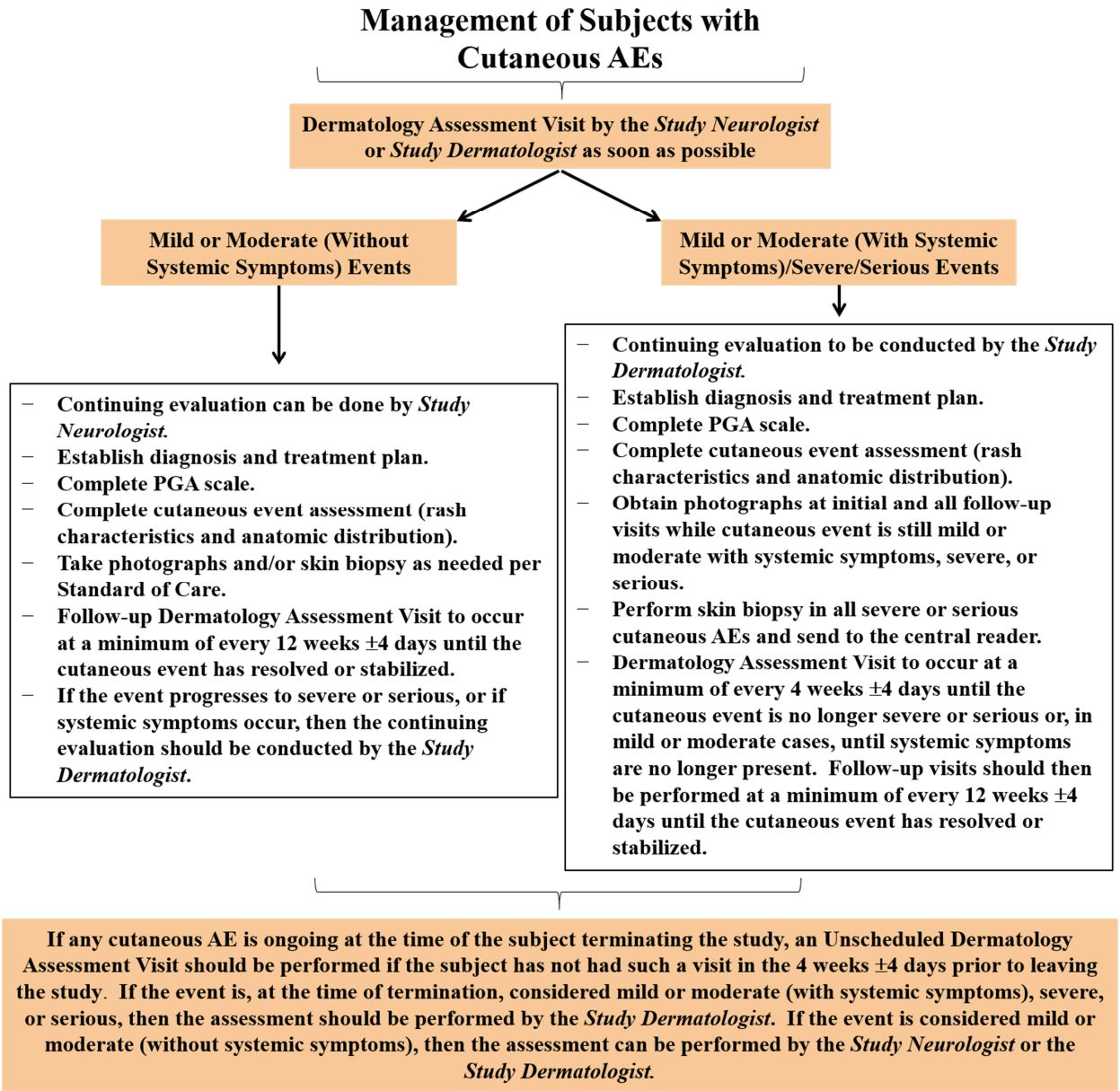
11.7.3. Cutaneous Events

Subjects participating in Study 205MS303 who develop a mild or moderate cutaneous AE that is not associated with 1 or more systemic symptoms or signs do not need to be evaluated by the *Study Dermatologist*; the *Study Neurologist* can complete the Unscheduled Dermatology Assessment Visit as soon as possible. In such cases, the *Study Neurologist* should complete the Physician's Global Assessment Scale form. Any subject participating in Study 205MS303 who develops 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) needs to be evaluated by the *Study Dermatologist* at an Unscheduled Dermatology Assessment Visit as soon as possible. Systemic symptoms associated with a mild or moderate cutaneous AE that would require evaluation by a dermatologist may include, but are not limited to, fever, hematological abnormalities, abnormalities of internal organs (as may be detected by renal and liver function tests), and lymphadenopathy.

If the *Study Neurologist* sees the subject prior to the *Study Dermatologist*, the *Study Neurologist* should, if possible, assess the cutaneous AE prior to the subject seeing the *Study Dermatologist*. The information from the assessment by the *Study Neurologist* will be captured in addition to the information from the assessment by the *Study Dermatologist*. If the cutaneous AE is assessed by the *Study Dermatologist* as a mild or moderate cutaneous AE not associated with 1 or more systemic symptoms or signs, any follow-up visits can be conducted by the *Study Neurologist*.

A flowchart is presented in Figure 2 to summarize how these subjects will be managed during the study.

Figure 2: Flowchart for Management of Subjects With Cutaneous AEs



AE = adverse event; PGA = Physician's Global Assessment.

Photographs can be taken by the *Study Neurologist* or designee at these visits for mild or moderate cutaneous AEs that are associated with more than 1 systemic symptom or sign, severe cutaneous AEs (with or without systemic symptoms or signs), or serious cutaneous AEs (with or without systemic symptoms or signs) if they have not been taken by the *Study Dermatologist* (see Section 4.2). The subjects will be asked for their consent to having their dermatological photographs used for educational purposes, if required.

Skin biopsy must be performed in subjects with severe or serious cutaneous AEs (with or without systemic symptoms or signs) at the Unscheduled Dermatology Assessment Visit, unless medically contraindicated.

Skin biopsies from study subjects with severe or serious cutaneous AEs (with or without systemic symptoms or signs) will be sent to a centralized laboratory for evaluation. Results of the skin biopsy will be provided back to the *Study Dermatologist* as soon as possible with a copy sent to the sponsor. Skin biopsy may also be locally evaluated per the discretion of the *Study Dermatologist*.

If the cutaneous AE is suspected to be an allergic or hypersensitivity reaction to study treatment, study treatment must be suspended until consultation with the *Study Dermatologist.* Under the consultation of the *Study Dermatologist*, the subject should also withhold all other non-essential medications, including protocol-required medications (as appropriate), and non-prescription drugs and supplements, at least until the cutaneous event has resolved. The decision to permanently discontinue study treatment should be made by the Investigator in consultation with the *Study Dermatologist*. If an allergic or hypersensitivity reaction to study treatment is confirmed, study treatment must be permanently discontinued.

11.7.4. Gastrointestinal Events of Inflammatory Colitis

For any subject participating in Study 205MS303 who develops symptoms of inflammatory colitis (e.g., persistent diarrhea and abdominal cramps, blood in the stool, and fever), treatment with DAC HYP should be stopped and the subject should be referred to a specialist. Some subjects with mild colitis who require DAC HYP therapy may be able to continue the study treatment if the benefit-risk profile is considered positive per Investigator's assessment and the subject's informed decision.

11.7.5. Lymphadenopathy or Lymphadenitis Events

Any subject participating in Study 205MS303 who develops clinically significant lymphadenopathy or lymphadenitis should be referred to a specialist. Additional diagnostic tests, such as imaging, blood tests, and/or biopsy, should be performed according to the local standard of care.

When diagnostic tests are performed, the results may be requested for internal safety review and, when available, biopsy materials will be sent to a centralized laboratory for evaluation. The results of the central laboratory biopsy report will be provided back to the *Study Neurologist* as soon as possible, with a copy sent to the Sponsor.

Study treatment may continue or be resumed after a temporary suspension in cases of uncomplicated lymphadenopathy if the benefit-risk profile is considered positive per the Investigator’s assessment and the subject’s informed decision. Subjects who discontinued study treatment for any reason while presenting with ongoing lymphadenopathy or lymphadenitis should be followed until the lymphadenopathy or lymphadenitis has stabilized or resolved or the study has terminated, whichever comes first.

11.8. Discontinuation of Study Treatment

A subject *must* permanently discontinue DAC HYP for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.5.4.
- The subject experiences a hypersensitivity or suspected allergic reaction (e.g., anaphylaxis and anaphylactoid reactions) to study treatment.
- The subject develops a chronic viral infection (e.g., hepatitis C, HIV).
- The subject develops elevated LFTs that meet any of the following criteria:
  - The subject develops an ALT/SGPT or AST/SGOT elevation >8×ULN that is confirmed by a repeat test (preferably within 24 hours). This requires *immediate* discontinuation of DAC HYP, and treatment may not resume unless a laboratory error is documented upon repeat testing.
  - ALT/SGPT or AST/SGOT >5×ULN for more than 2 weeks
  - ALT/SGPT or AST/SGOT >3×ULN with concomitant elevation of total bilirubin >2×ULN at any time unless a laboratory error is documented upon repeat testing
  - If a subject has treatment suspended for an LFT elevation and has also had a prior treatment suspension for an LFT elevation during DAC HYP use, DAC HYP must be permanently discontinued unless an alternative explanation for the LFT elevation unrelated to DAC HYP use is clearly identified by the Investigator.
  - The LFT abnormality that led to treatment discontinuation should continue to be monitored until resolution is documented. An Unscheduled Hepatic Assessment Visit is needed in the event of permanent discontinuation due to elevated LFTs (see Section 11.7.2).

    In addition, a careful review of all concomitant medications must be documented. The Investigator should consider discontinuation of all potential hepatotoxic medications. The subject should be referred to a physician with expertise in the diagnosis and treatment of liver disease, and additional hepatic studies should be performed according to local standard of care. The central laboratory may be utilized for additional hepatic testing per Investigator request.
- The subject experiences a cutaneous AE, which the Investigator (in consultation with the *Study Dermatologist*) considers to be a generalized allergic or hypersensitivity reaction to study treatment (see Section 11.7.3).
- The subject experiences inflammatory colitis, except in subjects with mild colitis who require DAC HYP therapy and have a positive benefit-risk profile per Investigator's assessment and the subject's informed decision (see Section 11.7.4).
- The subject requires treatment with any of the disallowed concomitant medications, unless approval is given by the Biogen Medical Director(s) or Advisory Committee. Note: IVMP for treatment of a protocol-defined relapse is allowed as detailed in the

protocol (see Section 11.5). Treatment with valproic acid, carbamazepine, lamotrigine, or phenytoin is only allowed under the conditions detailed in the protocol.

- The subject experiences a medical emergency that necessitates permanent discontinuation of treatment.
- The subject desires to discontinue treatment under this protocol.
- At the discretion of the Investigator for medical reasons or for non-compliance.
- Upon confirmatory tests 1 month apart, the subject's hematology results are as follows in the absence of an identified reversible cause by the Investigator (e.g., infection):
  - white blood cell count is <2500 cells/μL, or
  - lymphocyte count is <800 cells/μL, or
  - platelet count is <75,000 cells/μL

    Subjects who meet the above criteria must have study treatment withheld until hematology retest results are available.
- The subject experiences severe depression and/or suicidal ideation. Severe depression is defined as any episode that requires hospitalization, or at the discretion of the Investigator.

Subjects who permanently discontinue DAC HYP treatment should complete all post-treatment safety follow-up evaluations (see Section 13.3).

Subjects who permanently discontinue study treatment may be treated with alternative approved MS therapies according to local practices, and should remain in the study and complete safety follow-up evaluations as described in Section 4.2 and Section 13. However, subjects who desire to discontinue participation in this study or are unwilling or unable to comply with the protocol should be withdrawn from the study and complete an Early Termination Visit. As noted in Table 6 (Footnote 3) and Section 11.9, subjects terminating treatment with an ongoing cutaneous AE require an Unscheduled Dermatology Assessment Visit prior to leaving the study if the subject has not had such a visit in the 4 weeks±4 days prior to leaving the study. If the event is, at the time of termination, 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), then the assessment should be performed by the *Study Dermatologist*. If the event is considered mild or moderate and is not associated with 1 or more systemic symptoms or signs, then the assessment can be performed by the *Study Neurologist* or the *Study Dermatologist*.

The reason(s) for discontinuation of treatment must be recorded in the subject's CRF.

11.9. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.

Subjects who withdraw from the study should complete the End of Treatment Visit assessments as described in Section 14.9 (subjects should be encouraged to complete all other post-treatment safety follow-up visits). The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

For subjects with an ongoing mild or moderate cutaneous AE that is associated with more than 1 systemic symptom or sign, severe cutaneous AE (with or without systemic symptoms or signs), or serious cutaneous AE (with or without systemic symptoms or signs), the *Study Dermatologist* should perform an Unscheduled Dermatology Assessment Visit if this visit has not been performed in the 4 weeks±4 days prior to leaving the study (see Section 11.7.3). If the event is considered mild or moderate and is not associated with 1 or more systemic symptoms or signs, then the assessment can be performed by the *Study Neurologist* or the *Study Dermatologist.*

12. EFFICACY, DAC HYP CONCENTRATION, AND [redacted] ASSESSMENTS

12.1. Clinical Efficacy Assessments

The following clinical tests/assessments will be performed to assess the efficacy of DAC HYP:

- Relapse Assessment: Subjects who suspect they are experiencing new symptoms or worsening symptoms need to contact the *Study Neurologist* within 48 hours of the onset of the symptoms.
- Refer also to Section 14.6 Unscheduled Relapse Assessment Visit for additional details.
- EDSS [Kurtzke 1983]: Review of EDSS procedures will be performed prior to study start as necessary for training purposes.
- MSFC [Fischer 1999]: Timed 25-Foot Walk, 9HPT with both upper extremities, and PASAT 3
- SDMT: Data will be collected only from subjects enrolled from Study 205MS301, and test performance data will be collected beginning in Week 144 and every 24 weeks thereafter.
- PASAT 3: This test will be performed separately from the MSFC beginning in Week 144 and every 24 weeks thereafter. Data will be collected only from subjects enrolled from Study 205MS301.
- Brain MRI scan with and without Gd (T2 hyperintense lesions, T1 hypointense lesions, Gd+ lesions, brain atrophy).
- Subjects will complete the following questionnaires at various timepoints specified in Section 4.2:
  - EQ-5D quality of life questionnaire (the EQ-5D descriptive system and the EQ-VAS)
  - MSIS-29 (29-item physical and psychological assessment)
  - HRU (hospitalizations, emergency room visits, and unscheduled neurologist visits)
  - Treatment Satisfaction Questionnaire for Medication (with PFS use) or Treatment Satisfaction Survey (with autoinjector use)
  - HRPQ (productivity questionnaire)

Refer to Section 4.2 for the timing of assessments.

12.2. Pharmacokinetic Assessments

Blood samples 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])

Unscheduled PK/[redacted] Visits

Whole blood samples will be collected at Unscheduled PK/[redacted] Visits for potential determination of DAC HYP serum concentrations 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.

Refer to Section 4.2 for the timing of sample collection.

12.3. [redacted]

[redacted]

PK/[redacted]

[redacted] PK/[redacted]

12.4. [redacted]

[redacted]

13. SAFETY ASSESSMENTS

13.1. Clinical Safety Assessments

The following clinical assessments will be performed to determine the safety profile of DAC HYP:

- Medical history
- Physical and neurological examination
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate (subjects must remain in the same body position quietly for 5 minutes prior to having their pulse and blood pressure taken)
- Weight
- Concomitant therapy and procedure recording
- AE and SAE recording
- Beck Depression Inventory, Second Edition (BDI-II)
- Immunogenicity assessments
- Alcohol Use Disorders Identification Test - Consumption Questionnaire (AUDIT-C)

See Section 4.2 for the timing of assessments.

13.2. Laboratory Safety Assessments

The following laboratory tests will be performed to assess the safety profile of DAC HYP:

- Hematology: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell count, white blood cell count (with differential), and platelet count
- Blood chemistry: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT/SGPT AST/SGOT, lactate dehydrogenase, gamma glutamyl transferase, blood urea nitrogen (BUN), creatinine, and bicarbonate
- Comprehensive hepatic panel (only required for subjects who permanently discontinue dosing due to elevated LFTs as defined in Section 11.7.2). Testing will include screening for the following:
  - hepatitis A, B, C, and E
  - other viral infections: Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV-6), varicella zoster virus (VZV), herpes simplex virus (HSV), and Parvovirus B19
  - gamma-globulins, including IgG levels

  - autoantibodies: antinuclear antibody (ANA), anti-smooth muscle antibody (anti-SM), anti-liver/kidney microsome-1 antibody (anti-LKM1), antimitochondrial antibody (AMA), and anti-soluble liver antigen (SLA)

  Additional testing may be performed based on results of the above testing or the subject's clinical history. Additional hepatic assessments should be performed according to local standard of care.

- Thyroid function panel, including TSH and T4
- Urinalysis: protein, blood, glucose, ketones, nitrite, leukocytes, pH, specific gravity by dipstick and microscopy
- Urine pregnancy testing
- Skin biopsy (only required for subjects who experience cutaneous AEs reported as serious or severe as defined in Section 11.7.3)

Refer to Section 4.2 for the timing of assessments.

13.3. Study-Specific Safety Assessments

Blood serum collection for binding and neutralizing anti-drug antibody testing will be performed. Note: When necessary, samples drawn for one purpose (e.g., immunogenicity) may be used to meet another protocol-defined objective (e.g., DAC HYP concentration assessment).

14. SCHEDULE OF EVENTS

14.1. Overview

A written, signed Informed Consent Form (ICF) and all authorizations required by local law (e.g., Protected Health Information [PHI] in North America) must be obtained prior to performing any tests or assessments under this protocol.

For subjects entering from Study 205MS301, tests/assessments performed at the subject's last visit in Study 205MS301 and within 28 days of the subject's first dose of DAC HYP (Week 0) in Study 205MS303 may be used as baseline data for Study 205MS303; if final Study 205MS301 tests/assessments are not performed within the 28-day window, they must be repeated upon entry into Study 205MS303 and before the first dose of DAC HYP is administered.

Week 144 Visit of Study 205MS303 will be the Entry Visit for subjects enrolled from Study 205MS203 or Study 205MS302. 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; test/assessments performed >28 days before the Entry Visit must be repeated at the Entry Visit. Central LFT testing is *mandatory* at Entry Visit.

Clinic visits will occur once every 4 weeks for the first 12 weeks, then every 12 weeks thereafter.

On a dosing day, all tests and assessments must be performed prior to DAC HYP administration. When DAC HYP administration and MRI evaluation are required at the same visit, the MRI scan should be performed prior to DAC HYP administration (Note: MRI scan can be performed up to 4 days prior to the visit).

Before a monthly dose of DAC HYP is given, LFT results (ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only) from prior testing performed within the previous 32 days must be reviewed by the *Study Neurologist* or their backup, and must be within the protocol-required limits.

After Week 12, subjects will have the option of administering DAC HYP at home following Investigator review of monthly pre-dose LFT results. Subjects who are not able to administer their own dose or prefer not to administer their own dose of DAC HYP will be given the option to choose another individual (caregiver) to administer their treatment at home or to have their treatment administered by staff at the study site.

Follow-up visits will take place at 8, 12, 16, and 24 weeks after each subject's last dose of DAC HYP. Unscheduled Relapse Assessment Visits (if necessary) should be scheduled within 72 hours of the onset of any new neurological symptoms that may indicate neurological worsening or possible clinical relapse. Unscheduled Hepatic Assessment Visits (if necessary) should be scheduled as soon as possible (but within 1 week) following discontinuation of study treatment due to elevated LFTs. Unscheduled Dermatology Assessment Visits will be performed as per Section 11.7.3.

Unscheduled PK/[redacted] Visits should be scheduled as soon as possible following significant changes in subjects' medical conditions, as assessed by the Investigator. This visit must be approved by the Biogen Medical Director in advance.

14.2. Site Personnel

For each subject, the Principal Investigator will designate the following study site personnel:

- A primary *Study Neurologist* and backup neurologist
- A primary and backup *Nurse* (or Study Coordinator)
- A primary and backup *Examining Technician*
- An *MRI Technician*
- A *Pharmacist* (or authorized designee)
- A *Study Dermatologist*

The *Study Neurologist* must have a minimum of 2 years of neurology specialty training and anticipate at least a 3-year commitment to the study, or be approved by the study Advisory Committee. The *Study Neurologists* may designate another neurologist at the center who meets the same qualifications to perform the EDSS assessments and other neurologic assessment during the trial. Whenever possible, the EDSS and other neurologic assessments should be performed by the same examiner who performed these assessments in the parent study.

The primary *Study Neurologist* will be responsible for:

- Management of the routine neurological care of the subject
- Assessment (including assignment of causality) and treatment of AEs and MS relapses
- Obtaining an EDSS score based on a detailed neurological examination at the scheduled timepoints required in the protocol, and at every Unscheduled Relapse Assessment Visit
- Review of selected hematology and all blood chemistry results from the central laboratory
- Assessment of LFT results, as detailed in Section 11.7.2
- Monitoring and follow-up of any abnormal hepatic tests
- Referral of subjects to a dermatologist if that subject experiences a mild or moderate cutaneous AE that is associated with more than 1 systemic symptoms or signs, a severe cutaneous AE (with or without systemic symptoms or signs), or a serious cutaneous AE (with or without systemic symptoms or signs) as described in Section 11.7.3
- Performing Dermatology Assessments and Physician Global Assessment Scale in subjects with mild or moderate cutaneous AEs (not associated with 1 or more systemic symptoms or signs), as detailed in Section 11.7.3

- Assessment of injection sites, as detailed in Table 7

Hematology and blood chemistry data will be sent to the investigational sites to aid in management of the subject.

The primary *Nurse* or Study Coordinator will be responsible for:

- Assisting the *Study Neurologist* in subject management, including the treatment of AEs, the treatment and assessment of disease relapses, and the recording of AEs and concomitant medications
- Monitoring the EDSS scores and informing the *Study Neurologist* if a subject experiences at least a 1.0-point increase on the EDSS 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
- Administering the patient-reported questionnaires (BDI-II, MSIS-29, EQ-5D), HRU, and subject assessment of injection pain (VAS)
- Collection of blood samples and obtaining vital signs
- Study treatment administration/dispensation/accountability

To ensure consistency across sites, *Examining Technicians* must undergo a standardized training session prior to enrollment of subjects at their site. All sites should attempt to maintain the same *Examining Technician* throughout the study. If an *Examining Technician* has to be replaced, the new *Examining Technician* must undergo a training session. It is not necessary for the *Examining Technician* to be a healthcare professional as long as he/she is qualified, in the opinion of the Principal Investigator, to administer the MSFC (Note: MSFC was administered in this study only until Week 48; therefore, the role of the *Examining Technician* ended after that).

The *MRI Technician* will be responsible for:

- Performing a brain MRI scan with and without Gd at all protocol-required timepoints. Study-specific MRI scan procedures and protocols, which will be provided prior to study start, must be followed.

The *Pharmacist* (or authorized designee) will be responsible for:

- Storage, distribution, and accountability of study treatment.

The *Study Dermatologist* will be responsible for:

- Performing Cutaneous Assessments and Physician Global Assessment Scale in subjects with a mild or moderate cutaneous AE that is associated with more than 1 systemic symptoms or signs, a severe cutaneous AE (with or without systemic symptoms or signs), or a serious cutaneous AE (with or without systemic symptoms or signs), as detailed in Section 11.7.3
- Documenting cutaneous events, as per the protocol.
- Taking photograph(s) of the affected body areas, as required.
- Performing a skin biopsy, as required.

- Evaluating, treating, and managing mild or moderate cutaneous AEs that are associated with more than 1 systemic symptoms or signs, severe cutaneous AEs (with or without systemic symptoms or signs), or serious cutaneous AEs (with or without systemic symptoms or signs), as described in Section 11.7.3.

14.3. Subject Management

The following restrictions apply to all subjects enrolled into this study:

- Subjects must follow the restrictions for concomitant medications and procedures described in Section 11.5.
- Contraception requirements are to be followed as described in Section 15.5.3.
- Whenever possible, a subject should undergo protocol-required tests and assessments at the same time of day throughout the study.
- Subjects should not donate blood until 4 months after their last dose of DAC HYP.
- Subjects should not receive live or live-attenuated vaccines during DAC HYP treatment or for at least 6 months after treatment with DAC HYP.

14.4. Special Instructions for Tests and Assessments

Note: Information about the tests and assessments to be performed in this study is also provided in Section 12 and Section 13, and in the Study Reference Manual.

14.4.1. Rescreening

Subjects who are not eligible for participation at baseline due to a temporary condition (e.g., acute infection) are allowed to be rescreened once the condition has resolved, provided they are rescreened and enrolled within 6 months of completing Study 205MS301, Study 205MS203, or Study 205MS302.

14.4.2. Pregnancy Testing

- Pregnancy testing is only required for women of childbearing potential. A urine pregnancy test is to be performed at the Baseline/Entry Visit and at other timepoints designated in Section 4.2 Schedule of Events. Study treatment will be immediately discontinued if the subject has a positive pregnancy test at any time during the study.
- Results from all urine pregnancy tests must be reviewed by the study site prior to dosing and must be negative.

14.4.3. Liver Function Test Assessments Prior to DAC HYP Dosing

Before a monthly dose of DAC HYP is given, LFT results from prior testing performed within the previous 32 days must be reviewed by the *Study Neurologist* or their backup, and must be within protocol-required limits as described in Section 11.7.2.

LFTs can be performed as follows:

- Samples for LFTs must be drawn prior to administration of the monthly DAC HYP dose. These samples may be tested either locally inside or outside of the clinic (e.g., at a local laboratory or by visiting nurses) or at the central laboratory at the discretion of the Investigator and the results can then be used to determine whether dosing should continue or be suspended at the monthly dosing timepoint (see Section 11.1).
- 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).
- If the subject is administering DAC HYP injections at home, site personnel must contact the subject after review of prior LFT results performed within the previous 32 days to authorize the monthly injection, or if LFT results warrant, to instruct the subject to withhold their injection.
- LFTs following a treatment suspension must be performed through the central laboratory until the LFT abnormality has resolved. In cases where LFTs cannot be performed via central laboratory, repeat LFT results from local laboratory can be used for confirmation.

14.4.4. Other Assessments

- Vital signs include systolic and diastolic blood pressure, pulse, and body temperature, and should be measured pre-dose. The subject must rest quietly for 5 minutes prior to blood pressure and pulse measurements. Weight will be collected at Baseline/Entry Visit and at the time of first autoinjector use at selected sites.
- The MSIS-29 must be administered prior to the subject's visit with the *Study Neurologist*.
- Subject assessment of injection pain using a VAS should be completed as soon as possible after the injection is administered, but no later than 10 to 30 minutes post-injection.
- The first 4 DAC HYP injections (i.e., Weeks 0 through 12) must be given in the clinic. The first of these injections must be given by study personnel. At subsequent visits, subjects and/or caregivers will be instructed on DAC HYP self-administration and may administer their scheduled dose under staff supervision. After the subject completes the required in-clinic injections (i.e., after Week 12), DAC HYP may be dispensed to subjects for at-home administration if the subject chooses. If necessary, drug dispensation may occur at monthly intervals.
- Additional visits to assess elevated LFTs, cutaneous events, or PK/[redacted] markers may be required as described in Section 11.7.

14.5. Definition of MS Relapse and Disability Progression

14.5.1. MS Relapse

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** or their backup. The subject must have objective signs on the examination confirming the event.

*When possible subjects should be evaluated by the same neurologist assigned to them in the parent study.

New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse. New or recurrent neurological symptoms that occur less than 30 days following the onset of a protocol-defined relapse should be considered part of the same relapse. Management of MS relapse is described in Section 14.6.

14.5.2. Disability Progression

Disability progression can only be confirmed from the EDSS scores obtained according to the protocol-defined schedule of assessments at regular visits, and is defined as one of the following:

- at least a 1.0-point increase on the EDSS 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

14.6. Management of MS Relapse

Subjects who experience new or worsening neurological symptoms must contact the *Nurse* or *Study Neurologist* or their backup within 48 hours after the onset of symptoms. A standardized Suspected Relapse Questionnaire will be completed to determine the necessity of an Unscheduled Relapse Assessment Visit.

If required, the subject will then be evaluated in person by the *Study Neurologist* not more than 72 hours after the onset of the symptoms. At the Unscheduled Relapse Assessment Visit, the *Study Neurologist* is to perform a relapse assessment and obtain an EDSS score. New objective findings on neurological examination performed by the *Study Neurologist** are required to determine if a suspected protocol-defined relapse has occurred. Treatment of an acute relapse event with intravenous methylprednisolone (IVMP) [or equivalent] may proceed at the discretion of the *Study Neurologist* after the examination and will not affect the subject's eligibility to continue in the study.

*When possible subjects should be evaluated by the same neurologist assigned to them in the parent study.

Subjects who prematurely discontinue study treatment should complete safety follow-up evaluations (see Section 4.2 and Section 13).

Subjects who permanently discontinue DAC HYP treatment should complete the visit schedule described in Section 11.8.

14.7. Cutaneous Events

Subjects who experience a mild or moderate cutaneous AE that is associated with more than 1 systemic symptoms or signs, a severe cutaneous AE (with or without systemic symptoms or signs), or a serious cutaneous AE (with or without systemic symptoms or signs) must be referred to and evaluated and managed by the *Study Dermatologist* as per Section 11.7.3. An Unscheduled Dermatology Assessment Visit will be performed, at which time a photograph will be taken, whenever a subject experiences a mild or moderate cutaneous AE that is associated with more than 1 systemic symptoms or signs, a severe cutaneous AE (with or without systemic symptoms or signs), or a serious cutaneous AE (with or without systemic symptoms or signs), per Table 6. Subjects who develop a mild or moderate cutaneous AE that is not associated with 1 or more systemic symptoms or signs do not need to be evaluated by the *Study Dermatologist*; the *Study Neurologist* can complete the Unscheduled Dermatology Assessment Visit as soon as possible.

If a generalized allergic or hypersensitivity reaction to study treatment is confirmed, study treatment must be permanently discontinued as per Section 11.8.

14.8. Unscheduled Hepatic Assessment Visit

The following tests/assessments will be performed as soon as possible (but within 7 days) after discontinuation of study treatment for subjects who are required to discontinue dosing due to elevated LFTs as described in Table 6 and Section 11.8.

- Physical examination and vital signs
- Comprehensive hepatic panel
- Recording of concomitant therapy
- Monitor and record AE/SAEs
- Protocol compliance and DAC HYP accountability
- LFTs (ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only)

14.9. Lymphadenopathy and Lymphadenitis Events

Subjects who experience a clinically significant event of lymphadenopathy or lymphadenitis should be referred to a specialist as per Section 11.7.5.

Interruption or discontinuation of DAC HYP treatment due to events of lymphadenopathy or lymphadenitis is a clinical decision that should take the overall benefit-risk assessment of therapy into consideration. Subjects who discontinued study treatment for any reason while presenting with ongoing lymphadenopathy or lymphadenitis should be followed until the lymphadenopathy or lymphadenitis has stabilized or resolved or the study has terminated, whichever comes first.

14.10. Post-Treatment Safety Follow-Up Visit Schedule for All Subjects

All subjects should complete the following schedule of safety follow-up visits after their last dose of DAC HYP:

- End of Treatment Visit (i.e., the assessments required at Week 240). For subjects who prematurely discontinue study treatment before Week 240, these assessments should be performed 4 weeks (±4 days) after the subject's last dose of DAC HYP.
- Post-treatment safety follow-up visits at 8, 12, 16, and 24 weeks after the subject's last dose. The details of these visits are shown in Table 5.

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 from Week 156 Visit in Study 205MS303 (see Table 4) as long as they meet the eligibility criteria (Section 8).

15. SAFETY DEFINITIONS, MONITORING, AND REPORTING

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

At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Serious Pretreatment Event

A serious pretreatment event is any event that meets the criteria for SAE reporting (as defined in Section 15.1.3) and occurs after the subject signs the ICF, but before administration of study treatment.

15.1.2. Adverse Event

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

15.1.3. Serious Adverse Event

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

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

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.

15.2. Monitoring and Recording Events

15.2.1. Serious Pretreatment Events

A serious pretreatment event experienced by the subject after signing and dating the ICF but before administration of study treatment is to be recorded on the SAE Form and faxed to the contract research organization (CRO) within 24 hours of the study site staff becoming aware of the event (see Section 15.2.5).

15.2.2. Adverse Events

Any AE experienced by the subject between the time of signing the ICF and subject's final visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

15.2.3. Serious Adverse Events

Any SAE experienced by the subject between the time of the first dose of study treatment and subject's final visit is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to the CRO.

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

Subjects will be followed for all SAEs until the subject's final visit. Thereafter, the event should only be recorded if the Investigator considers it related to study treatment.

15.2.4. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.3.
- The relationship of the event to study treatment as defined in Section 15.3.1.
- The severity of the event as defined in Section 15.3.2.

15.2.5. Immediate Reporting of Serious Adverse Events

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

Reporting Information for SAEs

Any Serious Event that occurs between the time the subject has signed informed consent and subject's final visit must be reported to the CRO within 24 hours of the study site staff becoming aware of the event. **Thereafter, the event should only be recorded if the Investigator considers it related to study treatment**.

A report pertaining to an event that occurs between the time the subject has signed informed consent and subject's final visit ***must be submitted*** to the CRO regardless of the following:

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

To report initial or follow-up information on a Serious Event, fax a completed SAE form to the following:

North America: [redacted]
Latin America: [redacted]
Europe and Asia Pacific: [redacted]

(Country-specific fax numbers are provided in the Study Reference Guide.)

15.2.5.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate CRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen SABR or designee.

15.3. Safety Classifications

15.3.1. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

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

15.3.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.3.3. Expectedness of Events

Expectedness of all AEs will be determined according to the Investigator's Brochure.

15.4. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the

Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.

- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

15.5. Procedures for Handling Special Situations

15.5.1. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed to the CRO within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded in the CRF; dosing information is recorded on a CRF.

15.5.2. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator or designee should contact the CRO Medical Monitor at one of the following phone numbers:

North America (USA and Canada): [redacted]

Latin America: [redacted]

Europe and Asia Pacific: [redacted]

15.5.3. Contraception Requirements

All women of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 4 months after their last dose of study treatment.

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

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy

For the purposes of the study, effective contraception is defined as follows:

For females:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with spermicide; diaphragm, sponge, cervical cap)

- True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

15.5.4. Pregnancy

Subjects should not become pregnant during the study. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report the pregnancy by faxing the appropriate form to Pharmacovigilance at the CRO within 24 hours of the study site staff becoming aware of the pregnancy (refer to Section 15.2.5 for reporting information). The Investigator or study site staff must report the outcome of the pregnancy to Pharmacovigilance at the CRO.

Please note that congenital abnormalities/birth defects in the offspring of male or female subjects should be reported when conception occurred during the study treatment period.

15.5.5. Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Biogen Safety and Benefit-Risk Management (SABR) will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

15.6. Investigator Responsibilities

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow-up on the outcome of the pregnancy.
- Complete an SAE form for each serious event and fax it to the CRO within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the CRO within 24 hours of the study site staff becoming aware of new information.
- Complete an Adverse Event of Special Interest form for each transaminase elevation, hepatic event, and cutaneous event as described in the protocol and fax it to the CRO as soon as possible following the study site staff becoming aware of the event.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.

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

15.7. Biogen Responsibilities

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor or designee is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

16.1. Description of Objectives

See Section 6.1, Objectives.

16.2. Description of Endpoints

See Section 6.2, Endpoints.

16.3. Demography and Baseline Disease Characteristics

Demographic data collected at baseline will be summarized (i.e., age, gender, ethnicity, and weight). Medical history and baseline characteristic data (e.g., EDSS, number of relapses in the previous study, MRI endpoints) will also be summarized.

16.4. Safety and Efficacy

16.4.1. Analysis Population

Study 205MS303 Safety Population

The safety population will include all subjects who received at least 1 dose of DAC HYP in Study 205MS303. All safety analyses will be completed on the safety population.

Study 205MS303 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who received at least 1 dose of DAC HYP in Study 205MS303. This population will be utilized for the efficacy analyses.

Study 205MS301 and Study205MS303 Intent-to-Treat population

This population will include all subjects randomized to DAC HYP or Avonex in Study 205MS301 and received at least one dose of DAC HYP in Study 205MS303.

16.4.2. General Methods of Analysis

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include the number of subjects with data, mean, standard deviation, median, and range. Categorical endpoints will include the number of subjects with data and the percentage in each category.

Analyses will generally be descriptive in nature and will focus on data collected during Study 205MS303 only. However, for relevant efficacy analyses, the data may be summarized by previous treatment group (Avonex or DAC HYP). Also, statistical comparisons may be made between efficacy in Study 205MS301 and efficacy in Study 205MS303 among subjects previously randomized to Avonex in Study 205MS301.

All statistical tests will be 2-sided with an overall Type I error of 5%. Adjustments for multiple comparisons will not be considered.

16.4.3. Primary Endpoints Analysis

Clinical Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. All treatment-emergent events will be included in the evaluation of safety. Treatment emergent includes any event that either occurs or worsens in severity after the onset of study treatment. Overall incidence of treatment-emergent events will be summarized; in addition, summaries by severity and by relationship to study treatment will be provided. The summary tables will include incidence estimates for the overall system organ class as well as for preferred terms within each system organ class. In order to assess whether the incidence of events changes over time, the incidence of key events may also be summarized by time period (e.g., 6-month time intervals).

16.4.4. Other Safety Endpoint Analyses

Unless otherwise specified, the baseline measurement for safety assessments such as laboratory values and vital signs was the measurement acquired on the day of the first receipt of DAC HYP. The first receipt of dosing of DAC HYP could be either Study 205MS303 (for subjects who received Avonex in Study 205MS301) or the parent studies (i.e., Study 205MS301, Study 205MS203, or Study 205MS302) for all other subjects.

Laboratory Data

Changes in laboratory values will be summarized using shift tables. Shift tables will include hematology, LFTs, kidney function tests, electrolytes, and other blood chemistry tests. Shifts will be presented from baseline of DAC HYP treatment (the last measurement acquired before or on the day of the first receipt of DAC HYP, e.g., Study 205MS303 baseline for subjects randomized to Avonex in Study 205MS301 and Study 205MS301 baseline for subjects randomized to DAC HYP 150 mg in Study 205MS301). Summaries of worst post-baseline laboratory values by clinically relevant categories may also be presented for selected parameters of interest by treatment group. For example, for LFT (alkaline phosphatase, ALT, AST, GGT, and total bilirubin), categories may be defined based on cutoff values relative to the ULN.

Vital Signs

Vital signs collected will be examined to determine the incidence of clinically relevant abnormalities. These abnormalities are described in Table 8. For the purpose of the shifts from baseline, the baseline evaluation at the start of DAC HYP treatment will be used.

For each vital sign, the number of subjects evaluated and the number and percentage of subjects with the defined abnormality at any time post dosing will be presented by treatment group.

Table 8: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C or an increase from baseline of ≥1°C
Pulse	>120 beats per minute (bpm) or an increase from baseline of 20 bpm <50 bpm or a decrease from baseline of >20 bpm
Systolic Blood Pressure	>180 mmHg or an increase from baseline of >40 mmHg <90 mmHg or a decrease from baseline of >30 mmHg
Diastolic Blood Pressure	>105 mmHg or an increase from baseline of >30 mmHg <50 mmHg or a decrease from baseline of >20 mmHg

Physical Examination

The physical examination findings will be summarized.

16.4.5. Efficacy Endpoints Analyses

Annualized Relapse Rate

Relapses will be summarized over the follow-up period in Study 205MS303. For subjects in Study 205MS301 and Study 205MS303 ITT population, relapses may be summarized over the combined study period (Studies 205MS301 and 205MS303).

A negative binomial regression model will be used to estimate the adjusted ARR.

Proportion of Subjects with a Relapse

The proportion of subjects relapsed will be estimated using a Kaplan-Meier curve.

Disability Progression

Sustained disability progression is defined as at least a 1.0 point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 24 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS <1.0 that is sustained for 24 weeks. The proportion of subjects with progression will be summarized using a Kaplan-Meier curve. In addition, summary statistics for EDSS and for the change from baseline in EDSS will be presented by visit, and for subjects who participated in Study 205MS301, by previous treatment group.

MSFC

Changes in the MSFC z-score will be summarized by study visit, and for subjects who participated in Study 205MS301, by previous treatment group. For subjects in Study 205MS301 and Study 205MS303 ITT population, MSFC z-score may be summarized over the combined study period (Studies 205MS301 and 205MS303). Details on the calculations of the z-score for each component will be described in the statistical analysis plan.

SDMT

Changes in the SDMT scores will be summarized by study visit and by previous treatment group in Study 205MS301. Change in the SDMT scores over the combined study period (Studies 205MS301 and 205MS303) will be calculated using the Study 205MS301 baseline visit

as baseline. Change in the SDMT score over the Study 205MS303 study period will be calculated using the last SDMT measurement in Study 205MS301 as baseline.

PASAT 3

Changes in the PASAT 3 scores will be summarized by study visit and by previous treatment group in Study 205MS301. Change in the PASAT 3 scores over the combined study period (Studies 205MS301 and 205MS303) will be calculated using the Study 205MS301 baseline visit as baseline. Change in the PASAT 3 score over the Study 205MS303 study period will be calculated using the Week 0/baseline visit as baseline.

MRI Endpoints

MRI endpoints will be summarized with descriptive statistics both as a continuous variable and categorically. Over time summaries and summaries by previous treatment group (Avonex or DAC HYP 150 mg) may also be provided. A negative binomial regression model will be used for the analysis of new or newly enlarging T2 lesions. The change in volume of lesions will be analyzed using an analysis of covariance.

Quality of Life Outcomes

Actual scores and change from baseline in quality of life endpoints will be summarized by visit.

Pharmacokinetics

The population for DAC HYP concentration analyses will include all subjects who received at least 1 dose of study medication and who have at least 1 sample available for analysis.

Serum concentration levels will be summarized with descriptive statistics by visit.

Antigenicity/Immunogenicity Data

Immunogenicity (i.e., ADAs to DAC HYP) will be assessed on subjects. Positive samples will be further tested for NAbs to DAC HYP using a specific NAb assay. Results will be tabulated by time period and overall.

16.5. Interim Analyses

No formal interim analyses are planned for this study. However, analyses may be performed prior to the end of the study at the discretion of the Sponsor.

16.6. Sample Size Considerations

There is no formal sample size calculation. The number of subjects in this study is determined by the number of subjects who completed Study 205MS301, Study 205MS203, or Study 205MS302.

17. ETHICAL REQUIREMENTS

Biogen and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

17.1. Declaration of Helsinki

The Investigator and Biogen must adhere to the principles set forth by the Declaration of Helsinki dated October 2008.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor may submit documents on behalf of the study sites in countries other than the US as applicable.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

It is the responsibility of the Principal Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

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

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

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

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including Baseline/Entry Visit tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all subjects participating in a clinical study conducted by Biogen.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including Baseline/Entry Visit tests and assessments.

Each consent form should contain an authorization allowing the Principal Investigator(s) and Biogen to use and disclose PHI (i.e., subject-identifiable health information) in compliance with local law.

The signed consent form will be retained with the study records.

17.4. Subject Data Protection

Prior to any testing under this protocol, including Baseline/Entry Visit tests and assessments, candidates must also provide all authorizations required by local law (e.g., PHI authorization in North America).

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws.

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not enroll any subjects prior to completion of a study initiation visit, conducted by Biogen or designee. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Principal Investigator(s) must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the course of the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the study site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

Biogen will be responsible for all administrative aspects of this study including, but not limited to, study initiation, monitoring, management of AEs, and data management.

19.1. External Contract Organizations

19.1.1. Contract Research Organization

The CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Electronic or Remote Data Capture

Subject information will be captured and managed by study sites on electronic CRFs via a remote data capturing system.

19.1.3. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by Biogen to analyze all hematology, blood chemistry, and urine samples collected for this study.

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).

19.1.4. Central Facility for Independent Assessment of Biopsy Samples

A central laboratory service has been selected by Biogen to coordinate the collection and distribution of biopsy samples. A central assessor has been selected to subsequently analyze skin biopsies or lymph node biopsies (as applicable).

19.1.5. Central Facility for Other Assessments

MRI Reading Center

All scheduled MRI scans with and without Gd will be evaluated at a central MRI reading center. All study sites will be required to send a test scan to the MRI Reading Center for evaluation in order to ensure that the site's scanning techniques are appropriate. This review will take place before the study site is permitted to enroll any subjects into the study.

Original MRI images are to be sent to the MRI Reading Center for review (MRI shipping instructions will be provided prior to the start of enrollment at each site).

Additional and more detailed MRI scans with and without Gd procedures and instructions are included in the study MRI manual (to be provided under separate cover prior to start of the study).

19.2. Study Committees

19.2.1. Advisory Committee

The Advisory Committee from parent Study 205MS301 will oversee the administrative progress and provide scientific and medical direction for this study while Study 205MS301 is ongoing. Advisory Committee will monitor subject accrual and compliance with the protocol at individual study sites. The Advisory Committee will determine whether the study should be stopped or amended for reasons other than safety.

Members of the Advisory Committee will include the Medical Director, Clinical Trial Manager, and Project Statistician from Biogen (and/or their designees), and participating Investigators. Biogen will designate one of the participating Investigators to be the Chairperson of the Advisory Committee.

19.2.2. Internal Safety Monitoring Committee

An internal Safety Monitoring Committee will be formed to review interim safety data on an ongoing basis. Investigational sites will be notified of any relevant safety findings that may jeopardize subject safety.

19.3. Changes to Final Study Protocol

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

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

In the event of a protocol modification, the subject consent form may require similar modifications (see Section 17.2 and Section 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator

must notify Biogen of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate one of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors, including, but not limited to, the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by Biogen.

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

20. REFERENCES

Bielekova B, Howard T, Packer AN, et al. Effect of anti-CD25 antibody daclizumab in the inhibition of inflammation and stabilization of disease progression in multiple sclerosis. Arch Neurol. 2009;66(4):483-9.

Bielekova B, Richert N, Howard T, et al. Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta. Proc Natl Acad Sci U S A. 2004;101(23):8705-8.

Fischer JS, LaRocca NG, Miller DM, et al. Recent developments in the assessment of quality of life in multiple sclerosis (MS). Mult Scler. 1999;5(4):251-9.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52. Epub 1983/11/01.

Rose JW. Treatment of Multiple Sclerosis with a Humanized Monoclonal Antibody Specific for IL-2 Receptor Chain. Neurology. 2003;60(Suppl 1):A478-9.

Rose JW, Watt HE, White AT, et al. Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. Ann Neurol. 2004;56(6):864-7.

Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol. 2010;9(4):381-90.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "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 Who Have Completed Study 205MS301" and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

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

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

PROTOCOL NUMBER: 205MS303

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: 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 Who Have Completed Study 205MS301

EUDRA CT NO: 2012-003176-39

DATE: 29 January 2016
Version 3
Final

Supersedes previous Version 2 dated 01 April 2015.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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

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

Biogen Australia Pty Ltd
Level 3
123 Epping Road
North Ryde, NSW 2113
Australia

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

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

2. LIST OF ABBREVIATIONS

ADAs	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ARR	annualized relapse rate
AST	aspartate aminotransferase
AUDIT-C	Alcohol Use Disorders Identification Test - Consumption Questionnaire
BDI-II	Beck Depression Inventory, Second Edition
bpm	beats per minute
BUN	blood urea nitrogen
CRF	case report form
CRO	contract research organization
DAC HYP	Daclizumab High Yield Process
DHA	Directions for Handling and Administration
EDSS	Expanded Disability Status Scale
EQ-5D	European Quality of Life, 5-dimensions
EQ-VAS	European Quality of Life, visual analog scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gd	gadolinium
GGT	gamma-glutamyltransferase
HIV	human immunodeficiency virus
HRPQ	Health Related Productivity Questionnaire
HRU	health resource utilization
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFN	interferon
IL-2	interleukin-2
IM	intramuscular
ITT	intent-to-treat
IV	intravenous
IVIg	intravenous immunoglobulin
IVMP	intravenous methylprednisolone
LFT	liver function test
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale-29
NAbs	neutralizing antibodies
NK	natural killer cells

PASAT 3	3-Second Paced Auditory Serial Addition Test
[redacted]	[redacted]
PFS	prefilled syringe
PHI	protected health information
PK	pharmacokinetic(s)
RRMS	relapsing-remitting multiple sclerosis
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
SC	subcutaneous
SDMT	Symbol Digit Modalities Test
SGOT	serum glutamic oxaloacetic transaminase; see AST
SGPT	serum glutamic pyruvic transaminase; see ALT
SNP	single nucleotide polymorphism
SUSAR	suspected unexpected serious adverse reaction
T1	MRI hypointense designation
T2	MRI hyperintense designation
T4	thyroxine
ULN	upper limit of normal
US	United States
VAS	visual analog scale

3. SYNOPSIS

This is a brief summary. For details refer to the body of the protocol.

Protocol Number:	205MS303
Protocol Title:	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 Who Have Completed Study 205MS301
Version Number:	3
Name of Study Treatment:	Daclizumab High Yield Process (DAC HYP)
Study Indication:	Relapsing-Remitting Multiple Sclerosis (RRMS)
Phase of Development:	3
Rationale for the Study:	To evaluate the long-term safety, efficacy, and immunogenicity of DAC HYP in subjects with multiple sclerosis (MS) who have completed Study 205MS301 (DECIDE), Study 205MS203 (SELECTED), or Study 205MS302 (OBSERVE).
Study Objectives and Endpoints:	**Objectives** Primary: 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. Secondary: 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 Avonex® in Study 205MS301

Exploratory:

- [redacted]

Endpoints

Primary:

- Incidence of adverse events (AEs) and serious AEs (SAEs)

Secondary:

- 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, gadolinium-enhancing (Gd+) 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 (EQ-5D) and European Quality of Life, visual analog scale (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 analog scale [VAS]) and clinician injection site assessments
- Incidence of anti-drug antibodies to DAC HYP over time
- Incidence of neutralizing antibodies to DAC HYP over time

Study Design:	Multicenter, open-label, long-term extension study
Rationale for Dose and Schedule Selection:	The DAC HYP dose and schedule were used in the pivotal Phase 3 205MS301 study and will be the treatment regimen used in the commercial setting. The same DAC HYP dose and schedule were used in Study 205MS203 and Study 205MS302.
Study Location:	Global
Number of Planned Subjects:	Approximately 1600 subjects. This includes approximately 1200 subjects who completed Study 205MS301. Additionally, approximately 400 subjects from the other ongoing DAC HYP extension studies (Study 205MS203 and Study 203MS302) will be eligible to enter Study 205MS303 at Week 144 of Study 205MS303.

Study Population:	This study will be conducted in subjects with MS currently participating in Study 205MS301 who have completed either the Week 144 Visit or the End of Study Visit (Week 96) of Study 205MS301 OR subjects with MS currently participating in Study 205MS203 or Study 205MS302.
Treatment Groups:	This is a single-arm study. All subjects will receive open-label treatment with DAC HYP 150 mg by a subcutaneous injection using the PFS every 4 weeks. Depending on availability and local regulations, some subjects may dose with DAC HYP using a single-use autoinjector that contains a PFS.
Duration of Treatment and Follow-up:	Subjects will participate in this study for up to approximately 5 years, or until availability of commercial product (whichever is sooner), and in accordance with applicable laws and regulations. All subjects should complete safety follow-up evaluations at 8, 12, 16, and 24 weeks after the subject's last dose of DAC HYP.
Criteria for Evaluation:	
Efficacy:	Clinical relapse assessments, EDSS, MSFC (Timed 25-Foot Walk, Nine-Hole Peg Test with both upper extremities, PASAT 3), SDMT, and brain MRI scan with and without Gd (T2 hyperintense lesions, T1 hypointense lesions, Gd+ lesions, brain atrophy).
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]
	[redacted]
Safety:	Physical and neurological exams; vital signs; clinical laboratory assessments (hematology, blood chemistry,

	thyroid function panel [including thyroid-stimulating hormone and T4], urinalysis); urine pregnancy testing; Beck Depression Inventory, Second Edition; immunogenicity assessments; Alcohol Use Disorders Identification Test - Consumption Questionnaire (AUDIT-C); and AE and concomitant medication monitoring will be performed in this study. Additional comprehensive hepatic testing will be required for subjects who permanently discontinue study treatment due to elevated liver function tests.
Subject Reported Assessments:	Subject assessment of MSIS-29, EQ-5D quality of life questionnaire (the EQ-5D descriptive system and the respondent's self-rated health on a vertical visual analog scale [EQ-VAS]), Treatment Satisfaction Questionnaire for Medication (before the first use of a PFS and at multiple timepoints during the study), Treatment Satisfaction Survey at selected sites (before the first and last use of an autoinjector), HRU, and HRPQ.
Statistical Methods:	Analyses will generally be descriptive in nature and will focus on data collected during Study 205MS303 only. Efficacy endpoints will be summarized for all subjects using descriptive statistics. For relevant efficacy analyses, the data may be summarized for subjects by previous treatment group (Avonex® or DAC HYP 150 mg). The adjusted ARR and number of new or newly enlarging T2 lesions will be estimated using a negative binomial regression model. The proportion of subjects with sustained progression and the proportion with a relapse will be estimated from the Kaplan-Meier curve. The incidence of AEs and changes in clinical laboratory assessments will also be summarized. An analysis by 3- or 6-month intervals may also be performed. Summary statistics for other safety, efficacy, and pharmacokinetic (PK) endpoints will be presented.
Sample Size Determination:	There is no formal sample size calculation for this study. The number of subjects in this study is determined by the number of subjects who completed Study 205MS301, Study 205MS203, or Study 205MS302, and enrolled in Study 205MS303.

Study Stopping Rules:	Biogen may terminate this study, after informing Investigators, at any time. Investigators will be notified by Biogen or designee if the study is placed on hold, completed, or closed.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS TABLES FOR STUDY 205MS303

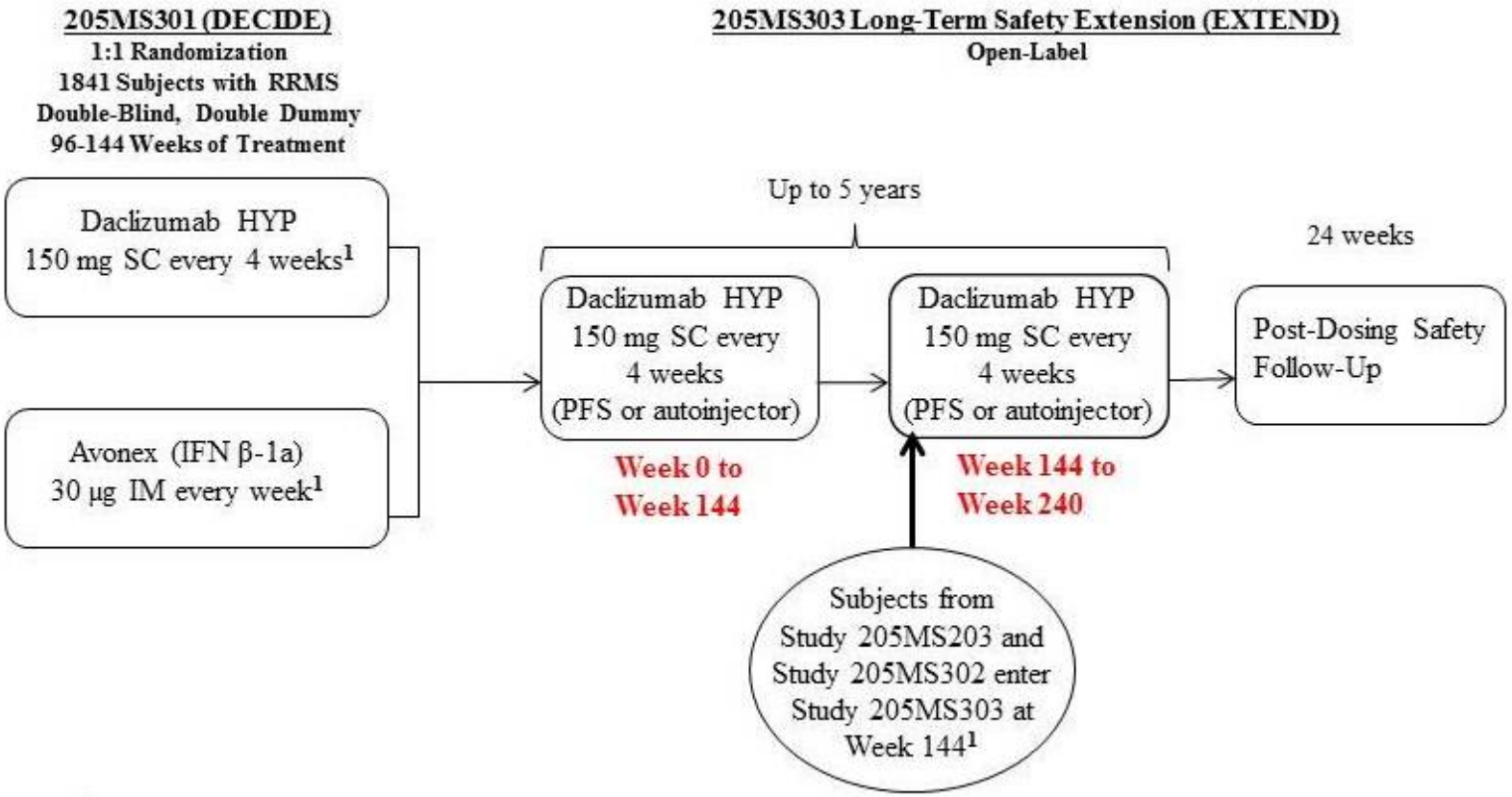
A schematic of the study design is provided in Section 4.1.

The tabulated schedule of events for this study is provided in Section 4.2.

4.1. Study Schematic

Figure 1 shows the design of Study 205MS301 and its open-label extension, Study 205MS303, in which subjects from Study 205MS203 and 205MS302 enter at Week 144.

Figure 1: Study Design



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

4.2. 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 for abnormal liver function tests (LFTs), LFTs must be re-evaluated as specified in 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 every 28±4 days (see 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			
[redacted]	X			X	X		X			
[redacted]	X						X			
[redacted]	X			X	X		X			
[redacted]										

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
Anti-Drug Antibody Sample	X			X	X		X			
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 clinically significant cutaneous events (see 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 [redacted] collection in 205MS301 will be re-approached for this consent upon entry into Study 205MS303. A separate informed consent form may be used for [redacted] sample collection. Samples for [redacted] 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 28(+4) 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 for abnormal LFTs, LFTs must be re-evaluated as per 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 every 28±4 days (see 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 clinically significant cutaneous events (see 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. 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 28(+4) 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 Assessment	X
Anti-Drug Antibody Sample	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 clinically significant cutaneous events (see 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]
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 28(+4) days must be reviewed by the *Study Neurologist* or their backup.

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 inclusion/exclusion criteria (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 every 28±4 days (see Section 14.4.3)							
Liver Function Tests at Central Laboratory[2, 3]	X	X	X	X	X	X	X	X
DAC HYP Concentration Assessment				X				X
Anti-Drug Antibody Sample				X				X
Urine Pregnancy Test[5]		X		X		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
EQ-5D and EQ-VAS				X				X
HRU				X				X
HRPQ		X		X		X		X
EDSS[6]		X		X		X		X
SDMT[7]		X		X		X		X
PASAT 3[7]		X		X		X		X
DAC HYP Administration/ Dispensation[8, 9]	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 clinically significant cutaneous events (see 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]

[6]When possible, subjects should be evaluated by the same neurologist assigned to them in the parent studies.
[7]Performed only for subjects originally enrolled from Study 205MS301.
[8]Before a monthly dose of DAC HYP is given, LFT results from a prior test performed within the previous 28(+4) days must be reviewed by the *Study Neurologist* or their backup.
[9]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 (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
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 clinically significant cutaneous events (see 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.
[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 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[redacted] Visit[4]
Cutaneous Event Assessment 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[redacted] 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] Any subject who develops a clinically significant cutaneous event should be evaluated by the *Study Dermatologist* at an Unscheduled Dermatology Assessment Visit as soon as possible. Refer to Section 11.7.3 for information on when to perform the follow-up visits.
[3]If any cutaneous AE is on-going at the time of the subject terminating from the study, the *Study Dermatologist* is to perform an Unscheduled Dermatology Assessment Visit if the subject has not had such a visit in the 4 weeks±4 days prior to leaving the study.
[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 Section 11.8.
[8]Whole blood samples will be collected for potential determination of DAC HYP serum concentrations [redacted]
[9]Performed by the *Study Neurologist* or their back-up within 72 hours of a suspected relapse.
[10] Refer to Section 11.7.3 for information on when to perform these assessments.

Table 7: Schedule of Activities: Autoinjector Use by Subjects at Selected Sites

Note: At the Sponsor's discretion, approximately 75-100 eligible subjects from Study 205MS303 at selected sites may begin using autoinjectors on any regularly scheduled dosing day, after they have received at least 6 consecutive monthly doses of DAC HYP by prefilled syringe (PFS) in Study 205MS303. Six consecutive DAC HYP injections will be administered by the subject. Doses 1 and 4 will be supervised during clinic visits, all other doses can be given at home or the clinic. Following the use of autoinjectors, subjects should resume administration of DAC HYP using the PFS.

Note: Subjects are to continue the visit schedule and evaluations listed in Table 1 through Table 6 while they are using autoinjectors.

	Autoinjector 1[1]		Autoinjector 2 4 weeks ±4 days		Autoinjector 3 8 weeks ±4 days		Autoinjector 4[1] 12 weeks ±4 days		Autoinjector 5 16 weeks ±4 days		Autoinjector 6 20 weeks ±4 days	
Tests and Assessments	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**
Informed Consent	X[2]											
Weight	X											
Waist Circumference[3]	X											
Abdominal Fold Thickness[3]	X											
DAC HYP Administration		X		X		X		X		X		X
Injection Site Assessment		X[4]					X					
Subject Assessment of Injection Pain (VAS)[5]		X						X				
Observer Report		X						X				
Treatment Satisfaction Survey[6]	X							X				X
Patient Usability Survey[6]								X				X
DAC HYP Concentration Assessment	X						X					
Anti-Drug Antibody Sample	X						X					

[1]To be administered during a scheduled clinic visit.

[2]Subjects must provide written informed consent for autoinjector use prior to first DAC HYP dose by autoinjector.
[3]The procedure for taking this measurement is provided in the Study Reference Manual.
[4]Injection Site Assessment to be completed as soon as possible but within 10 minutes after the injection at Visit 1.
[5]VAS to be completed as soon as possible after the injection is administered, but no later than 10-30 minutes post-injection.
[6]If the subject withdraws from the study or reverts to PFS use prior to receiving all 6 autoinjector doses, the subject should complete the Treatment Satisfaction Survey and the Patient Usability Survey provided for the Autoinjector 6 dosing day before returning to PFS or receiving alternative MS disease modifying therapy.

5. INTRODUCTION

5.1. Profile of Previous Experience with Daclizumab in MS

Background

DAC HYP is a humanized monoclonal IgG1 antibody specific for CD25 (α subunit of the IL-2 receptor). CD25 is expressed at low levels on resting T cells but is rapidly upregulated after T-cell activation, enabling high-affinity IL-2 signal transduction. The primary hypothesis for using DAC HYP to treat MS is to selectively inhibit activated T cells.

Anti-CD25 antibodies have multiple in vitro effects that suggest DAC HYP may directly decrease T-cell activation and proliferation. These include inhibition of IL-2 dependent lymphocyte proliferation, disruption of both IL-2 dependent and independent pathways of IFN-gamma production, and interference in CD28-dependent CD40 ligand expression. In vivo, daclizumab has been confirmed to cause expansion of $CD56^{bright}$ NK cells. This expansion has also been shown to correlate with MRI-defined therapeutic response of daclizumab in MS. $CD56^{bright}$ NK cells are believed to have an immunoregulatory function, and they have been shown to kill activated T cells through a contact-dependent mechanism. Therefore, selective inhibition of activated T cells with DAC HYP may occur through both direct and indirect mechanisms [Bielekova 2009; Bielekova 2004].

Clinical Experience With Daclizumab in Multiple Sclerosis

Initial clinical studies of daclizumab in MS were conducted with material manufactured by F. Hoffmann-La Roche, Ltd. (Roche) at their facilities in Nutley, New Jersey (DAC Nutley) [Bielekova 2004; Rose 2003; Rose 2004], and in Penzberg, Germany (DAC Penzberg) [Wynn 2010]. Study 205MS301 is conducted with DAC HYP, which is produced using a different manufacturing process than the previous versions of daclizumab. DAC HYP has characteristics that are similar to DAC Nutley and DAC Penzberg, although certain differences in physicochemical and biological characteristics have been observed (refer to the Investigator's Brochure for details).

Study 205MS201

Study 205MS201 (SELECT) was a double-blind, placebo-controlled study to evaluate the safety and efficacy of DAC HYP in subjects with RRMS that randomized 621 subjects in a 1:1:1 ratio to receive placebo, 150 mg DAC HYP, or 300 mg DAC HYP SC every 4 weeks over a 52-week treatment period. Among subjects randomized to DAC HYP (150 mg, 300 mg) versus placebo, there was a significantly lower annualized relapse rate (ARR; 0.21, 0.23 versus 0.46; $p < 0.001$), a higher proportion of relapse-free subjects (81%, 80% versus 64%; $p < 0.001$), and a trend towards improvement in the MSIS-29 physical score ($p = 0.128$ for DAC HYP 300 mg versus placebo; $p < 0.001$ for DAC HYP 150 mg versus placebo). There were significant reductions in the mean number of new or newly enlarging T2 lesions at 1 year (2.4, 1.7 versus 8.1) and in the mean number of new Gd+ lesions between Weeks 8 and 24 in a monthly MRI substudy ($n = 307$) (1.5, 1.0 versus 4.8) in the DAC HYP 150 mg and 300 mg groups versus placebo

($p < 0.001$ for all comparisons). The risk of 3-month sustained disability progression at 1 year, a tertiary study endpoint, was reduced by 57% ($p = 0.021$) in the DAC HYP 150 mg group and by 43% ($p = 0.091$) in the DAC HYP 300 mg group.

Analysis of safety data from Study 205MS201 showed that, overall, DAC HYP was well tolerated in this patient population. The most frequently reported (≥10%) AEs for subjects treated with DAC HYP, excluding MS relapse, were nasopharyngitis (14%), and headache and upper respiratory tract infection (10% each). In Study 205MS201, serious adverse events (SAEs) including MS relapses occurred in 26% of placebo-treated subjects and in 16% of subjects treated with DAC HYP. Excluding MS relapses, SAEs occurred in 6% of the placebo group, in 7% of the DAC HYP 150 mg group, and in 9% of the DAC HYP 300 mg group. One DAC HYP-treated subject died due to ischemic colitis following a complicated course of events. Adverse events observed more frequently in DAC HYP-treated patients included an increase in serious infections (2%), serious cutaneous events (1%), and elevations in LFTs (ALT/AST) >5× ULN (4%).

Upon completion of the 12-month treatment period in Study 205MS201, subjects were eligible to complete up to an additional 12 months of treatment with DAC HYP in a double-blind extension study (Study 205MS202 [SELECTION]), which was completed in 2012. Study 205MS202 also assessed the effects of DAC HYP washout in some subjects who were actively treated in Study 205MS201. Subjects completing Study 205MS202 continued long-term therapy with open-label DAC HYP in extension Study 205MS203 (SELECTED), which evaluated long-term safety and efficacy of DAC HYP monotherapy for up to an additional 144 weeks.

Study 205MS301

Study 205MS301 (DECIDE), a double-blind, randomized, parallel-group, active-controlled study testing the superiority of DAC HYP monotherapy compared to Avonex® (IFN β-1a) in preventing MS relapse, was initiated in May 2010; 1841 subjects with RRMS have been enrolled and randomized in a 1:1 ratio to receive 150 mg DAC HYP given SC every 4 weeks, or Avonex 30 mcg given IM once weekly over a 96- to 144-week treatment period. The primary endpoint was the annualized relapse rate. In this study, DAC HYP demonstrated statistically and clinically meaningful superiority to IFN β-1a, on validated clinical, radiographic, and patient-reported MS outcome measures. DAC HYP reduced the annualized relapse rate by 45% ($p<0.0001$) compared to IFN β-1a. DAC HYP's treatment effect on relapses was also evidenced by a 41% reduction in the risk of relapse in subjects in the DAC HYP group compared to the IFN β-1a group ($p<0.0001$). A reduction in the proportion of subjects relapsing was observed as early as 24 weeks after the initiation of treatment and persisted throughout the end of the study. The risk of 12-week confirmed disability progression was reduced by 16% in the DAC HYP group compared with the IFN β-1a group, a result that was not statistically significant ($p=0.1575$) in the primary analysis. In the pre-specified analysis of 24-week confirmed progression, disability progression was reduced by 27% ($p=0.0332$) in the DAC HYP group compared with the IFN β-1a group. Overall, the results of the 12-week and 24-week confirmed progression analyses were consistent with each other and supported a clinically meaningful effect of DAC HYP in preventing confirmed disability progression compared with IFN β-1a. DAC HYP reduced the number of new or newly enlarging T2 lesions at Week 96 by 54.4% ($p<0.0001$) compared to IFN β-1a. The magnitude of the treatment effect was consistent with

the results seen on the primary endpoint of annualized relapse rate. The tertiary MRI endpoints of T2, T1, and Gd-enhancing lesion count and volume were also consistent with the effect on new or enlarging T2 lesions and provide important confirmation of DAC HYP's ability to reduce focal and destructive areas of brain inflammation in RRMS patients. The treatment effect of DAC HYP on new or enlarging T2 lesions and other MRI endpoints was detectable by Week 24 ($p<0.0001$) and was sustained through to the Week 96 and Week 144 MRI at a similar magnitude.

In Study 205MS301, the safety profile of DAC HYP was characterized by an increased incidence of elevations of serum transaminases and serious hepatic events, cutaneous events, infections, and gastrointestinal events. The overall incidence of AEs was balanced across the 2 treatment groups (91% IFN β-1a vs. 91% DAC HYP). The majority of subjects with AEs had events that were mild to moderate in severity. The incidence of subjects with AEs that were considered severe was 14% in the DAC HYP group and 12% in the IFN β-1a group. AEs reported more frequently in the DAC HYP group than in the IFN β-1a group included nasopharyngitis, upper respiratory tract infections, influenza, oropharyngeal pain, rash, and lymphadenopathy, whereas influenza-like illness, pyrexia, chills, and hypertension were reported more frequently in the IFN β-1a group.

There was a higher incidence of SAEs in the DAC HYP group (24%) compared with the IFN β-1a group (21%). Excluding MS relapse, SAEs were reported in 10% of the IFN β-1a group and in 15% of the DAC HYP group. Five deaths were reported in the study (4 subjects in the IFN β-1a group, 1 subject in the DAC HYP group). None of the deaths were considered by the Investigators to be related to study treatment. While safety events were more common in the DAC HYP-treated subjects compared with IFN β-1a-treated subjects, the types of events were generally manageable with standard medical care, monitoring, and treatment discontinuation, as appropriate for the event. Overall, the results of the study support a positive benefit/risk profile for DAC HYP.

The PK and immunogenicity of DAC HYP 150 mg SC administered every 4 weeks using a prefilled syringe (PFS) were investigated in 26 subjects in Study 205MS302 (OBSERVE), a single-arm, open-label study that enrolled a total of 113 subjects with RRMS.

Refer to the Investigator's Brochure for additional details.

5.2. Study Rationale

This study will evaluate the long-term safety, efficacy, and immunogenicity of DAC HYP in subjects with MS who have completed Study 205MS301, Study 205MS203, or Study 205MS302. In addition, this study will assess the safety, tolerability, and efficacy of switching to DAC HYP in subjects previously on long-term treatment with interferon β-1a in Study 205MS301.

5.3. Rationale for Dose and Schedule Selection

The existing scientific and clinical experience with DAC HYP supports its further investigation in the management of MS. The DAC HYP dose and schedule in this protocol were used in the pivotal Phase 3 Study 205MS301 and will be the treatment regimen used in the commercial

setting. The same DAC HYP dose and schedule were used in Study 205MS203 and Study 205MS302.

A single-use, disposable PFS will be provided to simplify the injection process and thereby reduce the burden of administering a long-term therapy such as DAC HYP in the clinic or at home. At the Sponsor's discretion, single-use autoinjectors containing PFS may be used to administer DAC HYP in 75-100 subjects from Study 205MS303 at selected sites. Autoinjectors will be dispensed to each participating subject for use on up to 6 consecutive scheduled dosing days.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

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.

6.1.2. Secondary Objectives

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 PFS
- To assess the safety, tolerability, and efficacy of switching to DAC HYP in subjects previously on long-term treatment with interferon β-1a in Study 205MS301

6.1.3. Exploratory Objective

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoints

- Incidence of AEs and SAEs

6.2.2. Secondary Endpoints

- 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 (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 (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

7. STUDY DESIGN

7.1. Study Overview

The design of Study 205MS303 is provided in Figure 1. Approximately 1600 subjects will enroll in this study. This includes approximately 1200 subjects who completed Study 205MS301. Additionally, approximately 400 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 an 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).

7.2. Overall Study Duration and Follow-Up

The study period will consist of Baseline/Entry Visit assessments, treatment (for up to approximately 5 years), and post-treatment safety follow-up visits (from approximately 4 to 24 weeks after the last dose of DAC HYP).

7.2.1. Baseline/Entry Visit Assessments

Subjects Entering From Study 205MS301

Tests/assessments performed at the subject's last visit in Study 205MS301 and within 28 days of the subject's first dose of DAC HYP (Week 0) in Study 205MS303 may be used as the baseline for Study 205MS303; if final Study 205MS301 tests/assessments are not performed within the 28-day window, they must be repeated upon entry into Study 205MS303 and before the first dose of DAC HYP is administered.

Subjects Entering From Study 205MS203 or Study 205MS302

The Week 144 Visit of Study 205MS303 will be the Entry Visit for subjects enrolled from Study 205MS203 or Study 205MS302. 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. Central LFT testing is *mandatory* at the Entry Visit.

7.2.2. Treatment

Subjects from Study 205MS301 continuing in Study 205MS303 will receive DAC HYP treatment for up to approximately 5 years, or until availability of commercial product (whichever is sooner), under this protocol. Subjects from Study 205MS203 and Study 205MS302 entering Study 205MS303 at Week 144 will have DAC HYP treatment for up to approximately 2 years, or until availability of commercial product (whichever is sooner), under this protocol.

At the Sponsor's discretion, 75-100 subjects from Study 205MS303 at selected sites may dose with DAC HYP using a single-use autoinjector that contains a PFS on 6 consecutive scheduled dosing days (Table 7).

Eligible subjects will have clinic visits scheduled every 4 weeks for up to Week 12 in this study, followed by clinic visits scheduled every 12 weeks.

Subjects who are dosing at home must be instructed to not administer their monthly dose of DAC HYP until the study site has contacted them to authorize dosing (after the *Study Neurologist* or their backup has reviewed LFT results obtained during the previous 28[+4] days). Subjects need to record the date and time of dosing in their diary if they are dosing at home.

A window of ±4 days applies to scheduled visits and home dosing.

7.2.3. Post-Treatment Long-Term Follow-Up

Subjects are to return to the study site for follow-up visits at 8, 12, 16, and 24 weeks (±10 days) after the last dose of DAC HYP.

7.3. Study Stopping Rules

Biogen may terminate this study, after informing Investigators, at any time. Investigators will be notified by Biogen or designee if the study is placed on hold, completed, or closed.

7.4. End of Study

The End of Study is last subject, last visit for final collection of data.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the 205MS303 Baseline/Entry Visit or at the timepoint specified in the individual eligibility criterion listed (Note: Week 0/Day 1 is the Baseline Visit in Study 205MS303 for 205MS301 subjects. Week 144 is the Entry Visit in Study 205MS303 for 205MS203 and 205MS302 subjects):

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
2. Must be a subject currently participating in Study 205MS301 who has completed either the Week 144 Visit or the End of Study Visit (Week 96) of Study 205MS301 OR subject currently participating in Study 205MS203 or Study 205MS302.
3. Women of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 4 months after their last dose of study treatment.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the Study 205MS303 Baseline/Entry Visit or at the timepoint specified in the individual criterion listed (Note: Week 0/Day 1 is the Baseline Visit in Study 205MS303 for 205MS301 subjects. Week 144 is the Entry Visit in Study 205MS303 for 205MS203 and 205MS302 subjects):

Medical History

1. Any subject who permanently discontinued study treatment in Study 205MS301, Study 205MS203, or Study 205MS302 prior to the end of the study treatment period, or had an early termination in those studies OR any subject who has completed all the safety follow-up visits after Week 144 of Study 205MS303 per the original protocol.

   Note: Subjects for whom dosing was temporarily suspended in Study 205MS301, Study 205MS203, or Study 205MS302 are not excluded from participation in this extension study if the criteria for resuming DAC HYP treatment under the parent study protocol have been met at the time of enrollment into Study 205MS303.
2. Any significant change in the subject's medical history that would preclude administration of DAC HYP, including laboratory tests or a current clinically significant condition that, in the opinion of the Investigator, would have excluded the subject's participation in Study 205MS301, Study 205MS203, or Study 205MS302. The Investigator must re-review the subject's medical fitness for participation and consider any factors that would preclude treatment in Study 205MS303, including:

- History of any significant cardiac, endocrine, hematological, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurological (other than MS), and/or other major disease (e.g., malignancy) that would preclude administration of DAC HYP.
- Clinically significant laboratory abnormalities (hematology and blood chemistry) from the most recently available test in the parent study, as determined by the Investigator. Laboratory findings mandating discontinuation of study treatment as defined in parent study protocol are exclusionary.

3. Other medical reasons that, in the opinion of the Investigator and/or Biogen, make the subject unsuitable for enrollment.

Treatment History

4. Treatment with any prohibited concomitant medication during the parent study, as described in Section 11.5 of this protocol.

   Note: Subjects who start an approved, open-label IFN β preparation after completion of dosing in Study 205MS301 are not excluded, but IFN β treatment must be discontinued before the first dose of DAC HYP in Study 205MS303 is given.

Miscellaneous

5. Female subjects who are currently pregnant or breastfeeding, or considering becoming pregnant while in the study.
6. History of drug or alcohol abuse (as defined by the Investigator) at any time after the start of Study 205MS303 or any of the parent studies.
7. Unwillingness or inability to comply with the requirements of the protocol, including the presence of any condition (physical, mental, or social) that is likely to affect the subject's ability to comply with the protocol.

9. ENROLLMENT AND REGISTRATION PROCEDURES

9.1. Enrollment and Screening

Subjects must be consented before any procedures are performed. At the time of consent, the subject will be enrolled into the study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the enrollment log. Any test/assessment done at the subject's last visit in the parent studies and within 28 days of the subject's first dose in Study 205MS303 will be used as the baseline for Study 205MS303 and does not need to be repeated at entry into Study 205MS303 (Note: Central LFT testing is mandatory at the Week 144 Entry Visit for subjects rolling over from Study 205MS203 and Study 205MS302 into Study 205MS303). Testing required at the Baseline/Entry Visit that is done outside the 28-day window must be repeated upon entry into 205MS303.

9.2. Registration of Subjects

Subjects should be registered in the study after the Investigator has verified that they are eligible per the criteria in Section 8.1 and Section 8.2 and all baseline assessments have been performed. No subject may begin treatment prior to enrollment and registration.

As confirmation, the Investigator will be provided with written verification of the subject's registration by mail or fax.

Refer to the Study Reference Manual for details on registration.

10. STUDY TREATMENT MANAGEMENT

Study treatment (PFS or autoinjectors) must be stored in a secure location. Accountability for study treatment is the responsibility of the Investigator. Study treatment must only be dispensed by a Pharmacist or medically qualified staff, and stored in a secure, monitored, locked location in accordance with the conditions specified in current prescribing information or the Directions for Handling and Administration (DHA) included in the Study Reference Manual.

Study treatment is to be dispensed only to subjects enrolled in this study. Once treatment is dispensed to a subject, it can only be used by that subject.

10.1. DAC HYP

Prefilled Syringe

DAC HYP is supplied as a liquid in a 1-mL BD-staked PFS with a 29 gauge × ½ inch needle, comprising 150 mg/mL DAC HYP plus excipient materials (sodium succinate, sodium chloride, and polysorbate 80). At a minimum, the study treatment label will include a study reference code, drug identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. Depending on country requirements, the Investigator's name may also appear on the label. DAC HYP must not be used after the expiration date unless a written notification of an expiration date extension is provided by Biogen.

Autoinjector

The DAC HYP PFS is assembled inside a single-use, disposable autoinjector device.

The autoinjector label will include the DAC HYP product code "BIIB019," conditions for storage, Sponsor, and a caution statement. Depending on country requirements, the Investigator's name may also appear on the label. DAC HYP must not be used after the expiration date unless a written notification of an expiration date extension is provided by Biogen.

10.2. DAC HYP Preparation

Each DAC HYP PFS or autoinjector contains only one dose and is intended for SINGLE USE INJECTION ONLY. Any drug that remains in the PFS after injection must not be used for another dose or another subject.

After Week 12, subjects may choose to administer their DAC HYP dose at home, either by administering the injection themselves or by a designated caregiver. The subject or designated caregiver will be trained by clinic staff on the correct PFS injection technique prior to initiating at-home DAC HYP dosing.

Autoinjectors may be provided to selected sites and will be supplied injection-ready. Study personnel or subjects at these sites do not need to insert the PFS into the device. Study site personnel will receive appropriate autoinjector training from a Sponsor-designated trainer prior to initiation of autoinjector use.

10.3. DAC HYP Accountability

The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), any amount returned by subject, and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all PFS and autoinjectors, both used and unused, must be saved for study treatment accountability. At the end of the study, a final reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed or returned to Biogen.

A written explanation will be provided for any discrepancies. After reconciliation, the Investigator must destroy or return to Biogen all unused study treatment PFS and autoinjectors as instructed by Biogen.

If any study treatment supplies are to be destroyed at the site, the Principal Investigator(s) must obtain prior approval by Biogen. The Principal Investigator(s) must notify Biogen, in writing, of the method, date, and location of destruction.

11. TREATMENT OF SUBJECTS

Biogen will provide DAC HYP (PFS or autoinjectors) to all study sites.

Refer to Section 10 (Study Treatment Management) for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

11.1. Study Treatment Schedule and Administration

All subjects will receive one DAC HYP 150 mg SC injection every 4 weeks.

DAC HYP will be administered by clinic staff at the monthly visits for the first 12 weeks of this study. After Week 12, administration of DAC HYP may occur in the clinic or at home (by the subject or by a designated caregiver) depending on subject preference. The subject or designated caregiver will be trained by clinic staff on the correct injection technique prior to initiating at-home DAC HYP dosing. **Subjects who are dosing at home must be instructed to not administer their monthly dose of DAC HYP until the study site has contacted them to authorize dosing. A window of ±4 days applies to home dosing.**

Before a monthly dose of DAC HYP is given, LFT results from a prior test performed within the previous 28(+4) days must be reviewed by the *Study Neurologist* or their backup. Study personnel should promptly inform the subject whether the monthly dose of DAC HYP should be administered or whether study treatment is to be withheld based on the dosing criteria defined in Section 11.7.2. Study personnel will document this communication with the subject. Subjects should administer DAC HYP as soon as permission has been given as per the dosing schedule. Subjects need to record the date and time of dosing in their diary if they are dosing at home.

11.2. Placebo or Reference Product Agents

Not applicable.

11.3. Treatment Precautions

Anaphylactic-like and hypersensitivity reactions following administration of proteins such as DAC HYP can occur. DAC HYP will be administered in the clinic under observation by qualified medical personnel for the first 12 weeks of this study. Subjects will be educated by the *Study Neurologist* or their back-up on the signs and symptoms of hypersensitivity reactions and instructed to contact the site if they experience any acute or delayed reactions post injection.

11.4. Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by study site staff.

After Week 12, subjects who choose to administer their DAC HYP dose at home will record treatment in a dosing diary. The diary will be reviewed periodically by study site staff and the Clinical Monitor throughout the study. Subjects who choose at-home administration will return used PFS or autoinjectors to the clinic at their scheduled clinic visits.

11.5. Concomitant Therapy

A concomitant therapy is any drug or substance administered from the Baseline/Entry Visit until completion of the study. A concomitant procedure is defined as any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed from the time the subject is enrolled in the study until the subject's final clinic visit.

Concomitant treatment with any of the following is not allowed during the study, unless approved by the Biogen Medical Director(s) or the Advisory Committee, or as otherwise described in this protocol:

- Any alternative disease modifying MS drug treatment such as chronic immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to: IFN-β, IFN-α, glatiramer acetate, cyclophosphamide, methotrexate, mycophenolate mofetil, mitoxantrone, cyclosporine, azathioprine, or related products).
- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications.
- Any monoclonal antibodies other than DAC HYP.
- Intravenous immunoglobulin (IVIg), plasmapheresis or cytapheresis, total lymphoid irradiation, or T-cell or T-cell receptor vaccination.
- Any systemic steroid therapy including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IV methylprednisolone (IVMP), except for protocol-defined treatment of relapses as described in Section 14.6 or for limited, acute treatment of general medical conditions as per the discretion of *Study Neurologist*. Steroids that are administered by non-systemic routes (e.g., topical, inhaled) are allowed.
- Antineoplastic or chemotherapeutic agents, including, but not limited to, cyclophosphamide, methotrexate, azathioprine, cladribine, cytarabine, or flutamide.
- Valproic acid, carbamazepine, lamotrigine, or phenytoin. Subjects who have been taking **1** of these medications at a stable dose for at least 6 consecutive months may continue to receive the medication and may continue study treatment under this protocol. However, if any of these medications must be initiated or dose escalated, study treatment must be permanently discontinued as described in Section 11.8.

  Subjects who have been treated with any of these medications (which have not been approved by the Biogen Medical Director[s]) for fewer than 6 consecutive months, or who take more than 1 of these medications, or who have had dose escalations within the past 6 months must do 1 of the following:

  – Discontinue the medication (any agent used for <6 consecutive months must be discontinued). Subjects may use an alternative medication allowed by the protocol, if needed.

  - Subjects taking more than 1 agent must reduce to ≤1 agent (any agent that is continued must have been taken for at least 6 consecutive months).
  - In the case of dose escalation, revert to a previous dose that had been used for at least 6 months.
  - Permanently discontinue study treatment.
- Isoniazid, propylthiouracil, or nimesulide. Subjects who currently take any of these medications must either change to an alternative medication allowed by the protocol or permanently discontinue study treatment.

Subjects who receive any of these restricted medications may be required to permanently discontinue study treatment as outlined in Section 11.8. Subjects who permanently discontinue study treatment will be allowed to receive IVMP as treatment for MS relapse while they are participating in the study, as described in Section 11.8.

Use of the following medications is strongly discouraged during the study:

- Herbal or dietary supplements.
- Agents that have established risks of hepatotoxicity or serious rash according to labeling information (examples include, but are not limited to, amoxicillin/clavulanate, clarithromycin, ketoconazole, minocycline, nitrofurantoin, trimethoprim/sulfamethoxazole, diclofenac, sulfasalazine, amiodarone, methyldopa, nefazodone, and halothane). Alternatives to these therapies should be used whenever possible.

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue is not restricted, but should be optimized as early as possible in an attempt to maintain consistent treatment for the duration of the study. Initiation of Fampridine-SR after enrollment is permitted, including when it is used in the acute management of protocol-defined relapse (as described in Section 14.6).

Subjects should be instructed not to start taking any new medications, including non-prescribed medications, unless they have received permission from the Investigator. The use of live vaccines in humans concurrently treated with daclizumab has not been explored; therefore live vaccines should not be administered to MS subjects who are being treated with DAC HYP.

The use of concomitant therapies or procedures defined in this section must be recorded on the subject's case report form (CRF), according to instructions for CRF completion (Note: concomitant therapies in the parent study that continued at Study 205MS303 entry must be recorded on the CRF). AEs related to administration of these therapies or procedures must be documented on the appropriate CRF. For subjects who prematurely discontinue study treatment, all concomitant medications should be recorded throughout the remainder of the subject's participation in the study.

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If DAC HYP is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

11.7. Treatment Schedule Modifications

Subjects who experience a significant change in their medical status (e.g., neurological worsening/suspected MS relapse, possible injection-site reaction, infection, cutaneous event, fever, abdominal pain, persistent diarrhea, jaundice, nausea, vomiting, pruritus) must contact the *Study Neurologist* as soon as possible and no more than 48 hours after symptom onset. The subject should then be evaluated by the *Study Neurologist* within no more than 72 hours for physical and neurological assessments and further treatment recommendations if appropriate. These subjects should not administer additional DAC HYP until they have been evaluated by the *Study Neurologist* or their backup.

Unscheduled PK/[redacted] Visit (Table 6) can be performed in subjects who have evidence of significant changes in their medical conditions (as assessed by the Investigator). This visit must be approved by the Biogen Medical Director in advance.

Additional treatment considerations for specific events are described below.

11.7.1. Infections

Subjects who have evidence of a clinically significant infection will be instructed to notify the *Study Neurologist* or their backup within 48 hours of onset, and scheduled dosing of DAC HYP may be withheld. If the subject's infection resolves within 2 weeks of the scheduled DAC HYP dose, the subject may receive the previously scheduled dose of DAC HYP at that time. If the infection has not resolved within the 2 weeks, dosing of DAC HYP will remain suspended, and the subject will miss dosing until the infection is resolved.

11.7.2. Elevated Liver Function Tests

Before a monthly dose of DAC HYP is given, LFT results from a prior test (performed within 28[+4] days) must be reviewed by the *Study Neurologist* or their backup, and must be within the protocol-required limits shown below (LFT procedures are described in Section 14.4.3).

Study treatment *must be temporarily suspended* if a subject develops any of the following:

- ALT/SGPT or AST/SGOT >3×ULN
- any other clinically significant hepatic condition in the opinion of the Investigator including jaundice

Note: For subjects who present with jaundice, an LFT *must* be performed as soon as possible.

After a suspension, dosing of DAC HYP may be resumed when ALT/SGPT and AST/SGOT are <2×ULN provided that the criteria for permanent discontinuation have not been met (see Section 11.8).

Study treatment *must be permanently discontinued* if a subject develops any of the following:

- ALT/SGPT or AST/SGOT elevation >8×ULN that is confirmed by a repeat test (preferably within 24 hours)
- ALT/SGPT or AST/SGOT >5×ULN for more than 2 weeks

- ALT/SGPT or AST/SGOT >3×ULN with concomitant elevation of total bilirubin >2×ULN
- If a subject has treatment suspended for an LFT elevation and has also had a prior treatment suspension for an LFT elevation during DAC HYP use, DAC HYP must be permanently discontinued unless an alternative explanation for the LFT elevation unrelated to DAC HYP use is clearly identified by the Investigator.

All subjects with elevated LFTs (**ALT/SGPT or AST/SGOT >3×ULN**) should be managed per the guidelines below.

- Study treatment must be temporarily suspended and LFT elevation should be confirmed as soon as possible but no later than a week by a repeat test performed at the central laboratory. In cases where LFTs cannot be performed via the central laboratory, repeat LFT results from local laboratory can be used for confirmation.
- All subsequent testing after a treatment suspension or discontinuation is required to be performed centrally *at least weekly* until the LFT elevation has resolved.
- In subjects with treatment suspension or discontinuation, DAC HYP treatment may resume if a laboratory error is documented upon repeat testing OR when ALT/SGPT and AST/SGOT are <2×ULN provided that the criteria for permanent discontinuation have not been met (see Section 11.8).
- A careful review of all concomitant medications must be documented. The Investigator should consider discontinuation of all potential hepatotoxic medications. All recently started or non-essential concomitant medications should be suspended until the LFT elevation has resolved.
- An Unscheduled Hepatic Assessment Visit as soon as possible but within 7 days should be performed in the event of permanent discontinuation due to elevated LFTs (see Table 6).
- Subjects should be referred to a hepatic specialist if medically indicated.
- The LFT elevation that led to treatment discontinuation should continue to be monitored until LFT elevation has resolved.
- For subjects with initial **ALT/SGPT or AST/SGOT >3×ULN and concomitant elevation of total bilirubin >2×ULN**:
    - *Permanently discontinue* DAC HYP and monitor until the LFT elevation has resolved.
- For subjects with initial **ALT/SGPT or AST/SGOT >5×ULN but ≤8×ULN**:
    - *Suspend dosing* and confirm as soon as possible but no later than a week.
    - For subjects with ALT/SGPT or AST/SGOT >5×ULN for more than 2 weeks:
        - *Permanently discontinue* DAC HYP and monitor until the LFT elevation has resolved.

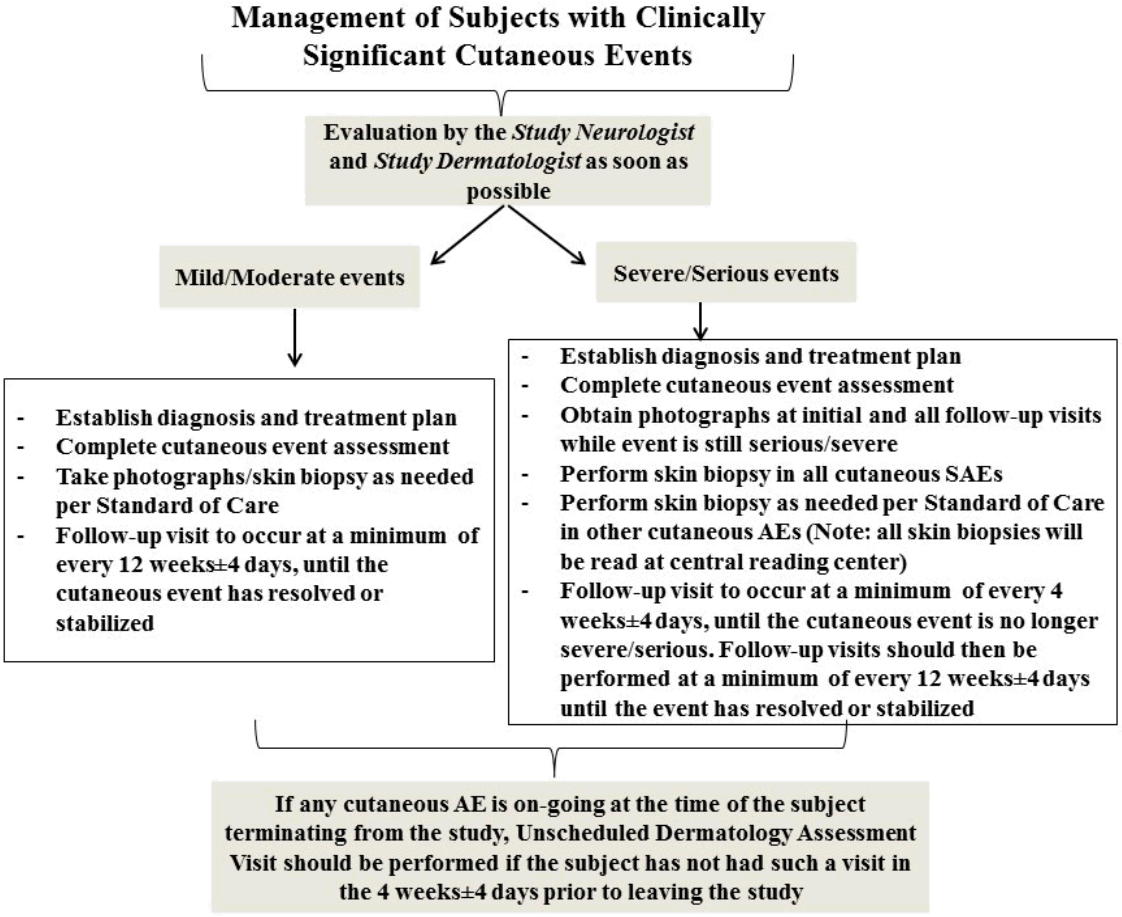
- For subjects with **ALT/SGPT or AST/SGOT >8×ULN**:
    - *Suspend dosing* and confirm by a repeat test (preferably within 24 hours).
        - **If AST/SGOT >8×ULN in repeat test**: *Permanently discontinue* DAC HYP and monitor until the LFT elevation has resolved.
- For subjects with **ALT/SGPT or AST/SGOT >10×ULN not resolving for more than 2 weeks**:
    - *In consultation with the hepatic specialist*, a full evaluation of alternative causes of liver injury should be performed, and if testing for viral hepatitis is negative, LFT elevations are not improving, DAC HYP is suspected as the cause of the LFT elevation, and there are no known contraindications for corticosteroids, then, in continued consultation with the hepatic specialist, empiric treatment with systemic corticosteroids should be considered.

11.7.3. Cutaneous Events

Any subject participating in Study 205MS303 who develops a clinically significant cutaneous event (e.g., rash, dermatitis, eczema, acne, folliculitis) should be evaluated by the *Study Dermatologist* at an Unscheduled Dermatology Assessment Visit as soon as possible (see Table 6).

A flowchart is presented in Figure 2 to summarize how these subjects will be managed during the study.

Figure 2: Flowchart for Management of Subjects With Clinically Significant Cutaneous Events



In addition to this, when the *Study Neurologist* and *Study Dermatologist* evaluate a subject with a clinically significant cutaneous AE (either at an unscheduled or scheduled clinical visit), they should also perform the Physician Global Assessment Scale as well as standard AE reporting. Photographs should also be taken by the *Study Neurologist* or designee at these visits for severe or serious cutaneous AEs if they have not been taken by the *Study Dermatologist* (see Section 4.2). The subjects will be asked for their consent to having their dermatological photographs used for educational purposes, if required.

Skin biopsy must be performed in subjects with cutaneous SAEs at the Unscheduled Dermatology Assessment Visit, unless medically contraindicated.

Skin biopsies from study subjects will be sent to a centralized laboratory for evaluation. Results of the skin biopsy will be provided back to the *Study Dermatologist* as soon as possible with a copy sent to the sponsor. Skin biopsy may also be locally evaluated per the discretion of the *Study Dermatologist*.

For subjects with a severe or serious cutaneous event, DAC HYP must be withheld until the cutaneous event has resolved. Under the consultation of the *Study Dermatologist*, the subject should also withhold all other non-essential medications, including protocol-required medications (as appropriate), and non-prescription drugs and supplements, at least until the cutaneous event has resolved. The decision to permanently discontinue study treatment should be made by the Investigator in consultation with the *Study Dermatologist*. If an allergic or hypersensitivity reaction to study treatment is suspected, study treatment must be permanently discontinued.

11.7.4. Gastrointestinal Events of Inflammatory Colitis

For any subject participating in Study 205MS303 who develops symptoms of inflammatory colitis (e.g., persistent diarrhea and abdominal cramps, blood in the stool, and fever), treatment with DAC HYP should be stopped and the subject should be referred to a specialist. Some subjects with mild colitis who require DAC HYP therapy may be able to continue the study treatment if the benefit-risk profile is considered positive per Investigator's assessment and the subject's informed decision.

11.7.5. Lymphadenopathy or Lymphadenitis Events

Any subject participating in Study 205MS303 who develops clinically significant lymphadenopathy or lymphadenitis should be referred to a specialist. Additional diagnostic tests, such as imaging, blood tests, and/or biopsy, should be performed according to the local standard of care.

When diagnostic tests are performed, the results may be requested for internal safety review and, when available, biopsy materials will be sent to a centralized laboratory for evaluation. The results of the central laboratory biopsy report will be provided back to the *Study Neurologist* as soon as possible, with a copy sent to the Sponsor.

Study treatment may continue or be resumed after a temporary suspension in cases of uncomplicated lymphadenopathy if the benefit-risk profile is considered positive per the Investigator's assessment and the subject's informed decision. Subjects who discontinued study treatment for any reason while presenting with ongoing lymphadenopathy or lymphadenitis should be followed until the lymphadenopathy or lymphadenitis has stabilized or resolved or the study has terminated, whichever comes first.

11.8. Discontinuation of Study Treatment

A subject *must* permanently discontinue DAC HYP for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.5.4.
- The subject experiences a hypersensitivity or suspected allergic reaction (e.g., anaphylaxis and anaphylactoid reactions) to study treatment.
- The subject develops a chronic viral infection (e.g., hepatitis C, HIV).
- The subject develops elevated LFTs that meet any of the following criteria:

- The subject develops an ALT/SGPT or AST/SGOT elevation >8×ULN that is confirmed by a repeat test (preferably within 24 hours). This requires *immediate* discontinuation of DAC HYP, and treatment may not resume unless a laboratory error is documented upon repeat testing.
- ALT/SGPT or AST/SGOT >5×ULN for more than 2 weeks
- ALT/SGPT or AST/SGOT >3×ULN with concomitant elevation of total bilirubin >2×ULN at any time unless a laboratory error is documented upon repeat testing
- If a subject has treatment suspended for an LFT elevation and has also had a prior treatment suspension for an LFT elevation during DAC HYP use, DAC HYP must be permanently discontinued unless an alternative explanation for the LFT elevation unrelated to DAC HYP use is clearly identified by the Investigator.
- The LFT abnormality that led to treatment discontinuation should continue to be monitored until resolution is documented. An Unscheduled Hepatic Assessment Visit is needed in the event of permanent discontinuation due to elevated LFTs (see Section 11.7.2).

  In addition, a careful review of all concomitant medications must be documented. The Investigator should consider discontinuation of all potential hepatotoxic medications. The subject should be referred to a physician with expertise in the diagnosis and treatment of liver disease, and additional hepatic studies should be performed according to local standard of care. The central laboratory may be utilized for additional hepatic testing per Investigator request.

- The subject experiences a clinically significant cutaneous event, which the Investigator (in consultation with the *Study Dermatologist*) considers to be a generalized allergic or hypersensitivity reaction to study treatment (see Section 11.7.3).
- The subject experiences inflammatory colitis, except in subjects with mild colitis who require DAC HYP therapy and have a positive benefit-risk profile per Investigator's assessment and the subject's informed decision (see Section 11.7.4).
- The subject requires treatment with any of the disallowed concomitant medications, unless approval is given by the Biogen Medical Director(s) or Advisory Committee. Note: IVMP for treatment of a protocol-defined relapse is allowed as detailed in the protocol (see Section 11.5). Treatment with valproic acid, carbamazepine, lamotrigine, or phenytoin is only allowed under the conditions detailed in the protocol.
- The subject experiences a medical emergency that necessitates permanent discontinuation of treatment.
- The subject desires to discontinue treatment under this protocol.
- At the discretion of the Investigator for medical reasons or for non-compliance.

- Upon confirmatory tests 1 month apart, the subject's hematology results are as follows in the absence of an identified reversible cause by the Investigator (e.g., infection):
  - white blood cell count is <2500 cells/μL, or
  - lymphocyte count is <800 cells/μL, or
  - platelet count is <75,000 cells/μL

  Subjects who meet the above criteria must have study treatment withheld until hematology retest results are available.
- The subject experiences severe depression and/or suicidal ideation. Severe depression is defined as any episode that requires hospitalization, or at the discretion of the Investigator.

Subjects who permanently discontinue DAC HYP treatment should complete all post-treatment safety follow-up evaluations (see Section 13.3).

Subjects who permanently discontinue study treatment may be treated with alternative approved MS therapies according to local practices, and should remain in the study and complete safety follow-up evaluations as described in Section 4.2 and Section 13. However, subjects who desire to discontinue participation in this study or are unwilling or unable to comply with the protocol should be withdrawn from the study and complete an Early Termination Visit. As noted in Table 6 (Footnote 3) and Section 11.9, subjects terminating treatment with an ongoing clinically significant cutaneous event require an Unscheduled Dermatology Assessment Visit with the *Study Dermatologist* prior to leaving the study if a visit with the *Study Dermatologist* has not been completed in the 4 weeks±4 days prior to leaving the study.

The reason(s) for discontinuation of treatment must be recorded in the subject's CRF.

11.9. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.

Subjects who withdraw from the study should complete the End of Treatment Visit assessments as described in Section 14.9 (subjects should be encouraged to complete all other post-treatment safety follow-up visits). The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

For subjects with an ongoing clinically significant cutaneous AE, the *Study Dermatologist* should perform an Unscheduled Dermatology Assessment Visit, if this visit has not been performed in the 4 weeks±4 days prior to leaving the study (see Section 11.7.3).

12. EFFICACY, DAC HYP CONCENTRATION, AND [redacted] ASSESSMENTS

12.1. Clinical Efficacy Assessments

The following clinical tests/assessments will be performed to assess the efficacy of DAC HYP:

- Relapse Assessment: Subjects who suspect they are experiencing new symptoms or worsening symptoms need to contact the *Study Neurologist* within 48 hours of the onset of the symptoms.
- Refer also to Section 14.6 Unscheduled Relapse Assessment Visit for additional details.
- EDSS [Kurtzke 1983]: Review of EDSS procedures will be performed prior to study start as necessary for training purposes.
- MSFC [Fischer 1999]: Timed 25-Foot Walk, 9HPT with both upper extremities, and PASAT 3
- SDMT: Data will be collected only from subjects enrolled from Study 205MS301, and test performance data will be collected beginning in Week 144 and every 24 weeks thereafter.
- PASAT 3: This test will be performed separately from the MSFC beginning in Week 144 and every 24 weeks thereafter. Data will be collected only from subjects enrolled from Study 205MS301.
- Brain MRI scan with and without Gd (T2 hyperintense lesions, T1 hypointense lesions, Gd+ lesions, brain atrophy).
- Subjects will complete the following questionnaires at various timepoints specified in Section 4.2:
  - EQ-5D quality of life questionnaire (the EQ-5D descriptive system and the EQ-VAS)
  - MSIS-29 (29-item physical and psychological assessment)
  - HRU (hospitalizations, emergency room visits, and unscheduled neurologist visits)
  - Treatment Satisfaction Questionnaire for Medication (with PFS use) or Treatment Satisfaction Survey (with autoinjector use)
  - HRPQ (productivity questionnaire)

Refer to Section 4.2 for the timing of assessments.

12.2. Pharmacokinetic Assessments

Blood samples 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]

Unscheduled PK/[redacted] Visits

Whole blood samples will be collected at Unscheduled PK/[redacted] Visits for potential determination of DAC HYP serum concentrations 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.

Refer to Section 4.2 for the timing of sample collection.

12.3. [redacted]

[redacted]

[redacted] PK/[redacted]

[redacted] PK/[redacted]

12.4. [redacted]

[redacted].

13. SAFETY ASSESSMENTS

13.1. Clinical Safety Assessments

The following clinical assessments will be performed to determine the safety profile of DAC HYP:

- Medical history
- Physical and neurological examination
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate (subjects must remain in the same body position quietly for 5 minutes prior to having their pulse and blood pressure taken)
- Weight
- Concomitant therapy and procedure recording
- AE and SAE recording
- Beck Depression Inventory, Second Edition (BDI-II)
- Immunogenicity assessments
- Alcohol Use Disorders Identification Test - Consumption Questionnaire (AUDIT-C)

See Section 4.2 for the timing of assessments.

13.2. Laboratory Safety Assessments

The following laboratory tests will be performed to assess the safety profile of DAC HYP:

- Hematology: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell count, white blood cell count (with differential), and platelet count
- Blood chemistry: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT/SGPT AST/SGOT, lactate dehydrogenase, gamma glutamyl transferase, blood urea nitrogen (BUN), creatinine, and bicarbonate
- Comprehensive hepatic panel (only required for subjects who permanently discontinue dosing due to elevated LFTs as defined in Section 11.7.2). Testing will include screening for the following:
  - hepatitis A, B, C, and E
  - other viral infections: Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV-6), varicella zoster virus (VZV), herpes simplex virus (HSV), and Parvovirus B19
  - gamma-globulins, including IgG levels

  - autoantibodies: antinuclear antibody (ANA), anti-smooth muscle antibody (anti-SM), anti-liver/kidney microsome-1 antibody (anti-LKM1), antimitochondrial antibody (AMA), and anti-soluble liver antigen (SLA)

  Additional testing may be performed based on results of the above testing or the subject's clinical history. Additional hepatic assessments should be performed according to local standard of care.

- Thyroid function panel, including TSH and T4
- Urinalysis: protein, blood, glucose, ketones, nitrite, leukocytes, pH, specific gravity by dipstick and microscopy
- Urine pregnancy testing
- Skin biopsy (only required for subjects who experience cutaneous events reported as serious or severe as defined in Section 11.7.3)

Refer to Section 4.2 for the timing of assessments.

13.3. Study-Specific Safety Assessments

Blood serum collection for binding and neutralizing anti-drug antibody testing will be performed. Note: When necessary, samples drawn for one purpose (e.g., immunogenicity) may be used to meet another protocol-defined objective (e.g., DAC HYP concentration assessment).

14. SCHEDULE OF EVENTS

14.1. Overview

A written, signed Informed Consent Form (ICF) and all authorizations required by local law (e.g., Protected Health Information [PHI] in North America) must be obtained prior to performing any tests or assessments under this protocol.

For subjects entering from Study 205MS301, tests/assessments performed at the subject's last visit in Study 205MS301 and within 28 days of the subject's first dose of DAC HYP (Week 0) in Study 205MS303 may be used as baseline data for Study 205MS303; if final Study 205MS301 tests/assessments are not performed within the 28-day window, they must be repeated upon entry into Study 205MS303 and before the first dose of DAC HYP is administered.

Week 144 Visit of Study 205MS303 will be the Entry Visit for subjects enrolled from Study 205MS203 or Study 205MS302. 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; test/assessments performed >28 days before the Entry Visit must be repeated at the Entry Visit. Central LFT testing is *mandatory* at Entry Visit.

Clinic visits will occur once every 4 weeks for the first 12 weeks, then every 12 weeks thereafter.

On a dosing day, all tests and assessments must be performed prior to DAC HYP administration. When DAC HYP administration and MRI evaluation are required at the same visit, the MRI scan should be performed prior to DAC HYP administration (Note: MRI scan can be performed up to 4 days prior to the visit).

Before a monthly dose of DAC HYP is given, LFT results (ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only) from prior testing performed within 28(+4) days must be reviewed by the *Study Neurologist* or their backup, and must be within the protocol-required limits.

After Week 12, subjects will have the option of administering DAC HYP at home following Investigator review of monthly pre-dose LFT results. Subjects who are not able to administer their own dose or prefer not to administer their own dose of DAC HYP will be given the option to choose another individual (caregiver) to administer their treatment at home or to have their treatment administered by staff at the study site.

Follow-up visits will take place at 8, 12, 16, and 24 weeks after each subject's last dose of DAC HYP. Unscheduled Relapse Assessment Visits (if necessary) should be scheduled within 72 hours of the onset of any new neurological symptoms that may indicate neurological worsening or possible clinical relapse. Unscheduled Hepatic Assessment Visits (if necessary) should be scheduled as soon as possible (but within 1 week) following discontinuation of study treatment due to elevated LFTs. Unscheduled Dermatology Assessment Visits will be performed as per Section 11.7.3.

Unscheduled PK/[redacted] Visits should be scheduled as soon as possible following significant changes in subjects' medical conditions, as assessed by the Investigator. This visit must be approved by the Biogen Medical Director in advance.

14.2. Site Personnel

For each subject, the Principal Investigator will designate the following study site personnel:

- A primary *Study Neurologist* and backup neurologist
- A primary and backup *Nurse* (or Study Coordinator)
- A primary and backup *Examining Technician*
- An *MRI Technician*
- A *Pharmacist* (or authorized designee)
- A *Study Dermatologist*

The *Study Neurologist* must have a minimum of 2 years of neurology specialty training and anticipate at least a 3-year commitment to the study, or be approved by the study Advisory Committee. The *Study Neurologists* may designate another neurologist at the center who meets the same qualifications to perform the EDSS assessments and other neurologic assessment during the trial. Whenever possible, the EDSS and other neurologic assessments should be performed by the same examiner who performed these assessments in the parent study.

The primary *Study Neurologist* will be responsible for:

- Management of the routine neurological care of the subject
- Assessment (including assignment of causality) and treatment of AEs and MS relapses
- Obtaining an EDSS score based on a detailed neurological examination at the scheduled timepoints required in the protocol, and at every Unscheduled Relapse Assessment Visit
- Review of selected hematology and all blood chemistry results from the central laboratory
- Assessment of LFT results, as detailed in Section 11.7.2
- Monitoring and follow-up of any abnormal hepatic tests
- Performing Physician Global Assessment Scale in subjects with clinically significant cutaneous event, as detailed in Section 11.7.3
- Assessment of injection sites, as detailed in Table 7
- Referral of subjects to a dermatologist if that subject experiences a cutaneous event as described in Section 14.7

Hematology and blood chemistry data will be sent to the investigational sites to aid in management of the subject.

The primary *Nurse* or Study Coordinator will be responsible for:

- Assisting the *Study Neurologist* in subject management, including the treatment of AEs, the treatment and assessment of disease relapses, and the recording of AEs and concomitant medications
- Monitoring the EDSS scores and informing the *Study Neurologist* if a subject experiences at least a 1.0-point increase on the EDSS 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
- Administering the patient-reported questionnaires (BDI-II, MSIS-29, EQ-5D), HRU, and subject assessment of injection pain (VAS)
- Collection of blood samples and obtaining vital signs
- Study treatment administration/dispensation/accountability

To ensure consistency across sites, *Examining Technicians* must undergo a standardized training session prior to enrollment of subjects at their site. All sites should attempt to maintain the same *Examining Technician* throughout the study. If an *Examining Technician* has to be replaced, the new *Examining Technician* must undergo a training session. It is not necessary for the *Examining Technician* to be a healthcare professional as long as he/she is qualified, in the opinion of the Principal Investigator, to administer the MSFC (Note: MSFC was administered in this study only until Week 48; therefore, the role of the *Examining Technician* ended after that).

The *MRI Technician* will be responsible for:

- Performing a brain MRI scan with and without Gd at all protocol-required timepoints. Study-specific MRI scan procedures and protocols, which will be provided prior to study start, must be followed.

The *Pharmacist* (or authorized designee) will be responsible for:

- Storage, distribution, and accountability of study treatment.

The *Study Dermatologist* will be responsible for:

- Documenting cutaneous events, as per the protocol.
- Taking photograph(s) of the affected body areas, as required.
- Performing a skin biopsy, as required.
- Evaluating, treating, and managing clinically significant cutaneous events as described in Section 11.7.3.
- Performing Physician Global Assessment Scale in subjects with clinically significant cutaneous event, as detailed in Section 11.7.3

14.3. Subject Management

The following restrictions apply to all subjects enrolled into this study:

- Subjects must follow the restrictions for concomitant medications and procedures described in Section 11.5.
- Contraception requirements are to be followed as described in Section 15.5.3.
- Whenever possible, a subject should undergo protocol-required tests and assessments at the same time of day throughout the study.
- Subjects should not donate blood until 4 months after their last dose of DAC HYP.
- Subjects should not receive live or live-attenuated vaccines during DAC HYP treatment or for at least 6 months after treatment with DAC HYP.

14.4. Special Instructions for Tests and Assessments

Note: Information about the tests and assessments to be performed in this study is also provided in Section 12 and Section 13, and in the Study Reference Manual.

14.4.1. Rescreening

Subjects who are not eligible for participation at baseline due to a temporary condition (e.g., acute infection) are allowed to be rescreened once the condition has resolved, provided they are rescreened and enrolled within 6 months of completing Study 205MS301, Study 205MS203, or Study 205MS302.

14.4.2. Pregnancy Testing

- Pregnancy testing is only required for women of childbearing potential. A urine pregnancy test is to be performed at the Baseline/Entry Visit and at other timepoints designated in Section 4.2 Schedule of Events. Study treatment will be immediately discontinued if the subject has a positive pregnancy test at any time during the study.
- Results from all urine pregnancy tests must be reviewed by the study site prior to dosing and must be negative.

14.4.3. Liver Function Test Assessments Prior to DAC HYP Dosing

Before a monthly dose of DAC HYP is given, LFT results from prior testing performed within the previous 28(+4) days must be reviewed by the *Study Neurologist* or their backup, and must be within protocol-required limits as described in Section 11.7.2.

LFTs can be performed as follows:

- Samples for LFTs must be drawn prior to administration of the monthly DAC HYP dose. These samples may be tested either locally inside or outside of the clinic (e.g., at a local laboratory or by visiting nurses) or at the central laboratory at the discretion of the Investigator and the results can then be used to determine whether

dosing should continue or be suspended at the monthly dosing timepoint (see Section 11.1).

- 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).
- If the subject is administering DAC HYP injections at home, site personnel must contact the subject after review of prior LFT results performed within 28(+4) days) to authorize the monthly injection, or if LFT results warrant, to instruct the subject to withhold their injection.
- LFTs following a treatment suspension must be performed through the central laboratory until the LFT abnormality has resolved. In cases where LFTs cannot be performed via central laboratory, repeat LFT results from local laboratory can be used for confirmation.

14.4.4. Other Assessments

- Vital signs include systolic and diastolic blood pressure, pulse, and body temperature, and should be measured pre-dose. The subject must rest quietly for 5 minutes prior to blood pressure and pulse measurements. Weight will be collected at Baseline/Entry Visit and at the time of first autoinjector use at selected sites.
- The MSIS-29 must be administered prior to the subject's visit with the *Study Neurologist*.
- Subject assessment of injection pain using a VAS should be completed as soon as possible after the injection is administered, but no later than 10 to 30 minutes post-injection.
- The first 4 DAC HYP injections (i.e., Weeks 0 through 12) must be given in the clinic. The first of these injections must be given by study personnel. At subsequent visits, subjects and/or caregivers will be instructed on DAC HYP self-administration and may administer their scheduled dose under staff supervision. After the subject completes the required in-clinic injections (i.e., after Week 12), DAC HYP may be dispensed to subjects for at-home administration if the subject chooses. If necessary, drug dispensation may occur at monthly intervals.
- Additional visits to assess elevated LFTs, cutaneous events, or PK/[redacted] may be required as described in Section 11.7.

14.5. Definition of MS Relapse and Disability Progression

14.5.1. MS Relapse

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** or their backup. The subject must have objective signs on the examination confirming the event.

*When possible subjects should be evaluated by the same neurologist assigned to them in the parent study.

New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse. New or recurrent neurological symptoms that occur less than 30 days following the onset of a protocol-defined relapse should be considered part of the same relapse. Management of MS relapse is described in Section 14.6.

14.5.2. Disability Progression

Disability progression can only be confirmed from the EDSS scores obtained according to the protocol-defined schedule of assessments at regular visits, and is defined as one of the following:

- at least a 1.0-point increase on the EDSS 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

14.6. Management of MS Relapse

Subjects who experience new or worsening neurological symptoms must contact the *Nurse* or *Study Neurologist* or their backup within 48 hours after the onset of symptoms. A standardized Suspected Relapse Questionnaire will be completed to determine the necessity of an Unscheduled Relapse Assessment Visit.

If required, the subject will then be evaluated in person by the *Study Neurologist* not more than 72 hours after the onset of the symptoms. At the Unscheduled Relapse Assessment Visit, the *Study Neurologist* is to perform a relapse assessment and obtain an EDSS score. New objective findings on neurological examination performed by the *Study Neurologist** are required to determine if a suspected protocol-defined relapse has occurred. Treatment of an acute relapse event with intravenous methylprednisolone (IVMP) [or equivalent] may proceed at the discretion of the *Study Neurologist* after the examination and will not affect the subject's eligibility to continue in the study.

*When possible subjects should be evaluated by the same neurologist assigned to them in the parent study.

Subjects who prematurely discontinue study treatment should complete safety follow-up evaluations (see Section 4.2 and Section 13).

Subjects who permanently discontinue DAC HYP treatment should complete the visit schedule described in Section 11.8.

14.7. Cutaneous Events

Subjects who experience a clinically significant cutaneous event (e.g., rash, dermatitis, eczema, acne, folliculitis) must be referred to and evaluated and managed by the *Study Dermatologist* as

per Section 11.7.3. An Unscheduled Dermatology Assessment Visit will be performed per Table 6.

If a generalized allergic or hypersensitivity reaction to study treatment is suspected, study treatment must be permanently discontinued as per Section 11.8.

14.8. Unscheduled Hepatic Assessment Visit

The following tests/assessments will be performed as soon as possible (but within 7 days) after discontinuation of study treatment for subjects who are required to discontinue dosing due to elevated LFTs as described in Table 6 and Section 11.8.

- Physical examination and vital signs
- Comprehensive hepatic panel
- Recording of concomitant therapy
- Monitor and record AE/SAEs
- Protocol compliance and DAC HYP accountability
- LFTs (ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only)

14.9. Lymphadenopathy and Lymphadenitis Events

Subjects who experience a clinically significant event of lymphadenopathy or lymphadenitis should be referred to a specialist as per Section 11.7.5.

Interruption or discontinuation of DAC HYP treatment due to events of lymphadenopathy or lymphadenitis is a clinical decision that should take the overall benefit-risk assessment of therapy into consideration. Subjects who discontinued study treatment for any reason while presenting with ongoing lymphadenopathy or lymphadenitis should be followed until the lymphadenopathy or lymphadenitis has stabilized or resolved or the study has terminated, whichever comes first.

14.10. Post-Treatment Safety Follow-Up Visit Schedule for All Subjects

All subjects should complete the following schedule of safety follow-up visits after their last dose of DAC HYP:

- End of Treatment Visit (i.e., the assessments required at Week 240). For subjects who prematurely discontinue study treatment before Week 240, these assessments should be performed 4 weeks (±4 days) after the subject's last dose of DAC HYP.
- Post-treatment safety follow-up visits at 8, 12, 16, and 24 weeks after the subject's last dose. The details of these visits are shown in Table 5.

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 from Week 156 Visit in Study 205MS303 (see Table 4) as long as they meet the inclusion/exclusion criteria (Section 8).

15. SAFETY DEFINITIONS, MONITORING, AND REPORTING

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

At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Serious Pretreatment Event

A serious pretreatment event is any event that meets the criteria for SAE reporting (as defined in Section 15.1.3) and occurs after the subject signs the ICF, but before administration of study treatment.

15.1.2. Adverse Event

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

15.1.3. Serious Adverse Event

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

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

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.

15.2. Monitoring and Recording Events

15.2.1. Serious Pretreatment Events

A serious pretreatment event experienced by the subject after signing and dating the ICF but before administration of study treatment is to be recorded on the SAE Form and faxed to the contract research organization (CRO) within 24 hours of the study site staff becoming aware of the event (see Section 15.2.5).

15.2.2. Adverse Events

Any AE experienced by the subject between the time of signing the ICF and subject's final visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

15.2.3. Serious Adverse Events

Any SAE experienced by the subject between the time of the first dose of study treatment and subject's final visit is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to the CRO.

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

Subjects will be followed for all SAEs until the subject's final visit. Thereafter, the event should only be recorded if the Investigator considers it related to study treatment.

15.2.4. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.3.
- The relationship of the event to study treatment as defined in Section 15.3.1.
- The severity of the event as defined in Section 15.3.2.

15.2.5. Immediate Reporting of Serious Adverse Events

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

Reporting Information for SAEs

Any Serious Event that occurs between the time the subject has signed informed consent and subject's final visit must be reported to the CRO within 24 hours of the study site staff becoming aware of the event. **Thereafter, the event should only be recorded if the Investigator considers it related to study treatment**.

A report pertaining to an event that occurs between the time the subject has signed informed consent and subject's final visit ***must be submitted*** to the CRO regardless of the following:

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

To report initial or follow-up information on a Serious Event, fax a completed SAE form to the following:

North America: [redacted]
Latin America: [redacted]
Europe and Asia Pacific: [redacted]

(Country-specific fax numbers are provided in the Study Reference Guide.)

15.2.5.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate CRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen SABR or designee.

15.3. Safety Classifications

15.3.1. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

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

15.3.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.3.3. Expectedness of Events

Expectedness of all AEs will be determined according to the Investigator's Brochure.

15.4. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the

Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.

- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

15.5. Procedures for Handling Special Situations

15.5.1. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed to the CRO within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded in the CRF; dosing information is recorded on a CRF.

15.5.2. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator or designee should contact the CRO Medical Monitor at one of the following phone numbers:

North America (USA and Canada): [redacted]

Latin America: [redacted]

Europe and Asia Pacific: [redacted]

15.5.3. Contraception Requirements

All women of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 4 months after their last dose of study treatment.

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

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy

For the purposes of the study, effective contraception is defined as follows:

For females:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with spermicide; diaphragm, sponge, cervical cap)

- True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

15.5.4. Pregnancy

Subjects should not become pregnant during the study. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report the pregnancy by faxing the appropriate form to Pharmacovigilance at the CRO within 24 hours of the study site staff becoming aware of the pregnancy (refer to Section 15.2.5 for reporting information). The Investigator or study site staff must report the outcome of the pregnancy to Pharmacovigilance at the CRO.

Please note that congenital abnormalities/birth defects in the offspring of male or female subjects should be reported when conception occurred during the study treatment period.

15.5.5. Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Biogen Safety and Benefit-Risk Management (SABR) will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

15.6. Investigator Responsibilities

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow-up on the outcome of the pregnancy.
- Complete an SAE form for each serious event and fax it to the CRO within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the CRO within 24 hours of the study site staff becoming aware of new information.
- Complete an Adverse Event of Special Interest form for each transaminase elevation, hepatic event, and cutaneous event as described in the protocol and fax it to the CRO as soon as possible following the study site staff becoming aware of the event.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.

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

15.7. Biogen Responsibilities

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor or designee is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

16.1. Description of Objectives

See Section 6.1, Objectives.

16.2. Description of Endpoints

See Section 6.2, Endpoints.

16.3. Demography and Baseline Disease Characteristics

Demographic data collected at baseline will be summarized (i.e., age, gender, ethnicity, and weight). Medical history and baseline characteristic data (e.g., EDSS, number of relapses in the previous study, MRI endpoints) will also be summarized.

16.4. Safety and Efficacy

16.4.1. Analysis Population

Study 205MS303 Safety Population

The safety population will include all subjects who received at least 1 dose of DAC HYP in Study 205MS303. All safety analyses will be completed on the safety population.

Study 205MS303 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who received at least 1 dose of DAC HYP in Study 205MS303. This population will be utilized for the efficacy analyses.

Study 205MS301 and Study205MS303 Intent-to-Treat population

This population will include all subjects randomized to DAC HYP or Avonex in Study 205MS301 and received at least one dose of DAC HYP in Study 205MS303.

16.4.2. General Methods of Analysis

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include the number of subjects with data, mean, standard deviation, median, and range. Categorical endpoints will include the number of subjects with data and the percentage in each category.

Analyses will generally be descriptive in nature and will focus on data collected during Study 205MS303 only. However, for relevant efficacy analyses, the data may be summarized by previous treatment group (Avonex or DAC HYP). Also, statistical comparisons may be made between efficacy in Study 205MS301 and efficacy in Study 205MS303 among subjects previously randomized to Avonex in Study 205MS301.

All statistical tests will be 2-sided with an overall Type I error of 5%. Adjustments for multiple comparisons will not be considered.

16.4.3. Primary Endpoints Analysis

Clinical Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. All treatment-emergent events will be included in the evaluation of safety. Treatment emergent includes any event that either occurs or worsens in severity after the onset of study treatment. Overall incidence of treatment-emergent events will be summarized; in addition, summaries by severity and by relationship to study treatment will be provided. The summary tables will include incidence estimates for the overall system organ class as well as for preferred terms within each system organ class. In order to assess whether the incidence of events changes over time, the incidence of key events may also be summarized by time period (e.g., 6-month time intervals).

16.4.4. Other Safety Endpoint Analyses

Unless otherwise specified, the baseline measurement for safety assessments such as laboratory values and vital signs was the measurement acquired on the day of the first receipt of DAC HYP. The first receipt of dosing of DAC HYP could be either Study 205MS303 (for subjects who received Avonex in Study 205MS301) or the parent studies (i.e., Study 205MS301, Study 205MS203, or Study 205MS302) for all other subjects.

Laboratory Data

Changes in laboratory values will be summarized using shift tables. Shift tables will include hematology, LFTs, kidney function tests, electrolytes, and other blood chemistry tests. Shifts will be presented from baseline of DAC HYP treatment (the last measurement acquired before or on the day of the first receipt of DAC HYP, e.g., Study 205MS303 baseline for subjects randomized to Avonex in Study 205MS301 and Study 205MS301 baseline for subjects randomized to DAC HYP 150 mg in Study 205MS301). Summaries of worst post-baseline laboratory values by clinically relevant categories may also be presented for selected parameters of interest by treatment group. For example, for LFT (alkaline phosphatase, ALT, AST, GGT, and total bilirubin), categories may be defined based on cutoff values relative to the ULN.

Vital Signs

Vital signs collected will be examined to determine the incidence of clinically relevant abnormalities. These abnormalities are described in Table 8. For the purpose of the shifts from baseline, the baseline evaluation at the start of DAC HYP treatment will be used.

For each vital sign, the number of subjects evaluated and the number and percentage of subjects with the defined abnormality at any time post dosing will be presented by treatment group.

Table 8: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C or an increase from baseline of ≥1°C
Pulse	>120 beats per minute (bpm) or an increase from baseline of 20 bpm <50 bpm or a decrease from baseline of >20 bpm
Systolic Blood Pressure	>180 mmHg or an increase from baseline of >40 mmHg <90 mmHg or a decrease from baseline of >30 mmHg
Diastolic Blood Pressure	>105 mmHg or an increase from baseline of >30 mmHg <50 mmHg or a decrease from baseline of >20 mmHg

Physical Examination

The physical examination findings will be summarized.

16.4.5. Efficacy Endpoints Analyses

Annualized Relapse Rate

Relapses will be summarized over the follow-up period in Study 205MS303. For subjects in Study 205MS301 and Study 205MS303 ITT population, relapses may be summarized over the combined study period (Studies 205MS301 and 205MS303).

A negative binomial regression model will be used to estimate the adjusted ARR.

Proportion of Subjects with a Relapse

The proportion of subjects relapsed will be estimated using a Kaplan-Meier curve.

Disability Progression

Sustained disability progression is defined as at least a 1.0 point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 24 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS <1.0 that is sustained for 24 weeks. The proportion of subjects with progression will be summarized using a Kaplan-Meier curve. In addition, summary statistics for EDSS and for the change from baseline in EDSS will be presented by visit, and for subjects who participated in Study 205MS301, by previous treatment group.

MSFC

Changes in the MSFC z-score will be summarized by study visit, and for subjects who participated in Study 205MS301, by previous treatment group. For subjects in Study 205MS301 and Study 205MS303 ITT population, MSFC z-score may be summarized over the combined study period (Studies 205MS301 and 205MS303). Details on the calculations of the z-score for each component will be described in the statistical analysis plan.

SDMT

Changes in the SDMT scores will be summarized by study visit and by previous treatment group in Study 205MS301. Change in the SDMT scores over the combined study period (Studies 205MS301 and 205MS303) will be calculated using the Study 205MS301 baseline visit

as baseline. Change in the SDMT score over the Study 205MS303 study period will be calculated using the last SDMT measurement in Study 205MS301 as baseline.

PASAT 3

Changes in the PASAT 3 scores will be summarized by study visit and by previous treatment group in Study 205MS301. Change in the PASAT 3 scores over the combined study period (Studies 205MS301 and 205MS303) will be calculated using the Study 205MS301 baseline visit as baseline. Change in the PASAT 3 score over the Study 205MS303 study period will be calculated using the Week 0/baseline visit as baseline.

MRI Endpoints

MRI endpoints will be summarized with descriptive statistics both as a continuous variable and categorically. Over time summaries and summaries by previous treatment group (Avonex or DAC HYP 150 mg) may also be provided. A negative binomial regression model will be used for the analysis of new or newly enlarging T2 lesions. The change in volume of lesions will be analyzed using an analysis of covariance.

Quality of Life Outcomes

Actual scores and change from baseline in quality of life endpoints will be summarized by visit.

Pharmacokinetics

The population for DAC HYP concentration analyses will include all subjects who received at least 1 dose of study medication and who have at least 1 sample available for analysis.

Serum concentration levels will be summarized with descriptive statistics by visit.

Antigenicity/Immunogenicity Data

Immunogenicity (i.e., ADAs to DAC HYP) will be assessed on subjects. Positive samples will be further tested for neutralizing antibodies to DAC HYP using a specific NAb assay. Results will be tabulated by time period and overall.

16.5. Interim Analyses

No formal interim analyses are planned for this study. However, analyses may be performed prior to the end of the study at the discretion of the Sponsor.

16.6. Sample Size Considerations

There is no formal sample size calculation. The number of subjects in this study is determined by the number of subjects who completed Study 205MS301, Study 205MS203, or Study 205MS302.

17. ETHICAL REQUIREMENTS

Biogen and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

17.1. Declaration of Helsinki

The Investigator and Biogen must adhere to the principles set forth by the Declaration of Helsinki dated October 2008.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor may submit documents on behalf of the study sites in countries other than the US as applicable.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

It is the responsibility of the Principal Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

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

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

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

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including Baseline/Entry Visit tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all subjects participating in a clinical study conducted by Biogen.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including Baseline/Entry Visit tests and assessments.

Each consent form should contain an authorization allowing the Principal Investigator(s) and Biogen to use and disclose PHI (i.e., subject-identifiable health information) in compliance with local law.

The signed consent form will be retained with the study records.

17.4. Subject Data Protection

Prior to any testing under this protocol, including Baseline/Entry Visit tests and assessments, candidates must also provide all authorizations required by local law (e.g., PHI authorization in North America).

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws.

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not enroll any subjects prior to completion of a study initiation visit, conducted by Biogen or designee. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Principal Investigator(s) must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the course of the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the study site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

Biogen will be responsible for all administrative aspects of this study including, but not limited to, study initiation, monitoring, management of AEs, and data management.

19.1. External Contract Organizations

19.1.1. Contract Research Organization

The CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Electronic or Remote Data Capture

Subject information will be captured and managed by study sites on electronic CRFs via a remote data capturing system.

19.1.3. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by Biogen to analyze all hematology, blood chemistry, and urine samples collected for this study.

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).

19.1.4. Central Facility for Independent Assessment of Biopsy Samples

A central laboratory service has been selected by Biogen to coordinate the collection and distribution of biopsy samples. A central assessor has been selected to subsequently analyze skin biopsies or lymph node biopsies (as applicable).

19.1.5. Central Facility for Other Assessments

MRI Reading Center

All scheduled MRI scans with and without Gd will be evaluated at a central MRI reading center. All study sites will be required to send a test scan to the MRI Reading Center for evaluation in order to ensure that the site's scanning techniques are appropriate. This review will take place before the study site is permitted to enroll any subjects into the study.

Original MRI images are to be sent to the MRI Reading Center for review (MRI shipping instructions will be provided prior to the start of enrollment at each site).

Additional and more detailed MRI scans with and without Gd procedures and instructions are included in the study MRI manual (to be provided under separate cover prior to start of the study).

19.2. Study Committees

19.2.1. Advisory Committee

The Advisory Committee from parent Study 205MS301 will oversee the administrative progress and provide scientific and medical direction for this study while Study 205MS301 is ongoing. Advisory Committee will monitor subject accrual and compliance with the protocol at individual study sites. The Advisory Committee will determine whether the study should be stopped or amended for reasons other than safety.

Members of the Advisory Committee will include the Medical Director, Clinical Trial Manager, and Project Statistician from Biogen (and/or their designees), and participating Investigators. Biogen will designate one of the participating Investigators to be the Chairperson of the Advisory Committee.

19.2.2. Internal Safety Monitoring Committee

An internal Safety Monitoring Committee will be formed to review interim safety data on an ongoing basis. Investigational sites will be notified of any relevant safety findings that may jeopardize subject safety.

19.3. Changes to Final Study Protocol

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

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

In the event of a protocol modification, the subject consent form may require similar modifications (see Section 17.2 and Section 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator

must notify Biogen of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate one of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors, including, but not limited to, the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by Biogen.

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

20. REFERENCES

Bielekova B, Howard T, Packer AN, et al. Effect of anti-CD25 antibody daclizumab in the inhibition of inflammation and stabilization of disease progression in multiple sclerosis. Arch Neurol. 2009;66(4):483-9.

Bielekova B, Richert N, Howard T, et al. Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta. Proc Natl Acad Sci U S A. 2004;101(23):8705-8.

Fischer JS, LaRocca NG, Miller DM, et al. Recent developments in the assessment of quality of life in multiple sclerosis (MS). Mult Scler. 1999;5(4):251-9.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52. Epub 1983/11/01.

Rose JW. Treatment of Multiple Sclerosis with a Humanized Monoclonal Antibody Specific for IL-2 Receptor Chain. Neurology. 2003;60(Suppl 1):A478-9.

Rose JW, Watt HE, White AT, et al. Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. Ann Neurol. 2004;56(6):864-7.

Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol. 2010;9(4):381-90.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "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 Who Have Completed Study 205MS301" and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

Signature Page

Document Name: 205MS303 Protocol V3 Final 29Jan16

Document Title: 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 Who Have Completed Study 205MS301

Signed by	Role	Date / Time (UTC)
[redacted]	Signing as Approver	02/01/2016 02:13:45

SIGNATURE PAGE

Protocol 205MS303 was approved by:

[redacted]

[redacted] MD, MAS

29FEB16
Date

[redacted]

Biogen MA Inc.

Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142, USA

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

PROTOCOL NUMBER: 205MS303

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: 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 Who Have Completed Study 205MS301

EUDRA CT NO: 2012-003176-39

DATE: 01 April 2015
Version 2
FINAL

Supersedes previous Version 1 dated 28 September 2012.

SIGNATURE PAGE

Protocol 205MS303 was approved by:

[redacted]

[redacted] MD, MAS

2 APR 15

Date

[redacted]

Biogen Idec MA Inc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142
USA

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

Biogen Idec Australia Pty Ltd
Suite 1, Level 5
123 Epping Road
North Ryde, NSW 2113
Australia

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

Biogen Idec may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen Idec retains overall accountability for these activities.

2. LIST OF ABBREVIATIONS

ADAs	anti-drug antibodies
AE	adverse event
AESI	Adverse Event of Special Interest
ALT	alanine aminotransferase
ARR	annualized relapse rate
AST	aspartate aminotransferase
AUDIT-C	Alcohol Use Disorders Identification Test - Consumption Questionnaire
BDI-II	Beck Depression Inventory, Second Edition
bpm	beats per minute
BUN	blood urea nitrogen
CRF	case report form
CRO	contract research organization
DAC HYP	Daclizumab High Yield Process
DHA	Directions for Handling and Administration
EDSS	Expanded Disability Status Scale
EQ-5D	European Quality of Life, 5-dimensions
EQ-VAS	European Quality of Life, visual analog scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gd	gadolinium
GGT	gamma-glutamyltransferase
HIV	human immunodeficiency virus
HRPQ	Health Related Productivity Questionnaire
HRU	health resource utilization
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFN	interferon
IL-2	interleukin-2
IM	intramuscular
ITT	intent-to-treat
IV	intravenous
IVIg	intravenous immunoglobulin
IVMP	intravenous methylprednisolone
LFT	liver function test
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale-29
NAbs	neutralizing antibodies

NK	natural killer cells
PASAT 3	3 Second Paced Auditory Serial Addition Test
[redacted]	[redacted]
PFS	prefilled syringe
PHI	protected health information
PK	pharmacokinetic(s)
[redacted]	[redacted]
RDC	remote data capture
RRMS	relapsing-remitting multiple sclerosis
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
SC	subcutaneous
SGOT	serum glutamic oxaloacetic transaminase; see AST
SGPT	serum glutamic pyruvic transaminase; see ALT
SNP	single nucleotide polymorphism
SUSAR	suspected unexpected serious adverse reaction
T1	MRI hypointense designation
T2	MRI hyperintense designation
T4	thyroxine
ULN	upper limit of normal
US	United States
VAS	visual analog scale

3. SYNOPSIS

This is a brief summary. For details refer to the body of the protocol.

Protocol Number:	205MS303
Protocol Title:	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 Who Have Completed Study 205MS301
Version Number:	2
Name of Study Treatment:	Daclizumab High Yield Process (DAC HYP)
Study Indication:	Relapsing-Remitting Multiple Sclerosis (RRMS)
Phase of Development:	3
Rationale for the Study:	To evaluate the long-term safety, efficacy, and immunogenicity of DAC HYP in subjects with multiple sclerosis (MS) who have completed Study 205MS301 (DECIDE), Study 205MS203 (SELECTED), or Study 205MS302 (OBSERVE).
Study Objectives and Endpoints:	**Objectives** Primary: 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. Secondary: 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 Avonex® in Study 205MS301

Exploratory:

- [redacted]

Endpoints

Primary:

- Incidence of adverse events (AEs) and serious AEs (SAEs)

Secondary:

- 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, gadolinium-enhancing (Gd+) lesions, T1 hypointense lesions, and brain volume change on brain MRI.
- Change in Multiple Sclerosis Functional Composite (MSFC) score
- Change in EDSS 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 (EQ-5D and European Quality of Life, visual analog scale

	[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 analog scale [VAS]) and clinician injection site assessments • Incidence of anti-drug antibodies to DAC HYP over time • Incidence of neutralizing antibodies to DAC HYP over time
Study Design:	Multicenter, open-label, long-term extension study
Rationale for Dose and Schedule Selection:	The DAC HYP dose and schedule were used in the pivotal Phase 3 205MS301 study, and will be the treatment regimen used in the commercial setting. The same DAC HYP dose and schedule were used in Study 205MS203 and Study 205MS302.
Study Location:	Global
Number of Planned Subjects:	Approximately 1600 subjects. This includes approximately 1200 subjects who completed Study 205MS301. Additionally, approximately 400 subjects from the other ongoing DAC HYP extension studies (Study 205MS203 and Study 203MS302) will be eligible to enter Study 205MS303 at Week 144 of Study 205MS303.
Study Population:	This study will be conducted in subjects with MS currently participating in Study 205MS301 who have completed either the Week 144 Visit or the End of Study Visit (Week 96) of Study 205MS301, OR subjects with MS currently participating in Study 205MS203 or Study 205MS302.

Treatment Groups:	This is a single-arm study. All subjects will receive open-label treatment with DAC HYP 150 mg by a subcutaneous injection using the PFS every 4 weeks. Depending on availability and local regulations, some subjects may dose with DAC HYP using a single-use autoinjector that contains a PFS.
Duration of Treatment and Follow-up:	Subjects will participate in this study for up to approximately 5 years, or until availability of commercial product (whichever is sooner), and in accordance with applicable laws and regulations. All subjects should complete safety follow-up evaluations at 8, 12, 16, and 24 weeks after the subject's last dose of DAC HYP.
Criteria for Evaluation:	
Efficacy:	Clinical relapse assessments, EDSS, MSFC (Timed 25-Foot Walk, Nine-Hole Peg Test with both upper extremities, PASAT 3), and brain MRI scan with and without Gd (T2 hyperintense lesions, T1 hypointense lesions, Gd+ lesions, brain atrophy).
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]
[redacted]*:*	[redacted]
Safety:	Physical and neurological exams, vital signs, clinical laboratory assessments (hematology, blood chemistry, thyroid function panel [including thyroid stimulating hormone and T4], urinalysis), urine pregnancy testing, Beck Depression Inventory, Second Edition, immunogenicity assessments, Alcohol Use Disorders Identification Test - Consumption Questionnaire (AUDIT-C), and AE and concomitant medication monitoring will be performed in this

	study. Additional comprehensive hepatic testing will be required for subjects who permanently discontinue study treatment due to elevated liver function tests.
Subject Reported Assessments:	Subject assessment of MSIS-29, EQ-5D quality of life questionnaire (the EQ-5D descriptive system and the respondent's self-rated health on a vertical visual analog scale [EQ-VAS]), Treatment Satisfaction Questionnaire for Medication (before the first use of a PFS and at multiple timepoints during the study), Treatment Satisfaction Survey at selected sites (before the first and last use of an autoinjector), HRU, and HRPQ.
Statistical Methods:	Analyses will generally be descriptive in nature and will focus on data collected during Study 205MS303 only. Efficacy endpoints will be summarized for all subjects using descriptive statistics. For relevant efficacy analyses, the data may be summarized for subjects by previous treatment group (Avonex® or DAC HYP 150 mg). The adjusted ARR and number of new or newly enlarging T2 lesions will be estimated using a negative binomial regression model. The proportion of subjects with sustained progression and the proportion with a relapse will be estimated from the Kaplan-Meier curve. The incidence of AEs and changes in clinical laboratory assessments will also be summarized. An analysis by 3- or 6-month intervals may also be performed. Summary statistics for other safety, efficacy, and pharmacokinetic (PK) endpoints will be presented.
Sample Size Determination:	There is no formal sample size calculation for this study. The number of subjects in this study is determined by the number of subjects who completed Study 205MS301, Study 205MS203, or Study 205MS302, and enrolled in Study 205MS303.
Study Stopping Rules:	Biogen Idec may terminate this study, after informing Investigators, at any time. Investigators will be notified by Biogen Idec or designee if the study is placed on hold, completed, or closed.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS TABLES FOR STUDY 205MS303

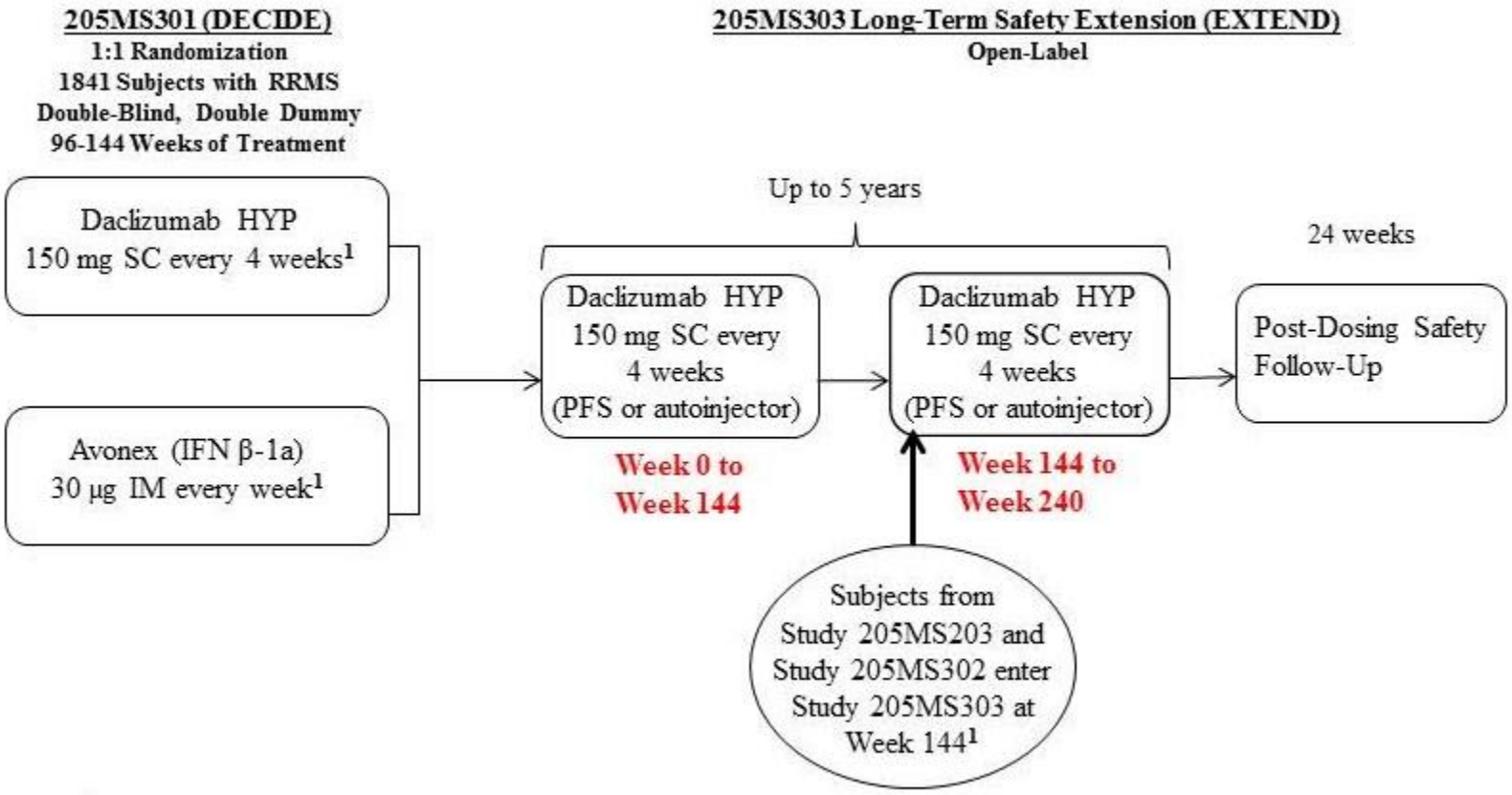
A schematic of the study design is provided in Section 4.1.

The tabulated schedule of events for this study is provided in Section 4.2.

4.1. Study Schematic

Figure 1 shows the design of Study 205MS301 and its open-label extension, Study 205MS303, in which subjects from Study 205MS203 and 205MS302 enter at Week 144.

Figure 1: Study Design



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

4.2. 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 for abnormal liver function tests (LFTs), LFTs must be re-evaluated as specified in 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 every 28±4 days (see 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			
[redacted]	X			X	X		X			
[redacted]	X						X			
[redacted]	X			X	X		X			
[redacted]										

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
Anti-Drug Antibody Sample	X			X	X		X			
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 clinically significant cutaneous events (see 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).
[6][redacted]
[7]Subjects who did not consent to [redacted] collection in 205MS301 will be re-approached for this consent upon entry into Study 205MS303. A separate informed consent form may be used for [redacted] sample collection. Samples for [redacted] 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 28(+4) 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 for abnormal LFTs, LFTs must be re-evaluated as per 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 every 28±4 days (see 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
DAC HYP Administration/Dispensation[8, 9]	X	X	X	X	X
Dosing Diary	Subject continues recording observations during home dosing only				
Physician Global Assessment Scale	Performed only in subjects with clinically significant cutaneous events (see 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]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]Before a monthly dose of DAC HYP is given, LFT results from a prior test performed within the previous 28(+4) days must be reviewed by the *Study Neurologist* or their backup.
[9]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 Assessment	X
Anti-Drug Antibody Sample	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 clinically significant cutaneous events (see 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 28(+4) days must be reviewed by the *Study Neurologist* or their backup.

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 inclusion/exclusion criteria (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 every 28±4 days (see Section 14.4.3)							
Liver Function Tests at Central Laboratory[2, 3]	X	X	X	X	X	X	X	X
DAC HYP Concentration Assessment				X				X
Anti-Drug Antibody Sample				X				X
Urine Pregnancy Test[5]		X		X		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
EQ-5D and EQ-VAS				X				X
HRU				X				X
HRPQ		X		X		X		X
EDSS[6]		X		X		X		X
DAC HYP Administration/ Dispensation[7, 8]	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 clinically significant cutaneous events (see 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]When possible, subjects should be evaluated by the same neurologist assigned to them in the parent studies.

[7]Before a monthly dose of DAC HYP is given, LFT results from a prior test performed within the previous 28(+4) days must be reviewed by the *Study Neurologist* or their backup.

[8]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 (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
Anti-Drug Antibody Sample				X
Urine Pregnancy Test				X
DAC HYP Concentration Assessment[4]				X
EDSS				X
Physician Global Assessment Scale	Performed only in subjects with ongoing clinically significant cutaneous events (see 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.
[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 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/[redacted] Visit[4]**
Cutaneous Event Assessment 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/[redacted] Assessments[8]				X
EDSS[9]	X			
Photographs[10]			X	
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] Any subject who develops a clinically significant cutaneous event should be evaluated by the *Study Dermatologist* at an Unscheduled Dermatology Assessment Visit as soon as possible. Refer to Section 11.7.3 for information on when to perform the follow-up visits.
[3]If any cutaneous AE is on-going at the time of the subject terminating from the study, the *Study Dermatologist* is to perform an Unscheduled Dermatology Assessment Visit if the subject has not had such a visit in the 4 weeks±4 days prior to leaving the study.
[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 Idec 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 Section 11.8.

[8]Whole blood samples will be collected for potential determination of DAC HYP serum concentrations [redacted]

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

Table 7: Schedule of Activities: Autoinjector Use by Subjects at Selected Sites

Note: At the Sponsor's discretion, approximately 75-100 eligible subjects from Study 205MS303 at selected sites may begin using autoinjectors on any regularly scheduled dosing day, after they have received at least 6 consecutive monthly doses of DAC HYP by prefilled syringe (PFS) in Study 205MS303. Six consecutive DAC HYP injections will be administered by the subject. Doses 1 and 4 will be supervised during clinic visits, all other doses can be given at home or the clinic. Following the use of autoinjectors, subjects should resume administration of DAC HYP using the PFS.

Note: Subjects are to continue the visit schedule and evaluations listed in Table 1 through Table 6 while they are using autoinjectors.

	Autoinjector 1[1]		Autoinjector 2 4 weeks ±4 days		Autoinjector 3 8 weeks ±4 days		Autoinjector 4[1] 12 weeks ±4 days		Autoinjector 5 16 weeks ±4 days		Autoinjector 6 20 weeks ±4 days	
Tests and Assessments	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**
Informed Consent	X[2]											
Weight	X											
Waist Circumference[3]	X											
Abdominal Fold Thickness[3]	X											
DAC HYP Administration		X		X		X		X		X		X
Injection Site Assessment		X[4]					X					
Subject Assessment of Injection Pain (VAS)[5]		X						X				
Observer Report		X						X				
Treatment Satisfaction Survey[6]	X							X				X
Patient Usability Survey[6]								X				X
DAC HYP Concentration Assessment	X						X					
Anti-Drug Antibody Sample	X						X					

[1]To be administered during a scheduled clinic visit.

[2]Subjects must provide written informed consent for autoinjector use prior to first DAC HYP dose by autoinjector.
[3]The procedure for taking this measurement is provided in the Study Reference Manual.
[4]Injection Site Assessment to be completed as soon as possible but within 10 minutes after the injection at Visit 1.
[5]VAS to be completed as soon as possible after the injection is administered, but no later than 10-30 minutes post-injection.
[6]If the subject withdraws from the study or reverts to PFS use prior to receiving all 6 autoinjector doses, the subject should complete the Treatment Satisfaction Survey and the Patient Usability Survey provided for the Autoinjector 6 dosing day before returning to PFS or receiving alternative MS disease modifying therapy.

5. INTRODUCTION

5.1. Profile of Previous Experience with Daclizumab in MS

Background

DAC HYP is a humanized monoclonal IgG1 antibody specific for CD25 (α subunit of the IL-2 receptor). CD25 is expressed at low levels on resting T cells but is rapidly upregulated after T-cell activation, enabling high-affinity IL-2 signal transduction. The primary hypothesis for using DAC HYP to treat MS is to selectively inhibit activated T cells.

Anti-CD25 antibodies have multiple in vitro effects that suggest DAC HYP may directly decrease T-cell activation and proliferation. These include inhibition of IL-2 dependent lymphocyte proliferation, disruption of both IL-2 dependent and independent pathways of IFN-gamma production, and interference in CD28-dependent CD40 ligand expression. In vivo, daclizumab has been confirmed to cause expansion of $CD56^{bright}$ NK cells. This expansion has also been shown to correlate with MRI-defined therapeutic response of daclizumab in MS. $CD56^{bright}$ NK cells are believed to have an immunoregulatory function, and they have been shown to kill activated T cells through a contact-dependent mechanism. Therefore, selective inhibition of activated T cells with DAC HYP may occur through both direct and indirect mechanisms [Bielekova 2009; Bielekova 2004].

Clinical Experience With Daclizumab in Multiple Sclerosis

Initial clinical studies of daclizumab in MS were conducted with material manufactured by F. Hoffmann-La Roche, Ltd. (Roche) at their facilities in Nutley, New Jersey (DAC Nutley) [Bielekova 2004; Rose 2003; Rose 2004], and in Penzberg, Germany (DAC Penzberg) [Wynn 2010]. Study 205MS301 is conducted with DAC HYP, which is produced using a different manufacturing process than the previous versions of daclizumab. DAC HYP has characteristics that are similar to DAC Nutley and DAC Penzberg, although certain differences in physicochemical and biological characteristics have been observed (refer to the Investigator's Brochure for details).

Study 205MS201

Study 205MS201 (SELECT) was a double-blind, placebo-controlled study to evaluate the safety and efficacy of DAC HYP in subjects with RRMS that randomized 621 subjects in a 1:1:1 ratio to receive placebo, 150 mg DAC HYP, or 300 mg DAC HYP SC every 4 weeks over a 52-week treatment period. Among subjects randomized to DAC HYP (150 mg, 300 mg) versus placebo, there was a significantly lower annualized relapse rate (ARR; 0.21, 0.23 versus 0.46; $p < 0.001$), a higher proportion of relapse-free subjects (81%, 80% versus 64%; $p < 0.001$), and a trend towards improvement in the MSIS-29 physical score ($p = 0.128$ for DAC HYP 300 mg versus placebo; $p < 0.001$ for DAC HYP 150 mg versus placebo). There were significant reductions in the mean number of new or newly enlarging T2 lesions at 1 year (2.4, 1.7 versus 8.1) and in the mean number of new Gd+ lesions between Weeks 8 and 24 in a monthly MRI substudy ($n = 307$) (1.5, 1.0 versus 4.8) in the DAC HYP 150 mg and 300 mg groups versus placebo ($p <$

0.001 for all comparisons). The risk of 3-month sustained disability progression at 1 year, a tertiary study endpoint, was reduced by 57% (p = 0.021) in the DAC HYP 150 mg group and by 43% (p = 0.091) in the DAC HYP 300 mg group.

Analysis of safety data from Study 205MS201 showed that, overall, DAC HYP was well tolerated in this patient population. The most frequently reported (≥10%) AEs for subjects treated with DAC HYP, excluding MS relapse, were nasopharyngitis (14%), and headache and upper respiratory tract infection (10% each). In Study 205MS201, serious adverse events (SAEs) including MS relapses occurred in 26% of placebo-treated subjects and in 16% of subjects treated with DAC HYP. Excluding MS relapses, SAEs occurred in 6% of the placebo group, in 7% of the DAC HYP 150 mg group, and in 9% of the DAC HYP 300 mg group. One DAC HYP-treated subject died due to ischemic colitis following a complicated course of events. Adverse events observed more frequently in DAC HYP-treated patients included an increase in serious infections (2%), serious cutaneous events (1%), and elevations in liver function tests (ALT/AST) >5× ULN (4%).

Upon completion of the 12-month treatment period in Study 205MS201, subjects were eligible to complete up to an additional 12 months of treatment with DAC HYP in a double-blind extension study (Study 205MS202 [SELECTION]), which was completed in 2012. Study 205MS202 also assessed the effects of DAC HYP washout in some subjects who were actively treated in Study 205MS201. Subjects completing Study 205MS202 continued long-term therapy with open-label DAC HYP in extension Study 205MS203 (SELECTED), which evaluated long-term safety and efficacy of DAC HYP monotherapy for up to an additional 144 weeks.

Study 205MS301

Study 205MS301 (DECIDE), a double-blind, randomized, parallel-group, active-controlled study testing the superiority of DAC HYP monotherapy compared to Avonex® (IFN β-1a) in preventing MS relapse, was initiated in May 2010; 1841 subjects with RRMS have been enrolled and randomized in a 1:1 ratio to receive 150 mg DAC HYP given SC every 4 weeks, or Avonex 30 mcg given IM once weekly over a 96- to 144-week treatment period. The primary endpoint was the annualized relapse rate. In this study, DAC HYP demonstrated statistically and clinically meaningful superiority to IFN β-1a, on validated clinical, radiographic, and patient-reported MS outcome measures. DAC HYP reduced the annualized relapse rate by 45% (p<0.0001) compared to IFN β-1a. DAC HYP's treatment effect on relapses was also evidenced by a 41% reduction in the risk of relapse in subjects in the DAC HYP group compared to the IFN β-1a group (p<0.0001). A reduction in the proportion of subjects relapsing was observed as early as 24 weeks after the initiation of treatment and persisted throughout the end of the study. The risk of 12-week confirmed disability progression was reduced by 16% in the DAC HYP group compared with the IFN β-1a group, a result that was not statistically significant (p=0.1575) in the primary analysis. In the pre-specified analysis of 24-week confirmed progression, disability progression was reduced by 27% (p=0.0332) in the DAC HYP group compared with the IFN β-1a group. Overall, the results of the 12-week and 24-week confirmed progression analyses were consistent with each other and supported a clinically meaningful effect of DAC HYP in preventing confirmed disability progression compared with IFN β-1a. DAC HYP reduced the number of new or newly enlarging T2 lesions at Week 96 by 54.4% (p<0.0001) compared to IFN β-1a. The magnitude of the treatment effect was consistent with

the results seen on the primary endpoint of annualized relapse rate. The tertiary MRI endpoints of T2, T1, and Gd-enhancing lesion count and volume were also consistent with the effect on new or enlarging T2 lesions and provide important confirmation of DAC HYP's ability to reduce focal and destructive areas of brain inflammation in RRMS patients. The treatment effect of DAC HYP on new or enlarging T2 lesions and other MRI endpoints was detectable by Week 24 ($p<0.0001$) and was sustained through to the Week 96 and Week 144 MRI at a similar magnitude.

In Study 205MS301, the safety profile of DAC HYP was characterized by an increased incidence of elevations of serum transaminases and serious hepatic events, cutaneous events, infections, and gastrointestinal events. The overall incidence of AEs was balanced across the 2 treatment groups (91% IFN β-1a vs. 91% DAC HYP). The majority of subjects with AEs had events that were mild to moderate in severity. The incidence of subjects with AEs that were considered severe was 14% in the DAC HYP group and 12% in the IFN β-1a group. AEs reported more frequently in the DAC HYP group than in the IFN β-1a group included nasopharyngitis, upper respiratory tract infections, influenza, oropharyngeal pain, rash, and lymphadenopathy, whereas influenza-like illness, pyrexia, chills, and hypertension were reported more frequently in the IFN β-1a group.

There was a higher incidence of SAEs in the DAC HYP group (24%) compared with the IFN β-1a group (21%). Excluding MS relapse, SAEs were reported in 10% of the IFN β-1a group and in 15% of the DAC HYP group. Five deaths were reported in the study (4 subjects in the IFN β-1a group, 1 subject in the DAC HYP group). None of the deaths were considered by the Investigators to be related to study treatment. While safety events were more common in the DAC HYP-treated subjects compared with IFN β-1a-treated subjects, the types of events were generally manageable with standard medical care, monitoring, and treatment discontinuation, as appropriate for the event. Overall, the results of the study support a positive benefit/risk profile for DAC HYP.

The PK and immunogenicity of DAC HYP 150 mg SC administered every 4 weeks using a prefilled syringe (PFS) were investigated in 26 subjects in Study 205MS302 (OBSERVE), a single-arm, open-label study that enrolled a total of 113 subjects with RRMS.

Refer to the Investigator's Brochure for additional details.

5.2. Study Rationale

This study will evaluate the long-term safety, efficacy, and immunogenicity of DAC HYP in subjects with MS who have completed Study 205MS301, Study 205MS203, or Study 205MS302. In addition, this study will assess the safety, tolerability, and efficacy of switching to DAC HYP in subjects previously on long-term treatment with interferon β-1a in Study 205MS301.

5.3. Rationale for Dose and Schedule Selection

The existing scientific and clinical experience with DAC HYP supports its further investigation in the management of MS. The DAC HYP dose and schedule in this protocol were used in the pivotal Phase 3 Study 205MS301, and will be the treatment regimen used in the commercial

setting. The same DAC HYP dose and schedule were used in Study 205MS203 and Study 205MS302.

A single-use, disposable PFS will be provided to simplify the injection process and thereby reduce the burden of administering a long-term therapy such as DAC HYP in the clinic or at home. At the Sponsor's discretion, single-use autoinjectors containing PFS may be used to administer DAC HYP in 75-100 subjects from Study 205MS303 at selected sites. Autoinjectors will be dispensed to each participating subject for use on up to 6 consecutive scheduled dosing days.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

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.

6.1.2. Secondary Objectives

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 PFS
- To assess the safety, tolerability, and efficacy of switching to DAC HYP in subjects previously on long-term treatment with interferon β-1a in Study 205MS301

6.1.3. Exploratory Objective

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoints

- Incidence of AEs and SAEs

6.2.2. Secondary Endpoints

- 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
- 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 (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 (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

7. STUDY DESIGN

7.1. Study Overview

The design of Study 205MS303 is provided in Figure 1. Approximately 1600 subjects will enroll in this study. This includes approximately 1200 subjects who completed Study 205MS301. Additionally, approximately 400 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 an 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).

7.2. Overall Study Duration and Follow-Up

The study period will consist of Baseline/Entry Visit assessments, treatment (for up to approximately 5 years), and post-treatment safety follow-up visits (from approximately 4 to 24 weeks after the last dose of DAC HYP).

7.2.1. Baseline/Entry Visit Assessments

Subjects Entering From Study 205MS301

Tests/assessments performed at the subject's last visit in Study 205MS301 and within 28 days of the subject's first dose of DAC HYP (Week 0) in Study 205MS303 may be used as the baseline for Study 205MS303; if final Study 205MS301 tests/assessments are not performed within the 28-day window, they must be repeated upon entry into Study 205MS303 and before the first dose of DAC HYP is administered.

Subjects Entering From Study 205MS203 or Study 205MS302

The Week 144 Visit of Study 205MS303 will be the Entry Visit for subjects enrolled from Study 205MS203 or Study 205MS302. 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. Central LFT testing is *mandatory* at the Entry Visit.

7.2.2. Treatment

Subjects from Study 205MS301 continuing in Study 205MS303 will receive DAC HYP treatment for up to approximately 5 years, or until availability of commercial product (whichever is sooner), under this protocol. Subjects from Study 205MS203 and Study 205MS302 entering Study 205MS303 at Week 144 will have DAC HYP treatment for up to approximately 2 years, or until availability of commercial product (whichever is sooner), under this protocol.

At the Sponsor's discretion, 75-100 subjects from Study 205MS303 at selected sites may dose with DAC HYP using a single-use autoinjector that contains a PFS on 6 consecutive scheduled dosing days (Table 7).

Eligible subjects will have clinic visits scheduled every 4 weeks for up to Week 12 in this study, followed by clinic visits scheduled every 12 weeks.

Subjects who are dosing at home must be instructed to not administer their monthly dose of DAC HYP until the study site has contacted them to authorize dosing (after the *Study Neurologist* or their backup has reviewed LFT results obtained during the previous 28(+4) days). Subjects need to record the date and time of dosing in their diary if they are dosing at home.

A window of ±4 days applies to scheduled visits and home dosing.

7.2.3. Post-Treatment Long-Term Follow-Up

Subjects are to return to the study site for follow-up visits at 8, 12, 16, and 24 weeks (±10 days) after the last dose of DAC HYP.

7.3. Study Stopping Rules

Biogen Idec may terminate this study, after informing Investigators, at any time. Investigators will be notified by Biogen Idec or designee if the study is placed on hold, completed, or closed.

7.4. End of Study

The End of Study is last subject, last visit for final collection of data.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the 205MS303 Baseline/Entry Visit or at the timepoint specified in the individual eligibility criterion listed (Note: Week 0/Day 1 is the Baseline Visit in Study 205MS303 for 205MS301 subjects. Week 144 is the Entry Visit in Study 205MS303 for 205MS203 and 205MS302 subjects):

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
2. Must be a subject currently participating in Study 205MS301 who has completed either the Week 144 Visit or the End of Study Visit (Week 96) of Study 205MS301 OR subject currently participating in Study 205MS203 or Study 205MS302.
3. Women of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 4 months after their last dose of study treatment.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the Study 205MS303 Baseline/Entry Visit or at the timepoint specified in the individual criterion listed (Note: Week 0/Day 1 is the Baseline Visit in Study 205MS303 for 205MS301 subjects. Week 144 is the Entry Visit in Study 205MS303 for 205MS203 and 205MS302 subjects):

Medical History

1. Any subject who permanently discontinued study treatment in Study 205MS301, Study 205MS203, or Study 205MS302 prior to the end of the study treatment period, or had an early termination in those studies OR any subject who has completed all the safety follow-up visits after Week 144 of Study 205MS303 per the original protocol.

   Note: Subjects for whom dosing was temporarily suspended in Study 205MS301, Study 205MS203, or Study 205MS302 are not excluded from participation in this extension study if the criteria for resuming DAC HYP treatment under the parent study protocol have been met at the time of enrollment into Study 205MS303.
2. Any significant change in the subject's medical history that would preclude administration of DAC HYP, including laboratory tests or a current clinically significant condition that, in the opinion of the Investigator, would have excluded the subject's participation in Study 205MS301, Study 205MS203, or Study 205MS302. The Investigator must re-review the subject's medical fitness for participation and consider any factors that would preclude treatment in Study 205MS303, including:

- History of any significant cardiac, endocrine, hematological, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurological (other than MS), and/or other major disease (e.g., malignancy) that would preclude administration of DAC HYP.
- Clinically significant laboratory abnormalities (hematology and blood chemistry) from the most recently available test in the parent study, as determined by the Investigator. Laboratory findings mandating discontinuation of study treatment as defined in parent study protocol are exclusionary.

3. Other medical reasons that, in the opinion of the Investigator and/or Biogen Idec, make the subject unsuitable for enrollment.

Treatment History

4. Treatment with any prohibited concomitant medication during the parent study.

   Note: Subjects who start an approved, open-label IFN β preparation after completion of dosing in Study 205MS301 are not excluded, but IFN β treatment must be discontinued before the first dose of DAC HYP in Study 205MS303 is given.

Miscellaneous

5. Female subjects who are currently pregnant or breastfeeding, or considering becoming pregnant while in the study.
6. History of drug or alcohol abuse (as defined by the Investigator) at any time after the start of Study 205MS303 or any of the parent studies.
7. Unwillingness or inability to comply with the requirements of the protocol, including the presence of any condition (physical, mental, or social) that is likely to affect the subject's ability to comply with the protocol.

9. ENROLLMENT AND REGISTRATION PROCEDURES

9.1. Enrollment and Screening

Subjects must be consented before any procedures are performed. At the time of consent, the subject will be enrolled into the study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the enrollment log. Any test/assessment done at the subject's last visit in the parent studies and within 28 days of the subject's first dose in Study 205MS303 will be used as the baseline for Study 205MS303 and does not need to be repeated at entry into Study 205MS303 (Note: Central LFT testing is mandatory at the Week 144 Entry Visit for subjects rolling over from Study 205MS203 and Study 205MS302 into Study 205MS303). Testing required at the Baseline/Entry Visit that is done outside the 28-day window must be repeated upon entry into 205MS303.

9.2. Registration of Subjects

Subjects should be registered in the study after the Investigator has verified that they are eligible per the criteria in Section 8.1 and Section 8.2 and all baseline assessments have been performed. No subject may begin treatment prior to enrollment and registration.

As confirmation, the Investigator will be provided with written verification of the subject's registration by mail or fax.

Refer to the Study Reference Manual for details on registration.

10. STUDY TREATMENT MANAGEMENT

Study treatment (PFS or autoinjectors) must be stored in a secure location. Accountability for study treatment is the responsibility of the Investigator. Study treatment must only be dispensed by a Pharmacist or medically qualified staff, and stored in a secure, monitored, locked location in accordance with the conditions specified in current prescribing information or the Directions for Handling and Administration (DHA) included in the Study Reference Manual.

Study treatment is to be dispensed only to subjects enrolled in this study. Once treatment is dispensed to a subject, it can only be used by that subject.

10.1. DAC HYP

Prefilled Syringe

DAC HYP is supplied as a liquid in a 1-mL BD-staked PFS with a 29 gauge × ½ inch needle, comprising 150 mg/mL DAC HYP plus excipient materials (sodium succinate, sodium chloride, and polysorbate 80). At a minimum, the study treatment label will include a study reference code, drug identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. Depending on country requirements, the Investigator's name may also appear on the label. DAC HYP must not be used after the expiration date unless a written notification of an expiration date extension is provided by Biogen Idec.

Autoinjector

The DAC HYP PFS is assembled inside a single-use, disposable autoinjector device.

The autoinjector label will include the DAC HYP product code "BIIB019," conditions for storage, Sponsor, and a caution statement. Depending on country requirements, the Investigator's name may also appear on the label. DAC HYP must not be used after the expiration date unless a written notification of an expiration date extension is provided by Biogen Idec.

10.2. DAC HYP Preparation

Each DAC HYP PFS or autoinjector contains only one dose and is intended for SINGLE USE INJECTION ONLY. Any drug that remains in the PFS after injection must not be used for another dose or another subject.

After Week 12, subjects may choose to administer their DAC HYP dose at home, either by administering the injection themselves or by a designated caregiver. The subject or designated caregiver will be trained by clinic staff on the correct PFS injection technique prior to initiating at-home DAC HYP dosing.

Autoinjectors may be provided to selected sites and will be supplied injection-ready. Study personnel or subjects at these sites do not need to insert the PFS into the device. Study site personnel will receive appropriate autoinjector training from a Sponsor-designated trainer prior to initiation of autoinjector use.

10.3. DAC HYP Accountability

The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), any amount returned by subject, and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all PFS and autoinjectors, both used and unused, must be saved for study treatment accountability. At the end of the study, a final reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed or returned to Biogen Idec.

A written explanation will be provided for any discrepancies. After reconciliation, the Investigator must destroy or return to Biogen Idec all unused study treatment PFS and autoinjectors as instructed by Biogen Idec.

If any study treatment supplies are to be destroyed at the site, the Principal Investigator(s) must obtain prior approval by Biogen Idec. The Principal Investigator(s) must notify Biogen Idec, in writing, of the method, date, and location of destruction.

11. TREATMENT OF SUBJECTS

Biogen Idec will provide DAC HYP (PFS or autoinjectors) to all study sites.

Refer to Section 10 (Study Treatment Management) for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

11.1. Study Treatment Schedule and Administration

All subjects will receive one DAC HYP 150 mg SC injection every 4 weeks.

DAC HYP will be administered by clinic staff at the monthly visits for the first 12 weeks of this study. After Week 12, administration of DAC HYP may occur in the clinic or at home (by the subject or by a designated caregiver) depending on subject preference. The subject or designated caregiver will be trained by clinic staff on the correct injection technique prior to initiating at-home DAC HYP dosing. **Subjects who are dosing at home must be instructed to not administer their monthly dose of DAC HYP until the study site has contacted them to authorize dosing. A window of ±4 days applies to home dosing.**

Before a monthly dose of DAC HYP is given, LFT results from a prior test performed within the previous 28(+4) days must be reviewed by the *Study Neurologist* or their backup. Study personnel should promptly inform the subject whether the monthly dose of DAC HYP should be administered or whether study treatment is to be withheld based on the dosing criteria defined in Section 11.7.2. Study personnel will document this communication with the subject. Subjects should administer DAC HYP as soon as permission has been given as per the dosing schedule. Subjects need to record the date and time of dosing in their diary if they are dosing at home.

11.2. Placebo or Reference Product Agents

Not applicable.

11.3. Treatment Precautions

Anaphylactic-like and hypersensitivity reactions following administration of proteins such as DAC HYP can occur. DAC HYP will be administered in the clinic under observation by qualified medical personnel for the first 12 weeks of this study. Subjects will be educated by the *Study Neurologist* or their back-up on the signs and symptoms of hypersensitivity reactions and instructed to contact the site if they experience any acute or delayed reactions post injection.

11.4. Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by study site staff.

After Week 12, subjects who choose to administer their DAC HYP dose at home will record treatment in a dosing diary. The diary will be reviewed periodically by study site staff and the Clinical Monitor throughout the study. Subjects who choose at-home administration will return used PFS or autoinjectors to the clinic at their scheduled clinic visits.

11.5. Concomitant Therapy

A concomitant therapy is any drug or substance administered from the Baseline/Entry Visit until completion of the study. A concomitant procedure is defined as any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed from the time the subject is enrolled in the study until the subject's final clinic visit.

Concomitant treatment with any of the following is not allowed during the study, unless approved by the Biogen Idec Medical Director(s) or the Advisory Committee, or as otherwise described in this protocol:

- Any alternative disease modifying MS drug treatment such as chronic immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to: IFN-β, IFN-α, glatiramer acetate, cyclophosphamide, methotrexate, mycophenolate mofetil, mitoxantrone, cyclosporine, azathioprine, 4-aminopyridine or related products), except for subjects who were on a stable dose of commercially available Fampridine-SR prior to study enrollment. Initiation of Fampridine-SR after enrollment is not permitted, with the exception of acute management of protocol-defined relapse (as described in Section 14.6).
- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications.
- Any monoclonal antibodies other than DAC HYP.
- Intravenous immunoglobulin (IVIg), plasmapheresis or cytapheresis, total lymphoid irradiation, or T-cell or T-cell receptor vaccination.
- Any systemic steroid therapy including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IV methylprednisolone (IVMP), except for protocol-defined treatment of relapses as described in Section 14.6 or for limited, acute treatment of general medical conditions as per the discretion of *Study Neurologist*. Steroids that are administered by non-systemic routes (e.g., topical, inhaled) are allowed.
- Antineoplastic or chemotherapeutic agents, including, but not limited to, cyclophosphamide, methotrexate, azathioprine, cladribine, cytarabine, or flutamide.
- Valproic acid, carbamazepine, lamotrigine, or phenytoin. Subjects who have been taking **1** of these medications at a stable dose for at least 6 consecutive months may continue to receive the medication and may continue study treatment under this protocol. However, if any of these medications must be initiated or dose escalated, study treatment must be permanently discontinued as described in Section 11.8.

  Subjects who have been treated with any of these medications for fewer than 6 consecutive months, or who take more than 1 of these medications, or who have had dose escalations within the past 6 months must do 1 of the following:

  - Discontinue the medication (any agent used for <6 consecutive months must be discontinued). Subjects may use an alternative medication allowed by the protocol, if needed.
  - Subjects taking more than 1 agent must reduce to ≤1 agent (any agent that is continued must have been taken for at least 6 consecutive months).
  - In the case of dose escalation, revert to a previous dose that had been used for at least 6 months.
  - Permanently discontinue study treatment.
- Isoniazid, propylthiouracil, or nimesulide. Subjects who currently take any of these medications must either change to an alternative medication allowed by the protocol or permanently discontinue study treatment.

Subjects who receive any of these restricted medications may be required to permanently discontinue study treatment as outlined in Section 11.8. Subjects who permanently discontinue study treatment will be allowed to receive IVMP as treatment for MS relapse while they are participating in the study, as described in Section 11.8.

Use of the following medications is strongly discouraged during the study:

- Herbal or dietary supplements.
- Agents that have established risks of hepatotoxicity or serious rash according to labeling information (examples include, but are not limited to, amoxicillin/clavulanate, clarithromycin, ketoconazole, minocycline, nitrofurantoin, trimethoprim/sulfamethoxazole, diclofenac, sulfasalazine, amiodarone, methyldopa, nefazodone, and halothane). Alternatives to these therapies should be used whenever possible.

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue is not restricted, but should be optimized as early as possible in an attempt to maintain consistent treatment for the duration of the study.

Subjects should be instructed not to start taking any new medications, including non-prescribed medications, unless they have received permission from the Investigator. The use of live vaccines in humans concurrently treated with daclizumab has not been explored; therefore live vaccines should not be administered to MS subjects who are being treated with DAC HYP.

The use of concomitant therapies or procedures defined in this section must be recorded on the subject's case report form (CRF), according to instructions for CRF completion (Note: concomitant therapies in the parent study that continued at Study 205MS303 entry must be recorded on the CRF). AEs related to administration of these therapies or procedures must be documented on the appropriate CRF. For subjects who prematurely discontinue study treatment, all concomitant medications should be recorded throughout the remainder of the subject's participation in the study.

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If DAC HYP is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

11.7. Treatment Schedule Modifications

Subjects who experience a significant change in their medical status (e.g., neurological worsening/suspected MS relapse, possible injection-site reaction, infection, cutaneous event, fever, abdominal pain, persistent diarrhea, jaundice, nausea, vomiting, pruritus) must contact the *Study Neurologist* as soon as possible and no more than 48 hours after symptom onset. The subject should then be evaluated by the *Study Neurologist* within no more than 72 hours for physical and neurological assessments and further treatment recommendations if appropriate. These subjects should not administer additional DAC HYP until they have been evaluated by the *Study Neurologist* or their backup.

Unscheduled PK/[redacted] Visit (Table 6) can be performed in subjects who have evidence of significant changes in their medical conditions (as assessed by the Investigator). This visit must be approved by the Biogen Idec Medical Director in advance.

Additional treatment considerations for specific events are described below.

11.7.1. Infections

Subjects who have evidence of a clinically significant infection will be instructed to notify the *Study Neurologist* or their backup within 48 hours of onset, and scheduled dosing of DAC HYP may be withheld. If the subject's infection resolves within 2 weeks of the scheduled DAC HYP dose, the subject may receive the previously scheduled dose of DAC HYP at that time. If the infection has not resolved within the 2 weeks, dosing of DAC HYP will remain suspended, and the subject will miss dosing until the infection is resolved.

11.7.2. Elevated Liver Function Tests

Before a monthly dose of DAC HYP is given, LFT results from a prior test (performed within 28[+4] days) must be reviewed by the *Study Neurologist* or their backup, and must be within the protocol-required limits shown below (LFT procedures are described in Section 14.4.3).

Study treatment *must be temporarily suspended* if a subject develops any of the following:

- ALT/SGPT or AST/SGOT >3×ULN
- any other clinically significant hepatic condition in the opinion of the Investigator including jaundice

Note: For subjects who present with jaundice, an LFT *must* be performed as soon as possible.

After a suspension, dosing of DAC HYP may be resumed when ALT/SGPT and AST/SGOT are <2×ULN provided that the criteria for permanent discontinuation have not been met (see Section 11.8).

Study treatment *must be permanently discontinued* if a subject develops any of the following:

- ALT/SGPT or AST/SGOT elevation >8×ULN that is confirmed by a repeat test (preferably within 24 hours)
- ALT/SGPT or AST/SGOT >5×ULN for more than 2 weeks
- ALT/SGPT or AST/SGOT >3×ULN with concomitant elevation of total bilirubin >2×ULN
- Subjects who previously had study treatment suspended for LFT elevations during the past 12 months (including the parent studies) and then resumed dosing, now meet the criteria for LFT elevations that require a new suspension of study treatment

All subjects with elevated LFTs (**ALT/SGPT or AST/SGOT >3×ULN**) should be managed per the guidelines below.

- Study treatment must be temporarily suspended and LFT elevation should be confirmed as soon as possible but no later than a week by a repeat test performed at the central laboratory. In cases where LFTs cannot be performed via the central laboratory, repeat LFT results from local laboratory can be used for confirmation.
- All subsequent testing after a treatment suspension or discontinuation is required to be performed centrally *at least weekly* until the LFT elevation has resolved.
- In subjects with treatment suspension or discontinuation, DAC HYP treatment may resume if a laboratory error is documented upon repeat testing OR when ALT/SGPT and AST/SGOT are <2×ULN provided that the criteria for permanent discontinuation have not been met (see Section 11.8).
- DAC HYP treatment should be *permanently discontinued* in subjects who previously had study treatment suspended for another LFT elevation during the past 12 months (including the parent studies) and then resumed dosing, and now meet the LFT elevation criteria that require a new suspension of study treatment.
- A careful review of all concomitant medications must be documented. The Investigator should consider discontinuation of all potential hepatotoxic medications. All recently started or non-essential concomitant medications should be suspended until the LFT elevation has resolved.
- An Unscheduled Hepatic Assessment Visit as soon as possible but within 7 days should be performed in the event of permanent discontinuation due to elevated LFTs (see Table 6)
- Subjects should be referred to a hepatic specialist if medically indicated.
- The LFT elevation that led to treatment discontinuation should continue to be monitored until LFT elevation has resolved.
- For subjects with initial **ALT/SGPT or AST/SGOT >3×ULN and concomitant elevation of total bilirubin >2×ULN**:
    - *Permanently discontinue* DAC HYP and monitor until the LFT elevation has resolved.

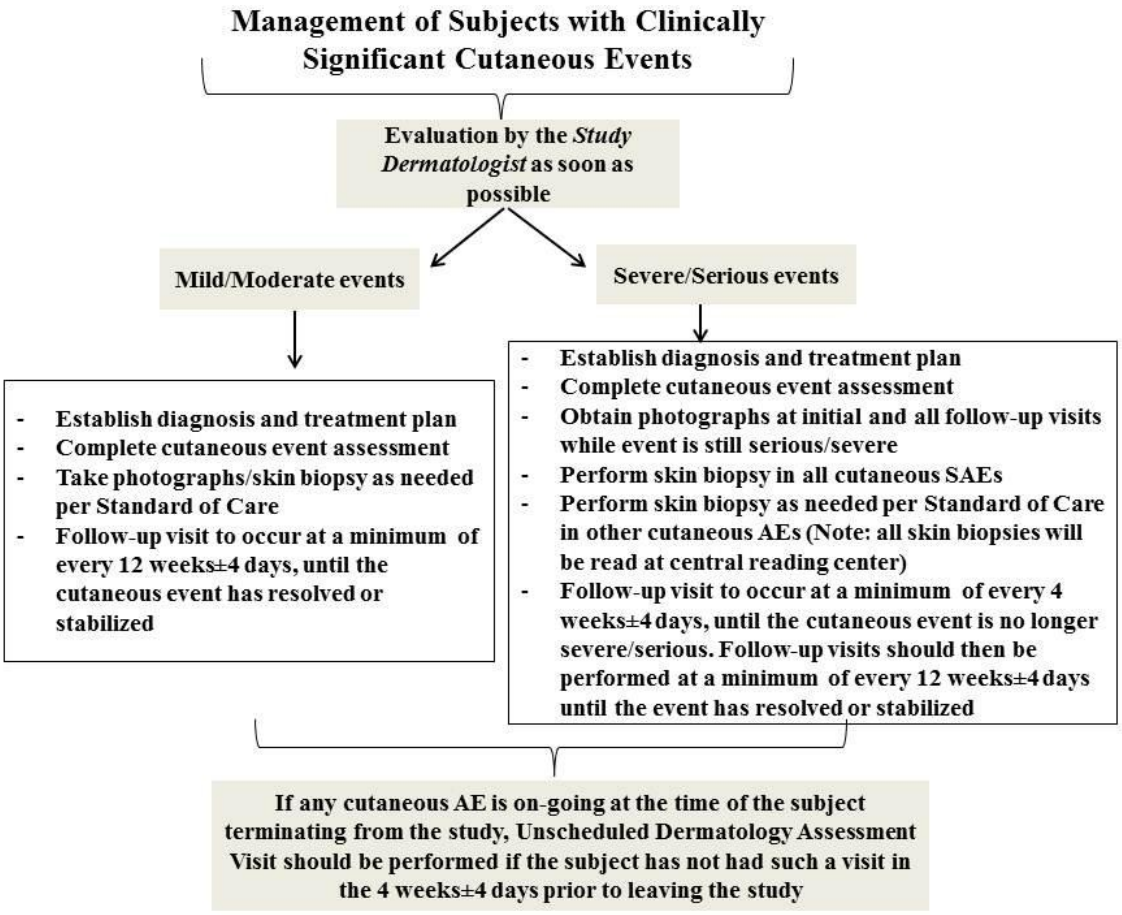
- For subjects with initial **ALT/SGPT or AST/SGOT >5×ULN but ≤8×ULN**:
    - *Suspend dosing* and confirm as soon as possible but no later than a week.
    - For subjects with ALT/SGPT or AST/SGOT >5×ULN for more than 2 weeks:
        - *Permanently discontinue* DAC HYP and monitor until the LFT elevation has resolved.
- For subjects with **ALT/SGPT or AST/SGOT >8×ULN**:
    - *Suspend dosing* and confirm by a repeat test (preferably within 24 hours).
        - **If AST/SGOT >8×ULN in repeat test**: *Permanently discontinue* DAC HYP and monitor until the LFT elevation has resolved.
- For subjects with **ALT/SGPT or AST/SGOT >10×ULN not resolving for more than 2 weeks**:
    - *In consultation with the hepatic specialist*, a full evaluation of alternative causes of liver injury should be performed, and if testing for viral hepatitis is negative, LFT elevations are not improving, DAC HYP is suspected as the cause of the LFT elevation, and there are no known contraindications for corticosteroids, then, in continued consultation with the hepatic specialist, empiric treatment with systemic corticosteroids should be considered.

11.7.3. Cutaneous Events

Any subject participating in Study 205MS303 who develops a clinically significant cutaneous event (e.g., rash, dermatitis, eczema, acne, folliculitis) should be evaluated by the *Study Dermatologist* at an Unscheduled Dermatology Assessment Visit as soon as possible (see Table 6).

A flowchart is presented in Figure 2 to summarize how these subjects will be managed during the study.

Figure 2: Flowchart for Management of Subjects With Clinically Significant Cutaneous Events



In addition to this, when the *Study Neurologist* evaluates a subject with a clinically significant cutaneous AE (either at an unscheduled or scheduled clinical visit), he or she should also perform the Physician Global Assessment Scale as well as standard AE reporting. Photographs should also be taken by the *Study Neurologist* or designee at these visits for severe or serious cutaneous AEs if they have not been taken by the *Study Dermatologist* (see Section 4.2).

Skin biopsy must be performed in subjects with cutaneous SAEs at the Unscheduled Dermatology Assessment Visit, unless medically contraindicated.

Skin biopsies from study subjects will be sent to a centralized laboratory for evaluation. Results of the biopsy will be provided back to the *Study Dermatologist* as soon as possible with a copy sent to the sponsor. Skin biopsy may also be locally evaluated per the discretion of the *Study Dermatologist*.

For subjects with a severe or serious cutaneous event, DAC HYP must be withheld until the cutaneous event has resolved. Under the consultation of the *Study Dermatologist*, the subject should also withhold all other non-essential medications, including protocol-required

medications (as appropriate), and non-prescription drugs and supplements, at least until the cutaneous event has resolved. The decision to permanently discontinue study treatment should be made by the Investigator in consultation with the *Study Dermatologist*. If an allergic or hypersensitivity reaction to study treatment is suspected, study treatment must be permanently discontinued.

11.7.4. Gastrointestinal Events of Inflammatory Colitis

For any subject participating in Study 205MS303 who develops symptoms of inflammatory colitis (e.g., persistent diarrhea and abdominal cramps, blood in the stool, and fever), treatment with DAC HYP should be stopped and the subject should be referred to a specialist. Some subjects with mild colitis who require DAC HYP therapy may be able to continue the study treatment if the benefit-risk profile is considered positive per Investigator's assessment and the subject's informed decision.

11.8. Discontinuation of Study Treatment

A subject *must* permanently discontinue DAC HYP for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.5.4.
- The subject experiences a hypersensitivity or suspected allergic reaction (e.g. anaphylaxis and anaphylactoid reactions) to study treatment.
- The subject develops a chronic viral infection (e.g., hepatitis C, HIV).
- The subject develops elevated LFTs that meet any of the following criteria:
  - The subject develops an ALT/SGPT or AST/SGOT elevation >8×ULN that is confirmed by a repeat test (preferably within 24 hours). This requires *immediate* discontinuation of DAC HYP, and treatment may not resume unless a laboratory error is documented upon repeat testing.
  - ALT/SGPT or AST/SGOT >5×ULN for more than 2 weeks
  - ALT/SGPT or AST/SGOT >3×ULN with concomitant elevation of total bilirubin >2×ULN at any time unless a laboratory error is documented upon repeat testing
  - Subjects who previously had study treatment suspended for LFT elevation during the past 12 months (including the parent studies) and then resumed dosing, and now meet the LFT abnormalities that require a new suspension of study treatment.

    The LFT abnormality that led to treatment discontinuation should continue to be monitored until resolution is documented. An Unscheduled Hepatic Assessment Visit is needed in the event of permanent discontinuation due to elevated LFTs (see Section 11.7.2).

    In addition, a careful review of all concomitant medications must be documented. The Investigator should consider discontinuation of all potential hepatotoxic medications. The subject should be referred to a physician with expertise in the diagnosis and treatment of liver disease, and additional hepatic studies should be

performed according to local standard of care. The central laboratory may be utilized for additional hepatic testing per Investigator request.

- The subject experiences a clinically significant cutaneous event, which the Investigator (in consultation with the *Study Dermatologist*) considers to be a generalized allergic or hypersensitivity reaction to study treatment (see Section 11.7.3).
- The subject experiences inflammatory colitis, except in subjects with mild colitis who require DAC HYP therapy and have a positive benefit-risk profile per Investigator's assessment and the subject's informed decision (see Section 11.7.4).
- The subject requires treatment with any of the disallowed concomitant medications, unless approval is given by the Biogen Idec Medical Director(s) or Advisory Committee. Note: IVMP for treatment of a protocol-defined relapse is allowed as detailed in the protocol (see Section 11.5). Treatment with valproic acid, carbamazepine, lamotrigine, or phenytoin is only allowed under the conditions detailed in the protocol.
- The subject experiences a medical emergency that necessitates permanent discontinuation of treatment.
- The subject desires to discontinue treatment under this protocol.
- At the discretion of the Investigator for medical reasons or for non-compliance.
- Upon confirmatory tests 1 month apart, the subject's hematology results are as follows in the absence of an identified reversible cause by the Investigator (e.g., infection):
  - white blood cell count is <2500 cells/μL, or
  - lymphocyte count is <800 cells/μL, or
  - platelet count is <75,000 cells/μL

  Subjects who meet the above criteria must have study treatment withheld until hematology retest results are available.
- The subject experiences severe depression. Severe depression is defined as any episode that requires hospitalization, or at the discretion of the Investigator.

Subjects who permanently discontinue DAC HYP treatment should complete all post-treatment safety follow-up evaluations (see Section 13.3).

Subjects who permanently discontinue study treatment may be treated with alternative approved MS therapies according to local practices, and should remain in the study and complete safety follow-up evaluations as described in Section 4.2 and Section 13. However, subjects who desire to discontinue participation in this study or are unwilling or unable to comply with the protocol should be withdrawn from the study and complete an Early Termination Visit. As noted in Table 6 (Footnote 3) and Section 11.9, subjects terminating treatment with an ongoing clinically significant cutaneous event require an Unscheduled Dermatology Assessment Visit with the

Study Dermatologist prior to leaving the study if a visit with the *Study Dermatologist* has not been completed in the 4 weeks±4 days prior to leaving the study.

The reason(s) for discontinuation of treatment must be recorded in the subject's CRF.

11.9. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.

Subjects who withdraw from the study should complete the End of Treatment Visit assessments as described in Section 14.9 (subjects should be encouraged to complete all other post-treatment safety follow-up visits). The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

For subjects with an ongoing clinically significant cutaneous AE, the *Study Dermatologist* should perform an Unscheduled Dermatology Assessment Visit, if this visit has not been performed in the 4 weeks±4 days prior to leaving the study (see Section 11.7.3).

12. EFFICACY, DAC HYP CONCENTRATION, AND [redacted] ASSESSMENTS

12.1. Clinical Efficacy Assessments

The following clinical tests/assessments will be performed to assess the efficacy of DAC HYP:

- Relapse Assessment: Subjects who suspect they are experiencing new symptoms or worsening symptoms need to contact the *Study Neurologist* within 48 hours of the onset of the symptoms.
- Refer also to Section 14.6 Unscheduled Relapse Assessment Visit for additional details.
- EDSS [Kurtzke 1983]: Review of EDSS procedures will be performed prior to study start as necessary for training purposes.
- MSFC [Fischer 1999]: Timed 25-Foot Walk, 9HPT with both upper extremities and PASAT 3
- Brain MRI scan with and without Gd (T2 hyperintense lesions, T1 hypointense lesions, Gd+ lesions, brain atrophy).
- Subjects will complete the following questionnaires at various timepoints specified in Section 4.2:
  - EQ-5D quality of life questionnaire (the EQ-5D descriptive system and the EQ-VAS)
  - MSIS-29 (29-item physical and psychological assessment)
  - HRU (hospitalizations, emergency room visits, and unscheduled neurologist visits)
  - Treatment Satisfaction Questionnaire for Medication (with PFS use) or Treatment Satisfaction Survey (with autoinjector use)
  - HRPQ (productivity questionnaire)

Refer to Section 4.2 for the timing of assessments.

12.2. Pharmacokinetic Assessments

Blood samples 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]

Unscheduled PK[redacted] Visits

Whole blood samples will be collected at Unscheduled PK[redacted] Visits for potential determination of DAC HYP serum concentrations in subjects with significant changes in their medical

conditions, as assessed by the Investigator. This visit must be approved by the Biogen Idec Medical Director in advance.

Refer to Section 4.2 for the timing of sample collection.

12.3. [redacted]

[redacted]

[redacted]

[redacted]

[redacted] **PK/**[redacted]

[redacted] PK/[redacted]

[redacted]

12.4. [redacted]

[redacted]

13. SAFETY ASSESSMENTS

13.1. Clinical Safety Assessments

The following clinical assessments will be performed to determine the safety profile of DAC HYP:

- Medical history
- Physical and neurological examination
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate (subjects must remain in the same body position quietly for 5 minutes prior to having their pulse and blood pressure taken)
- Weight
- Concomitant therapy and procedure recording
- AE and SAE recording
- Beck Depression Inventory, Second Edition (BDI-II)
- Immunogenicity assessments
- Alcohol Use Disorders Identification Test - Consumption Questionnaire (AUDIT-C)

See Section 4.2 for the timing of assessments.

13.2. Laboratory Safety Assessments

The following laboratory tests will be performed to assess the safety profile of DAC HYP:

- Hematology: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell count, white blood cell count (with differential), and platelet count
- Blood chemistry: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT/SGPT AST/SGOT, lactate dehydrogenase, gamma glutamyl transferase, blood urea nitrogen (BUN), creatinine, and bicarbonate
- Comprehensive hepatic panel (only required for subjects who permanently discontinue dosing due to elevated liver function tests as defined in Section 11.7.2). Testing will include screening for the following:
  - hepatitis A, B, C, and E
  - other viral infections: Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV-6), varicella zoster virus (VZV), herpes simplex virus (HSV), and Parvovirus B19
  - gamma-globulins, including IgG levels

  - autoantibodies: antinuclear antibody (ANA), anti-smooth muscle antibody (anti-SM), anti-liver/kidney microsome-1 antibody (anti-LKM1), antimitochondrial antibody (AMA), and anti-soluble liver antigen (SLA)

  Additional testing may be performed based on results of the above testing or the subject's clinical history. Additional hepatic assessments should be performed according to local standard of care.

- Thyroid function panel, including TSH and T4
- Urinalysis: protein, blood, glucose, ketones, nitrite, leukocytes, pH, specific gravity by dipstick and microscopy
- Urine pregnancy testing

Refer to Section 4.2 for the timing of assessments.

13.3. Study-Specific Safety Assessments

Blood serum collection for binding and neutralizing anti-drug antibody testing will be performed. Note: When necessary, samples drawn for one purpose (e.g., immunogenicity) may be used to meet another protocol-defined objective (e.g., DAC HYP concentration assessment).

14. SCHEDULE OF EVENTS

14.1. Overview

A written, signed Informed Consent Form (ICF) and all authorizations required by local law (e.g., Protected Health Information [PHI] in North America) must be obtained prior to performing any tests or assessments under this protocol.

For subjects entering from Study 205MS301, tests/assessments performed at the subject's last visit in Study 205MS301 and within 28 days of the subject's first dose of DAC HYP (Week 0) in Study 205MS303 may be used as baseline data for Study 205MS303; if final Study 205MS301 tests/assessments are not performed within the 28-day window, they must be repeated upon entry into Study 205MS303 and before the first dose of DAC HYP is administered.

Week 144 Visit of Study 205MS303 will be the Entry Visit for subjects enrolled from Study 205MS203 or Study 205MS302. 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; test/assessments performed >28 days before the Entry Visit must be repeated at the Entry Visit. Central LFT testing is *mandatory* at Entry Visit.

Clinic visits will occur once every 4 weeks for the first 12 weeks, then every 12 weeks thereafter.

On a dosing day, all tests and assessments must be performed prior to DAC HYP administration. When DAC HYP administration and MRI evaluation are required at the same visit, the MRI scan should be performed prior to DAC HYP administration (Note: MRI scan can be performed up to 4 days prior to the visit).

Before a monthly dose of DAC HYP is given, LFT results (ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only) from prior testing performed within 28(+4) days must be reviewed by the *Study Neurologist* or their backup, and must be within the protocol-required limits.

After Week 12, subjects will have the option of administering DAC HYP at home following Investigator review of monthly pre-dose LFT results. Subjects who are not able to administer their own dose or prefer not to administer their own dose of DAC HYP will be given the option to choose another individual (caregiver) to administer their treatment at home or to have their treatment administered by staff at the study site.

Follow-up visits will take place at 8, 12, 16, and 24 weeks after each subject's last dose of DAC HYP. Unscheduled Relapse Assessment Visits (if necessary) should be scheduled within 72 hours of the onset of any new neurological symptoms that may indicate neurological worsening or possible clinical relapse. Unscheduled Hepatic Assessment Visits (if necessary) should be scheduled as soon as possible (but within 1 week) following discontinuation of study treatment due to elevated LFTs. Unscheduled Dermatology Assessment Visits will be performed as per Section 11.7.3.

Unscheduled PK/[redacted] Visits should be scheduled as soon as possible following significant changes in subjects' medical conditions, as assessed by the Investigator. This visit must be approved by the Biogen Idec Medical Director in advance.

14.2. Site Personnel

For each subject, the Principal Investigator will designate the following study site personnel:

- A primary *Study Neurologist* and backup neurologist
- A primary and backup *Nurse* (or Study Coordinator)
- A primary and backup *Examining Technician*
- An *MRI Technician*
- A *Pharmacist* (or authorized designee)
- A *Study Dermatologist*

The *Study Neurologist* must have a minimum of 2 years of neurology specialty training and anticipate at least a 3-year commitment to the study, or be approved by the study Advisory Committee. The *Study Neurologists* may designate another neurologist at the center who meets the same qualifications to perform the EDSS assessments and other neurologic assessment during the trial. Whenever possible, the EDSS and other neurologic assessments should be performed by the same examiner who performed these assessments in the parent study.

The primary *Study Neurologist* will be responsible for:

- Management of the routine neurological care of the subject
- Assessment (including assignment of causality) and treatment of AEs and MS relapses
- Obtaining an EDSS score based on a detailed neurological examination at the scheduled timepoints required in the protocol, and at every Unscheduled Relapse Assessment Visit
- Review of selected hematology and all blood chemistry results from the central laboratory
- Assessment of LFT results, as detailed in Section 11.7.2
- Monitoring and follow-up of any abnormal hepatic tests
- Performing Physician Global Assessment Scale in subjects with clinically significant cutaneous event, as detailed in Section 11.7.3
- Assessment of injection sites, as detailed in Table 7
- Referral of subjects to a dermatologist if that subject experiences a cutaneous event as described in Section 14.7

Hematology and blood chemistry data will be sent to the investigational sites to aid in management of the subject.

The primary *Nurse* or Study Coordinator will be responsible for:

- Assisting the *Study Neurologist* in subject management, including the treatment of AEs, the treatment and assessment of disease relapses, and the recording of AEs and concomitant medications
- Monitoring the EDSS scores and informing the *Study Neurologist* if a subject experiences at least a 1.0-point increase on the EDSS 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
- Administering the patient-reported questionnaires (BDI-II, MSIS-29, EQ-5D), HRU, and subject assessment of injection pain (VAS)
- Collection of blood samples and obtaining vital signs
- Study treatment administration/dispensation/accountability

To ensure consistency across sites, *Examining Technicians* must undergo a standardized training session prior to enrollment of subjects at their site. All sites should attempt to maintain the same *Examining Technician* throughout the study. If an *Examining Technician* has to be replaced, the new *Examining Technician* must undergo a training session. It is not necessary for the *Examining Technician* to be a healthcare professional as long as he/she is qualified, in the opinion of the Principal Investigator, to administer the MSFC (Note: MSFC was administered in this study only until Week 48; therefore, the role of the *Examining Technician* ended after that).

The *MRI Technician* will be responsible for:

- Performing a brain MRI scan with and without Gd at all protocol-required timepoints. Study-specific MRI scan procedures and protocols, which will be provided prior to study start, must be followed.

The *Pharmacist* (or authorized designee) will be responsible for:

- Storage, distribution, and accountability of study treatment.

The *Study Dermatologist* will be responsible for:

- Documenting cutaneous events, as per the protocol.
- Taking photograph(s) of the affected body areas, as required.
- Performing a skin biopsy, as required.
- Evaluating, treating, and managing clinically significant cutaneous events as described in Section 11.7.3.

14.3. Subject Management

The following restrictions apply to all subjects enrolled into this study:

- Subjects must follow the restrictions for concomitant medications and procedures described in Section 11.5.
- Contraception requirements are to be followed as described in Section 15.5.3.
- Whenever possible, a subject should undergo protocol-required tests and assessments at the same time of day throughout the study.
- Subjects should not donate blood until 4 months after their last dose of DAC HYP.
- Subjects should not receive live or live-attenuated vaccines during DAC HYP treatment or for at least 6 months after treatment with DAC HYP.

14.4. Special Instructions for Tests and Assessments

Note: Information about the tests and assessments to be performed in this study is also provided in Section 12 and Section 13, and in the Study Reference Manual.

14.4.1. Rescreening

Subjects who are not eligible for participation at baseline due to a temporary condition (e.g., acute infection) are allowed to be rescreened once the condition has resolved, provided they are rescreened and enrolled within 6 months of completing Study 205MS301, Study 205MS203, or Study 205MS302.

14.4.2. Pregnancy Testing

- Pregnancy testing is only required for women of childbearing potential. A urine pregnancy test is to be performed at the Baseline/Entry Visit and at other timepoints designated in Section 4.2 Schedule of Events. Study treatment will be immediately discontinued if the subject has a positive pregnancy test at any time during the study.
- Results from all urine pregnancy tests must be reviewed by the study site prior to dosing and must be negative.

14.4.3. Liver Function Test Assessments Prior to DAC HYP Dosing

Before a monthly dose of DAC HYP is given, LFT results from prior testing performed within the previous 28(+4) days must be reviewed by the *Study Neurologist* or their backup, and must be within protocol-required limits as described in Section 11.7.2.

LFTs can be performed as follows:

- Samples for LFTs must be drawn prior to administration of the monthly DAC HYP dose. These samples may be tested either locally inside or outside of the clinic (e.g., at a local laboratory or by visiting nurses) or at the central laboratory at the discretion of the Investigator and the results can then be used to determine whether dosing should continue or be suspended at the monthly dosing timepoint (see Section 11.1).
- 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).

- If the subject is administering DAC HYP injections at home, site personnel must contact the subject after review of prior LFT results performed within 28(+4) days) to authorize the monthly injection, or if LFT results warrant, to instruct the subject to withhold their injection.
- LFTs following a treatment suspension must be performed through the central laboratory until the LFT abnormality has resolved. In cases where LFTs cannot be performed via central laboratory, repeat LFT results from local laboratory can be used for confirmation.

14.4.4. Other Assessments

- Vital signs include systolic and diastolic blood pressure, pulse, and body temperature, and should be measured pre-dose. The subject must rest quietly for 5 minutes prior to blood pressure and pulse measurements. Weight will be collected at Baseline/Entry Visit and at the time of first autoinjector use at selected sites.
- The MSIS-29 must be administered prior to the subject's visit with the *Study Neurologist*.
- Subject assessment of injection pain using a VAS should be completed as soon as possible after the injection is administered, but no later than 10 to 30 minutes post-injection.
- The first 4 DAC HYP injections (i.e., Weeks 0 through 12) must be given in the clinic. The first of these injections must be given by study personnel. At subsequent visits, subjects and/or caregivers will be instructed on DAC HYP self-administration and may administer their scheduled dose under staff supervision. After the subject completes the required in-clinic injections (i.e., after Week 12), DAC HYP may be dispensed to subjects for at-home administration if the subject chooses. If necessary, drug dispensation may occur at monthly intervals.
- Additional visits to assess elevated LFTs, cutaneous events, or PK/[redacted] may be required as described in Section 11.7.

14.5. Definition of MS Relapse and Disability Progression

14.5.1. MS Relapse

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** or their backup. The subject must have objective signs on the examination confirming the event.

*When possible subjects should be evaluated by the same neurologist assigned to them in the parent study.

New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse. New or recurrent neurological symptoms that occur less than 30 days following the onset of a protocol-defined relapse should be considered part of the same relapse. Management of MS relapse is described in Section 14.6.

14.5.2. Disability Progression

Disability progression can only be confirmed from the EDSS scores obtained according to the protocol-defined schedule of assessments at regular visits, and is defined as one of the following:

- at least a 1.0-point increase on the EDSS 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

14.6. Management of MS Relapse

Subjects who experience new or worsening neurological symptoms must contact the *Nurse* or *Study Neurologist* or their backup within 48 hours after the onset of symptoms. A standardized Suspected Relapse Questionnaire will be completed to determine the necessity of an Unscheduled Relapse Assessment Visit.

If required, the subject will then be evaluated in person by the *Study Neurologist* not more than 72 hours after the onset of the symptoms. At the Unscheduled Relapse Assessment Visit, the *Study Neurologist* is to perform a relapse assessment and obtain an EDSS score. New objective findings on neurological examination performed by the *Study Neurologist** are required to determine if a suspected protocol-defined relapse has occurred. Treatment of an acute relapse event with intravenous methylprednisolone (IVMP) [or equivalent] may proceed at the discretion of the *Study Neurologist* after the examination and will not affect the subject's eligibility to continue in the study.

*When possible subjects should be evaluated by the same neurologist assigned to them in the parent study.

Subjects who prematurely discontinue study treatment should complete safety follow-up evaluations (see Section 4.2 and Section 13).

Subjects who permanently discontinue DAC HYP treatment should complete the visit schedule described in Section 11.8.

14.7. Cutaneous Events

Subjects who experience a clinically significant cutaneous event (e.g., rash, dermatitis, eczema, acne, folliculitis) must be referred to and evaluated and managed by the *Study Dermatologist* as per Section 11.7.3. An Unscheduled Dermatology Assessment Visit will be performed per Table 6.

If a generalized allergic or hypersensitivity reaction to study treatment is suspected, study treatment must be permanently discontinued as per Section 11.8.

14.8. Unscheduled Hepatic Assessment Visit

The following tests/assessments will be performed as soon as possible (but within 7 days) after discontinuation of study treatment for subjects who are required to discontinue dosing due to elevated LFTs as described in Table 6 and Section 11.8.

- Physical examination and vital signs
- Comprehensive hepatic panel
- Recording of concomitant therapy
- Monitor and record AE/SAEs
- Protocol compliance and DAC HYP accountability
- Liver function tests (ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only)

14.9. Post-Treatment Safety Follow-Up Visit Schedule for All Subjects

All subjects should complete the following schedule of safety follow-up visits after their last dose of DAC HYP:

- End of Treatment Visit (i.e., the assessments required at Week 240). For subjects who prematurely discontinue study treatment before Week 240, these assessments should be performed 4 weeks (±4 days) after the subject's last dose of DAC HYP.
- Post-treatment safety follow-up visits at 8, 12, 16, and 24 weeks after the subject's last dose. The details of these visits are shown in Table 5.

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 from Week 156 Visit in Study 205MS303 (see Table 4) as long as they meet the inclusion/exclusion criteria (Section 8).

15. SAFETY DEFINITIONS, MONITORING, AND REPORTING

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

At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Serious Pretreatment Event

A serious pretreatment event is any event that meets the criteria for SAE reporting (as defined in Section 15.1.3) and occurs after the subject signs the ICF, but before administration of study treatment.

15.1.2. Adverse Event

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

15.1.3. Serious Adverse Event

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

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

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.

15.2. Monitoring and Recording Events

15.2.1. Serious Pretreatment Events

A serious pretreatment event experienced by the subject after signing and dating the ICF, but before administration of study treatment is to be recorded on the SAE Form and faxed to the contract research organization (CRO), [redacted] within 24 hours of the study site staff becoming aware of the event (see Section 15.2.5).

15.2.2. Adverse Events

Any AE experienced by the subject between the time of signing the ICF and subject's final visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

15.2.3. Serious Adverse Events

Any SAE experienced by the subject between the time of the first dose of study treatment and subject's final visit is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to [redacted].

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

Subjects will be followed for all SAEs until the subject's final visit. Thereafter, the event should only be recorded if the Investigator considers it related to study treatment.

15.2.4. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.3.
- The relationship of the event to study treatment as defined in Section 15.3.1.
- The severity of the event as defined in Section 15.3.2.

15.2.5. Immediate Reporting of Serious Adverse Events

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

Reporting Information for SAEs

Any Serious Event that occurs between the time the subject has signed informed consent and subject's final visit must be reported to [redacted] within 24 hours of the study site staff becoming aware of the event. **Thereafter, the event should only be recorded if the Investigator considers it related to study treatment**.

A report pertaining to an event that occurs between the time the subject has signed informed consent and subject's final visit ***must be submitted*** to [redacted] regardless of the following:

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

To report initial or follow-up information on a Serious Event, fax a completed SAE form to the following:

North America: [redacted]
Latin America: [redacted]
Europe and Asia Pacific: [redacted]

(Country-specific fax numbers are provided in the Study Reference Guide.)

15.2.5.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate CRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen Idec SABR or designee.

15.3. Safety Classifications

15.3.1. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

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

15.3.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.3.3. Expectedness of Events

Expectedness of all AEs will be determined according to the Investigator's Brochure.

15.4. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the

Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.

- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

15.5. Procedures for Handling Special Situations

15.5.1. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed to [redacted] within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded in the CRF; dosing information is recorded on a CRF.

15.5.2. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator or designee should contact the [redacted] Medical Monitor at one of the following phone numbers:

North America (USA and Canada): [redacted]

Latin America: [redacted]

Europe and Asia Pacific: [redacted]

15.5.3. Contraception Requirements

All women of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 4 months after their last dose of study treatment.

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

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy

For the purposes of the study, effective contraception is defined as follows:

For females:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with spermicide; diaphragm, sponge, cervical cap)

- True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

15.5.4. Pregnancy

Subjects should not become pregnant during the study. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report the pregnancy by faxing the appropriate form to [redacted] Pharmacovigilance within 24 hours of the study site staff becoming aware of the pregnancy (refer to Section 15.2.5 for reporting information). The Investigator or study site staff must report the outcome of the pregnancy to [redacted] Pharmacovigilance.

Please note that congenital abnormalities/birth defects in the offspring of male or female subjects should be reported when conception occurred during the study treatment period.

15.5.5. Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Biogen Idec Safety and Benefit-Risk Management (SABR) will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

15.6. Investigator Responsibilities

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow-up on the outcome of the pregnancy.
- Complete an SAE form for each serious event and fax it to [redacted] within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to [redacted] within 24 hours of the study site staff becoming aware of new information.
- Complete an Adverse Event of Special Interest form for each transaminase elevation, hepatic event, and cutaneous event as described in the protocol and fax it to [redacted] as soon as possible following the study site staff becoming aware of the event.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.

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

15.7. Biogen Idec Responsibilities

Biogen Idec's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor or designee is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen Idec is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

16.1. Description of Objectives

See Section 6.1, Objectives.

16.2. Description of Endpoints

See Section 6.2, Endpoints.

16.3. Demography and Baseline Disease Characteristics

Demographic data collected at baseline will be summarized (i.e., age, gender, ethnicity, and weight). Medical history and baseline characteristic data (e.g., EDSS, number of relapses in the previous study, MRI endpoints) will also be summarized.

16.4. Safety and Efficacy

16.4.1. Analysis Population

Study 205MS303 Safety Population

The safety population will include all subjects who received at least 1 dose of DAC HYP in Study 205MS303. All safety analyses will be completed on the safety population.

Study 205MS303 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who received at least 1 dose of DAC HYP in Study 205MS303. This population will be utilized for the efficacy analyses.

Study 205MS301 and Study205MS303 Intent-to-Treat population

This population will include all subjects randomized to DAC HYP or Avonex in Study 205MS301 and received at least one dose of DAC HYP in Study 205MS303.

16.4.2. General Methods of Analysis

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include the number of subjects with data, mean, standard deviation, median, and range. Categorical endpoints will include the number of subjects with data and the percentage in each category.

Analyses will generally be descriptive in nature and will focus on data collected during Study 205MS303 only. However, for relevant efficacy analyses, the data may be summarized by previous treatment group (Avonex or DAC HYP). Also, statistical comparisons may be made between efficacy in Study 205MS301 and efficacy in Study 205MS303 among subjects previously randomized to Avonex in Study 205MS301.

All statistical tests will be 2-sided with an overall Type I error of 5%. Adjustments for multiple comparisons will not be considered.

16.4.3. Primary Endpoints Analysis

Clinical Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. All treatment-emergent events will be included in the evaluation of safety. Treatment emergent includes any event that either occurs or worsens in severity after the onset of study treatment. Overall incidence of treatment-emergent events will be summarized; in addition, summaries by severity and by relationship to study treatment will be provided. The summary tables will include incidence estimates for the overall system organ class as well as for preferred terms within each system organ class. In order to assess whether the incidence of events changes over time, the incidence of key events may also be summarized by time period (e.g., 6-month time intervals).

16.4.4. Other Safety Endpoint Analyses

Unless otherwise specified, the baseline measurement for safety assessments such as laboratory values and vital signs was the measurement acquired on the day of the first receipt of DAC HYP. The first receipt of dosing of DAC HYP could be either Study 205MS303 (for subjects who received Avonex in Study 205MS301) or the parent studies (i.e., Study 205MS301, Study 205MS203, or Study 205MS302) for all other subjects.

Laboratory Data

Changes in laboratory values will be summarized using shift tables. Shift tables will include hematology, LFTs, kidney function tests, electrolytes, and other blood chemistry tests. Shifts will be presented from baseline of DAC HYP treatment (the last measurement acquired before or on the day of the first receipt of DAC HYP, e.g., Study 205MS303 baseline for subjects randomized to Avonex in Study 205MS301 and Study 205MS301 baseline for subjects randomized to DAC HYP 150 mg in Study 205MS301). Summaries of worst post-baseline laboratory values by clinically relevant categories may also be presented for selected parameters of interest by treatment group. For example, for LFT (alkaline phosphatase, ALT, AST, GGT, and total bilirubin), categories may be defined based on cutoff values relative to the ULN.

Vital Signs

Vital signs collected will be examined to determine the incidence of clinically relevant abnormalities. These abnormalities are described in Table 8. For the purpose of the shifts from baseline, the baseline evaluation at the start of DAC HYP treatment will be used.

For each vital sign, the number of subjects evaluated and the number and percentage of subjects with the defined abnormality at any time post dosing will be presented by treatment group.

Table 8: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C or an increase from baseline of ≥1°C
Pulse	>120 beats per minute (bpm) or an increase from baseline of 20 bpm <50 bpm or a decrease from baseline of >20 bpm
Systolic Blood Pressure	>180 mmHg or an increase from baseline of >40 mmHg <90 mmHg or a decrease from baseline of >30 mmHg
Diastolic Blood Pressure	>105 mmHg or an increase from baseline of >30 mmHg <50 mmHg or a decrease from baseline of >20 mmHg

Physical Examination

The physical examination findings will be summarized.

16.4.5. Efficacy Endpoints Analyses

Annualized Relapse Rate

Relapses will be summarized over the follow-up period in Study 205MS303. For subjects in Study 205MS301 and Study 205MS303 ITT population, relapses may be summarized over the combined study period (Studies 205MS301 and 205MS303).

A negative binomial regression model will be used to estimate the adjusted ARR.

Proportion of Subjects with a Relapse

The proportion of subjects relapsed will be estimated using a Kaplan-Meier curve.

Disability Progression

Sustained disability progression is defined as at least a 1.0 point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 24 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS <1.0 that is sustained for 24 weeks. The proportion of subjects with progression will be summarized using a Kaplan-Meier curve. In addition, summary statistics for EDSS and for the change from baseline in EDSS will be presented by visit, and for subjects who participated in Study 205MS301, by previous treatment group.

MSFC

Changes in the MSFC z-score will be summarized by study visit, and for subjects who participated in Study 205MS301, by previous treatment group. For subjects in Study 205MS301 and Study 205MS303 ITT population, MSFC z-score may be summarized over the combined study period (Studies 205MS301 and 205MS303). Details on the calculations of the z-score for each component will be described in the statistical analysis plan.

MRI Endpoints

MRI endpoints will be summarized with descriptive statistics both as a continuous variable and categorically. Over time summaries and summaries by previous treatment group (Avonex or DAC HYP 150 mg) may also be provided. A negative binomial regression model will be used

for the analysis of new or newly enlarging T2 lesions. The change in volume of lesions will be analyzed using an analysis of covariance.

Quality of Life Outcomes

Actual scores and change from baseline in quality of life endpoints will be summarized by visit.

Pharmacokinetics

The population for DAC HYP concentration analyses will include all subjects who received at least 1 dose of study medication and who have at least 1 sample available for analysis.

Serum concentration levels will be summarized with descriptive statistics by visit.

Antigenicity/Immunogenicity Data

Immunogenicity (i.e., ADAs to DAC HYP) will be assessed on subjects. Positive samples will be further tested for neutralizing antibodies to DAC HYP using a specific NAb assay. Results will be tabulated by time period and overall.

16.5. Interim Analyses

No formal interim analyses are planned for this study. However, analyses may be performed prior to the end of the study at the discretion of the Sponsor.

16.6. Sample Size Considerations

There is no formal sample size calculation. The number of subjects in this study is determined by the number of subjects who completed Study 205MS301, Study 205MS203, or Study 205MS302.

17. ETHICAL REQUIREMENTS

Biogen Idec and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

17.1. Declaration of Helsinki

The Investigator and Biogen Idec must adhere to the principles set forth by the Declaration of Helsinki dated October 2008.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor may submit documents on behalf of the study sites in countries other than the US as applicable.

If the Investigator makes any changes to the ICF, Biogen Idec must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen Idec. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen Idec.

It is the responsibility of the Principal Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

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

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

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

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including Baseline/Entry Visit tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all subjects participating in a clinical study conducted by Biogen Idec.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including Baseline/Entry Visit tests and assessments.

Each consent form should contain an authorization allowing the Principal Investigator(s) and Biogen Idec to use and disclose PHI (i.e., subject-identifiable health information) in compliance with local law.

The signed consent form will be retained with the study records.

17.4. Subject Data Protection

Prior to any testing under this protocol, including Baseline/Entry Visit tests and assessments, candidates must also provide all authorizations required by local law (e.g., PHI authorization in North America).

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen Idec, its partner(s) and designee(s), ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen Idec maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws.

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

Biogen Idec will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not enroll any subjects prior to completion of a study initiation visit, conducted by Biogen Idec or designee. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Principal Investigator(s) must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the course of the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the study site and its facilities.

18.4. Study Funding

Biogen Idec is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen Idec.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

Biogen Idec will be responsible for all administrative aspects of this study including, but not limited to, study initiation, monitoring, management of AEs, and data management.

19.1. External Contract Organizations

19.1.1. Contract Research Organization

[redacted] will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports. Before subjects are screened at each study site, [redacted] will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Electronic or Remote Data Capture

Subject information will be captured and managed by study sites on electronic CRFs via a remote data capture (RDC) developed and supported by [redacted] and configured by Biogen Idec.

19.1.3. Central Laboratories for Laboratory Assessments

[redacted] has been selected by Biogen Idec to analyze all hematology, blood chemistry, and urine samples collected for this study.

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).

19.1.4. Central Facility for Biopsy Assessments

[redacted] has been has been selected by Biogen Idec to analyze skin biopsy samples collected for this study.

19.1.5. Central Facility for Other Assessments

MRI Reading Center

All scheduled MRI scans with and without Gd will be evaluated at a central MRI reading center. All study sites will be required to send a test scan to the MRI Reading Center for evaluation in order to ensure that the site's scanning techniques are appropriate. This review will take place before the study site is permitted to enroll any subjects into the study.

Original MRI images are to be sent to the MRI Reading Center for review (MRI shipping instructions will be provided prior to the start of enrollment at each site).

Additional and more detailed MRI scans with and without Gd procedures and instructions are included in the study MRI manual (to be provided under separate cover prior to start of the study).

19.2. Study Committees

19.2.1. Advisory Committee

The Advisory Committee from parent Study 205MS301 will oversee the administrative progress and provide scientific and medical direction for this study while Study 205MS301 is ongoing. Advisory Committee will monitor subject accrual and compliance with the protocol at individual study sites. The Advisory Committee will determine whether the study should be stopped or amended for reasons other than safety.

Members of the Advisory Committee will include the Medical Director, Clinical Trial Manager, and Project Statistician from Biogen Idec (and/or their designees), and participating Investigators. Biogen Idec will designate one of the participating Investigators to be the Chairperson of the Advisory Committee.

19.2.2. Internal Safety Monitoring Committee

An internal Safety Monitoring Committee will be formed to review interim safety data on an ongoing basis. Investigational sites will be notified of any relevant safety findings that may jeopardize subject safety.

19.3. Changes to Final Study Protocol

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

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

In the event of a protocol modification, the subject consent form may require similar modifications (see Section 17.2 and Section 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen Idec in writing and

receive written authorization from Biogen Idec to destroy study records. In addition, the Investigator must notify Biogen Idec of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen Idec will designate one of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors, including, but not limited to, the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by Biogen Idec.

Biogen Idec will follow all applicable local regulations pertaining to study report signatories.

20. REFERENCES

Bielekova B, Howard T, Packer AN, et al. Effect of anti-CD25 antibody daclizumab in the inhibition of inflammation and stabilization of disease progression in multiple sclerosis. Arch Neurol. 2009;66(4):483-9.

Bielekova B, Richert N, Howard T, et al. Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta. Proc Natl Acad Sci U S A. 2004;101(23):8705-8.

Fischer JS, LaRocca NG, Miller DM, et al. Recent developments in the assessment of quality of life in multiple sclerosis (MS). Mult Scler. 1999;5(4):251-9.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52. Epub 1983/11/01.

Rose JW. Treatment of Multiple Sclerosis with a Humanized Monoclonal Antibody Specific for IL-2 Receptor Chain. Neurology. 2003;60(Suppl 1):A478-9.

Rose JW, Watt HE, White AT, et al. Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. Ann Neurol. 2004;56(6):864-7.

Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol. 2010;9(4):381-90.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "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 Who Have Completed Study 205MS301" and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142, USA

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

PROTOCOL NUMBER: 205MS303

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: 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 Who Have Completed Study 205MS301

EUDRA CT NO: 2012-003176-39

DATE: 28 September 2012
Version 1
Final

SIGNATURE PAGE

Protocol 205MS303 was approved by:

[redacted]

[redacted] MD, PhD

02 Oct 12
Date

[redacted]
Biogen Idec MA Inc.

SIGNATURE PAGE

Protocol 205MS303 was approved by:

[redacted]

1st October 2012

[redacted], MB, MRCPI, M Med Sci
[redacted]
Biogen Idec MA Inc.

Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142
USA

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

Biogen Idec Australia Pty Ltd
Suite 1, Level 5
123 Epping Road
North Ryde, NSW 2113
Australia

Primary contact for urgent medical issues:

Biogen Idec Program Director: [redacted], MD
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

Biogen Idec Study Director: [redacted], MD
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

Please refer to the Official Study Contact List for complete contact information.

2. LIST OF ABBREVIATIONS

9HPT	Nine-Hole Peg Test
ADAbs	anti-DAC HYP binding antibodies
AE	adverse event
ALT	alanine aminotransferase
ARR	annualized relapse rate
AST	aspartate aminotransferase
AUDIT-C	Alcohol Use Disorders Identification Test - Consumption Questionnaire
BDI-II	Beck Depression Inventory, Second Edition
bpm	beats per minute
BUN	blood urea nitrogen
CRF	case report form
CRO	contract research organization
DAC HYP	Daclizumab High Yield Process
DHA	Directions for Handling and Administration
EDSS	Expanded Disability Status Scale
EQ-5D	European Quality of Life, 5-dimensions
EQ-VAS	European Quality of Life, visual analog scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gd	gadolinium
GGT	gamma-glutamyltransferase
HIV	human immunodeficiency virus
HRPQ	Health Related Productivity Questionnaire
HRU	healthcare resource utilization
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IL-2	interleukin-2
IFN	interferon
IM	intramuscular
ITT	intent-to-treat
IV	intravenous
IVIg	intravenous immunoglobulin
IVMP	intravenous methylprednisolone
LFT	liver function test
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale-29
NAbs	anti-DAC HYP neutralizing antibodies

NK	natural killer cells
PASAT 3	3 Second Paced Auditory Serial Addition Test
PD	pharmacodynamic(s)
PFS	prefilled syringe
PHI	protected health information
PK	pharmacokinetic(s)
[redacted]	[redacted]
RDC	remote data capture
RRMS	relapsing-remitting multiple sclerosis
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
SC	Subcutaneous
SGPT	serum glutamic pyruvic transaminase; see ALT
SGOT	serum glutamic oxaloacetic transaminase; see AST
SMC	Safety Monitoring Committee
SNP	single nucleotide polymorphism
SUSAR	suspected unexpected serious adverse reaction
T1	MRI hypointense designation
T2	MRI hyperintense designation
T4	thyroxine
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
VAS	visual analog scale

3. SYNOPSIS

This is a brief summary. For details refer to the body of the protocol.

Protocol Number:	205MS303
Protocol Title:	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 Who Have Completed Study 205MS301
Version Number:	1
Name of Study Treatment:	Daclizumab High Yield Process (DAC HYP)
Study Indication:	Relapsing-Remitting Multiple Sclerosis (RRMS)
Phase of Development:	3
Rationale for the Study:	This study will provide subjects who complete Phase 3 Study 205MS301 with the opportunity to receive open-label DAC HYP monotherapy prior to local product marketing approval for evaluation of long-term safety, efficacy, and immunogenicity of DAC HYP in subjects with RRMS.
Study Objectives and Endpoints:	**Objectives** Primary: 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. Secondary: Secondary objectives of this study in this study population are as follows: • To assess the long-term immunogenicity of DAC HYP administered by prefilled syringe (PFS) • 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 safety, tolerability, and efficacy of switching to DAC HYP in subjects previously on

long-term treatment with interferon β-1a in Study 205MS301

- To evaluate pharmacodynamic (PD) parameters that may be associated with treatment response

Endpoints

Primary:

- Incidence of adverse events (AEs) and serious adverse events (SAEs)

Secondary:

- Shifts in clinical laboratory assessments (hematology and blood chemistry)
- Incidence of depression as assessed by the Beck Depression Inventory, Second Edition (BDI-II)
- Incidence of anti-DAC HYP binding antibodies (ADAbs) over time
- Incidence of anti-DAC HYP neutralizing antibodies (NAbs) over time
- 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 12 weeks, or at least a 1.5-point increase on the EDSS from a baseline EDSS <1.0 that is sustained for 12 weeks
- Magnetic resonance imaging (MRI) outcomes: total number and volume of new or newly enlarging T2 hyperintense lesions, gadolinium (Gd)-enhancing lesions, T1 hypointense lesions, and brain atrophy on brain MRI (Note: The decision to collect and analyze brain atrophy data will be made after the analysis of Study 205MS301 is complete. Brain atrophy analysis may be omitted.)
- Change in Multiple Sclerosis Functional Composite (MSFC) score

- Change in EDSS score
- Proportion of subjects who are free from disease activity.
- Proportion of subjects with sustained improvement in disability as defined by the number of subjects with baseline EDSS of at least 2.0 who experience ≥1.0 decrease in EDSS that is sustained for 24 weeks.
- 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 (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)

Study Design:	Multicenter, open-label, long-term extension study
Rationale for Dose and Schedule Selection:	The DAC HYP dose and schedule were used in the Phase 3 205MS301 (DECIDE) study, and will be the treatment regimen used in the commercial setting.
Study Location:	Global (approximately 261 study sites participating in 205MS301)
Number of Planned Subjects:	Up to 1841 subjects may be treated in the study
Study Population:	This study will be conducted in subjects with RRMS who have completed Study 205MS301.
Treatment Groups:	This is a single-arm study. All subjects will receive open-label treatment with DAC HYP 150 mg by an SC injection using the PFS every 4 weeks for up to approximately 3 years, or until availability of commercial product (whichever is sooner), and in accordance with

	applicable laws and regulations. Depending on availability and local regulations, some subjects may dose with DAC HYP using a single-use autoinjector that contains a PFS.
Duration of Treatment and Follow-up:	Subjects will participate in this study for up to approximately 3 years, or until availability of commercial product (whichever is sooner), and in accordance with applicable laws and regulations. All subjects should complete safety follow-up evaluations at 4, 8, 12, 16, and 24 weeks after the subject's last dose of DAC HYP.
Criteria for Evaluation:	
Efficacy:	Clinical relapse assessments, EDSS, MSFC (Timed 25-Foot Walk, Nine-Hole Peg Test [9HPT] with both upper extremities, PASAT 3), and brain MRI scan with and without Gd (T2 hyperintense lesions, T1 hypointense lesions, Gd+ lesions, brain atrophy).
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 [redacted]
Pharmacodynamics:	[redacted]
Safety:	Physical and neurological exams, vital signs, clinical laboratory assessments (hematology, blood chemistry, thyroid function panel [including TSH and T4], urinalysis), urine pregnancy testing, BDI-II, immunogenicity assessments, Alcohol Use Disorders Identification Test - Consumption Questionnaire (AUDIT-C), and AE and concomitant medication monitoring throughout study participation. Additional comprehensive hepatic testing will be required for subjects who permanently discontinue study

	treatment due to elevated liver function tests (LFTs).
Subject Reported Assessments:	Subject assessment of 29-item Multiple Sclerosis Impact Scale (MSIS-29), EQ-5D quality of life questionnaire (the EQ-5D descriptive system and the respondent's self-rated health on a vertical visual analog scale [EQ-VAS]), Treatment Satisfaction Questionnaire for Medication (before the first use of a PFS and at multiple timepoints during the study), Treatment Satisfaction Survey at selected sites (before the first and last use of an autoinjector), HRU, and HRPQ.
Statistical Methods:	Efficacy endpoints will be summarized by previous treatment group (Avonex® or DAC HYP 150 mg during Study 205MS301), all subjects (DAC HYP 150 mg during the 3-year extension study), and the combined 5- to 6-year follow-up period (Study 205MS301 and the 3-year extension study) using descriptive statistics. The adjusted ARR and number of new or newly enlarging T2 lesions will be estimated using a negative binomial regression model. The proportion of subjects with sustained progression and the proportion with a relapse will be estimated from the Kaplan-Meier curve. The incidence of AEs and shifts in clinical laboratory assessments will also be summarized by treatment group during similar time periods. An analysis by 3- or 6-month intervals may also be performed. Summary statistics for other safety, efficacy, pharmacokinetic (PK), and PD endpoints will be presented.
Sample Size Determination:	There is no formal sample size calculation for this study. The number of subjects in this study is determined by the number of subjects who participate in Study 205MS301.
Study Stopping Rules:	Until the analysis of Study 205MS301 is complete, an independent Safety Monitoring Committee (SMC) will make recommendations for the continuation of Study 205MS303 based on a review of safety data from this study and from other ongoing studies of DAC HYP in subjects with MS conducted by the Sponsor. Thereafter, the independent SMC will no longer monitor Study 205MS303 and the decision to continue the study will be made by the Sponsor.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS TABLES FOR STUDY 205MS303

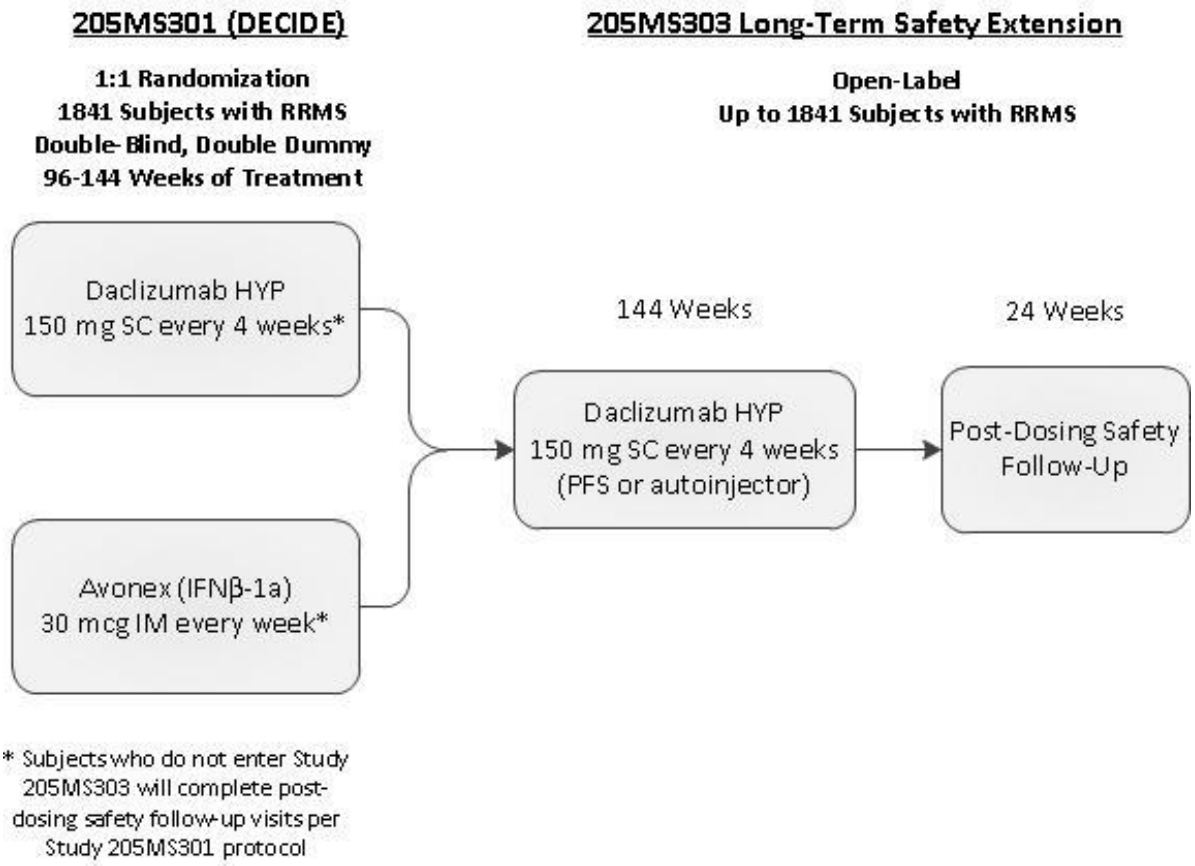
A schematic of the study design is provided in Section 4.1.

The tabulated schedule of events for this study is provided in Section 4.2.

4.1. Study Schematic

Figure 1 shows the design of Study 205MS301 and its open-label extension, Study 205MS303.

Figure 1: Study Design



4.2. Schedule of Events

Table 1: Schedule of Activities: Baseline Through Week 84

Note: If study treatment is temporarily suspended for abnormal liver function tests (LFTs), LFTs must be re-evaluated as specified in Section 11.7.2. A window of ±4 days applies to scheduled visits; however, for monitoring of LFTs prior to dosing, collection of samples for all laboratory assessments may be performed within 7 days prior to dosing.

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[4]	X[5]			X[5]	X[5]		X[5]		X[5]	
Liver Function Tests[4, 6]		Pre-dose liver function testing to performed monthly throughout study participation								
Thyroid Function Panel	X									
DAC HYP Concentration Assessment	X			X	X		X			
[redacted]	X			X	X		X			
[redacted]	X						X			
[redacted]	X			X	X		X			
[redacted]										
Anti-Drug Antibody Sample	X			X	X		X			
Urinalysis	X									
Urine Pregnancy Test	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
EQ-5D[9]	X			X	X		X			
MSIS-29[10]	X			X	X		X			
HRU	X				X		X			
BDI-II	X			X	X		X			
AUDIT-C	X						X			
Treatment Satisfaction Questionnaire for Medication	X[11]			X	X		X		X	
HRPQ	X			X	X		X		X	
MRI	X						X			
MSFC	X			X	X		X			
EDSS[12]	X			X	X		X		X	
DAC HYP[4] Administration/Dispensation	X	X[13]	X[13]	X[13]	X	X	X	X	X	X
Dosing Diary	Subject to record observations starting at Week 16									
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. Pregnancy test results must be negative.

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

[3] Baseline Visit must take place within 6 months of completing Study 205MS301. With the exception of LFTs, 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 will 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. LFTs must be performed within 7 days prior to administration of DAC HYP.

[4] LFT results must be reviewed by the *Treating Neurologist* or their backup prior to administration of the scheduled monthly DAC HYP dose. LFTs may be done as described in the protocol.

[5] If pre-dose LFTs have been performed locally, they must be repeated through the central laboratory at this visit.

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

[redacted]

[9] EQ-5D including both the questionnaire and the VAS components.
[10] MSIS-29 to be administered prior to seeing the *Treating Neurologist*.
[11] To be performed after the DAC HYP injection at this visit.
[12] If a subject experiences at least a 1.0-point increase on the EDSS from a baseline EDSS ≥1.0 or a 1.5-point increase on the EDSS from a baseline EDSS <1.0 , then the EDSS must be repeated within 12 weeks to determine whether protocol-defined disability progression has occurred.
[13] 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 (End of Treatment)

Note: If study treatment is temporarily suspended for abnormal LFTs, LFTs must be re-evaluated as per Section 11.7.2. A window of ±4 days applies to scheduled visits; however, for monitoring of LFTs prior to dosing, collection of samples for all laboratory assessments may be performed within 7 days prior to dosing.

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 ±4 days End of Treatment/ Early Termination Visit[2] 4 weeks after last dose
Physical Exam	X		X		X
Vital Signs (Pre-dose)	X		X		X
Hematology	X		X		X
Blood Chemistry[3]	X[4]		X[4]		X
Liver Function Tests[3, 5]	Pre-dose liver function testing to performed monthly throughout study participation				
DAC HYP Concentration Assessment	X				X
[redacted]					X
Anti-Drug Antibody Sample	X				X
[redacted]					X
Urine Pregnancy Test	X		X		X
EQ-5D[7]	X		X		X
MSIS-29[8]	X		X		X
HRU	X				X
BDI-II	X		X		X
AUDIT-C	X				
Treatment Satisfaction Questionnaire for Medication	X		X		X
HRPQ	X		X		X
EDSS[9]	X		X		X
DAC HYP Administration/Dispensation[3]	X	X	X	X	
Dosing Diary	Subject continues recording observations				

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 ±4 days End of Treatment/ Early Termination Visit[2] 4 weeks after last dose
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. Pregnancy test results must be negative.
[2] For subjects who prematurely discontinue dosing, the End of Treatment (Early Termination) Visit should be performed 30 days ±4 days following the subject's last dose of study treatment.
[3] LFT results must be reviewed by the *Treating Neurologist* or their backup prior to administration of the scheduled monthly DAC HYP dose. LFTs may be done as described in the protocol.
[4] If pre-dose LFTs have been performed locally, they must be repeated through the central laboratory at this visit.
[5] ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, and GGT only.
[redacted]
[7] EQ-5D including both the questionnaire and the VAS components.
[8] MSIS-29 to be administered prior to seeing the *Treating Neurologist*.
[9] If a subject experiences at least a 1.0-point increase on the EDSS from a baseline EDSS ≥1.0 or a 1.5-point increase on the EDSS from a baseline EDSS <1.0, then the EDSS must be repeated within 12 weeks to determine whether protocol-defined disability progression has occurred.

Table 3: Schedule of Activities: Post-Treatment Safety Follow-Up and Unscheduled Assessments

Tests and Assessments	Post-Treatment Safety Follow-Up[1]				Unscheduled Assessments	
	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 (Final Study Visit) 24 weeks after last dose ±10 days	Relapse (within 72 hours of symptoms)	Hepatic[2]
Physical Exam		X		X	X	
Vital Signs		X		X	X	X
Hematology		X		X		
Blood Chemistry		X		X		
Liver Function Tests[3]	X		X			X
Hepatic Panel						X
Anti-Drug Antibody Sample				X		
Urinalysis					X	
Urine Pregnancy Test				X		
DAC HYP Concentration Assessment				X		
EDSS				X	X[4, 5]	
Dosing Diary	Subject continues recording observations					
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.

[2] To be performed as soon as possible (but within 1 week) following permanent discontinuation of study treatment due to elevated LFTs unless a definite cause of the LFT abnormality leading to treatment discontinuation has already been established through other testing.

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

[4] If a subject experiences at least a 1.0-point increase on the EDSS from a baseline EDSS ≥1.0 or a 1.5-point increase on the EDSS from a baseline EDSS <1.0 , then the EDSS must be repeated within 12 weeks to determine whether protocol-defined disability progression has occurred.

[5] Performed by the *Examining Neurologist* or their back-up within 72 hours of a suspected relapse.

Table 4: Schedule of Activities: Autoinjector Use by Subjects at Selected Sites

Note: At the Sponsor's discretion, approximately 75-100 eligible subjects at selected sites may begin using autoinjectors on any regularly scheduled dosing day, after they have received at least 6 consecutive monthly doses of DAC HYP by PFS in Study 205MS303. Six consecutive DAC HYP injections will be administered by the subject. Doses 1 and 4 will be supervised during clinic visits, all other doses can be given at home or the clinic. Following the use of autoinjectors, subjects should resume administration of DAC HYP using the PFS.

Note: Subjects are to continue the visit schedule and evaluations listed in Table 1 while they are using autoinjectors.

	Autoinjector 1[1]		**Autoinjector 2**	**Autoinjector 3**	**Autoinjector 4**[1]	**Autoinjector 5**	**Autoinjector 6**
			Minutes/Hours/Weeks After First Autoinjection				
Tests and Assessments	**Pre-Dose**	**Post-Dose**	**4 weeks ±4 days**	**8 weeks ±4 days**	**12 weeks ±4 days**	**16 weeks ±4 days**	**20 weeks ±4 days**
Informed Consent	X[2]						
Weight	X						
Waist Circumference[3]	X						
Abdominal Fold Thickness[3]	X						
DAC HYP Administration		X	X	X	X	X	X
Injection Site Assessment		X			X		
Subject Assessment of Injection Pain (VAS)		X[4]			X		
Observer Report		X			X		
Treatment Satisfaction Survey[5]	X						X[6]
DAC HYP Concentration Assessment	X				X[7]		
Anti-Drug Antibody Sample	X				X		

[1] To be administered during a scheduled clinic visit.
[2] Subjects must provide written informed consent for autoinjector use prior to first DAC HYP dose by autoinjector.
[3] The procedure for taking this measurement is provided in the Study Reference Manual.
[4] VAS to be completed as soon as possible but within 10 minutes after the injection.
[5] If the subject withdraws from the study or reverts to PFS use prior to receiving all 6 autoinjector doses, the subject should complete the Treatment Satisfaction Survey provided for the Autoinjector 6 dosing day.
[6] To be administered immediately prior to dosing.
[7] Blood sample should be collected pre-dose.

5. INTRODUCTION

5.1. Profile of Previous Experience with Daclizumab in MS

Background

DAC HYP is a humanized monoclonal IgG1 antibody specific for CD25 (α subunit of the IL-2 receptor). CD25 is expressed at low levels on resting T cells but is rapidly upregulated after T-cell activation, enabling high-affinity IL-2 signal transduction. The primary hypothesis for using DAC HYP to treat MS is to selectively inhibit activated T cells.

Anti-CD25 antibodies have multiple in vitro effects that suggest DAC HYP may directly decrease T-cell activation and proliferation. These include inhibition of IL-2 dependent lymphocyte proliferation, disruption of both IL-2 dependent and independent pathways of IFN-gamma production, and interference in CD28-dependent CD40 ligand expression. In vivo, daclizumab has been confirmed to cause expansion of $CD56^{bright}$ NK cells. This expansion has also been shown to correlate with MRI-defined therapeutic response of daclizumab in MS. $CD56^{bright}$ NK cells are believed to have an immunoregulatory function, and they have been shown to kill activated T cells through a contact-dependent mechanism. Therefore, selective inhibition of activated T cells with DAC HYP may occur through both direct and indirect mechanisms [Bielekova 2004; Bielekova 2009].

Clinical Experience with Daclizumab in Multiple Sclerosis

Initial clinical studies of daclizumab in MS were conducted with material manufactured by F. Hoffmann-La Roche, Ltd. (Roche) at their facilities in Nutley, New Jersey (DAC Nutley) [Bielekova 2004; Rose 2003; Rose 2004], and in Penzberg, Germany (DAC Penzberg) [Wynn 2010]. Study 205MS301 is conducted with DAC HYP, which is produced using a different manufacturing process than the previous versions of daclizumab. DAC HYP has characteristics that are similar to DAC Nutley and DAC Penzberg, although certain differences in physicochemical and biological characteristics have been observed (refer to the Investigator's Brochure for details).

Study 205MS201 (SELECT) was a double-blind, placebo-controlled study to evaluate the safety and efficacy of DAC HYP in subjects with RRMS that randomized 621 subjects in a 1:1:1 ratio to receive placebo, 150 mg DAC HYP, or 300 mg DAC HYP SC every 4 weeks over a 52-week treatment period. Among subjects randomized to DAC HYP (150 mg, 300 mg) versus placebo, there was a significantly lower annualized relapse rate (ARR; 0.21, 0.23 versus 0.46; $p < 0.001$), a higher proportion of relapse-free subjects (81%, 80% versus 64%; $p < 0.001$), and a trend towards improvement in the MSIS-29 physical score ($p = 0.128$ for DAC HYP 300 mg versus placebo; $p < 0.001$ for DAC HYP 150 mg versus placebo). There were significant reductions in the mean number of new or newly enlarging T2 lesions at 1 year (2.4, 1.7 versus 8.1) and in the mean number of new Gd+ lesions between Weeks 8 and 24 in a monthly MRI substudy ($n = 307$) (1.5, 1.0 versus 4.8) in the DAC HYP 150 mg and 300 mg groups versus placebo ($p < 0.001$ for all comparisons). The risk of 3-month sustained disability progression at 1 year, a

tertiary study endpoint, was reduced by 57% (p = 0.021) in the DAC HYP 150 mg group and by 43% (p = 0.091) in the DAC HYP 300 mg group.

Analysis of safety data from the SELECT study showed that, overall, DAC HYP was well tolerated in this patient population. The most frequently reported (≥10%) AEs for subjects treated with DAC HYP, excluding MS relapse, were nasopharyngitis (14%), and headache and upper respiratory tract infection (10% each). In the SELECT study, serious adverse events (SAEs) including MS relapses occurred in 26% of placebo-treated subjects and in 16% of subjects treated with DAC HYP. Excluding MS relapses, SAEs occurred in 6% of the placebo group, in 7% of the DAC HYP 150 mg group, and in 9% of the DAC HYP 300 mg group. One DAC HYP-treated subject died due to ischemic colitis following a complicated course of events. Adverse events observed more frequently in DAC HYP-treated patients included an increase in serious infections (2%), serious cutaneous events (1%), and elevations in liver function tests (ALT/AST) >5× ULN (4%).

Upon completion of the 12-month treatment period in Study 205MS201 (SELECT), subjects were eligible to complete up to an additional 12 months of treatment with DAC HYP in a double-blind extension study (Study 205MS202 [SELECTION]), which will be completed in 2012. SELECTION also assesses the effects of DAC HYP washout in some subjects who were actively treated in Study 205MS201. Subjects completing SELECTION can continue long-term therapy with open-label DAC HYP in ongoing extension Study 205MS203 (SELECTED), which will evaluate long-term safety and efficacy of DAC HYP monotherapy for an additional 144 weeks.

Study 205MS301 (DECIDE), an ongoing double-blind randomized, parallel-group study testing the superiority of DAC HYP monotherapy compared to Avonex® in preventing MS relapse, was initiated in May 2010; 1841 subjects with RRMS have been enrolled and randomized in a 1:1 ratio to receive 150 mg DAC HYP given SC every 4 weeks, or Avonex 30 mcg given IM once weekly over a 96- to 144-week treatment period. The primary endpoint is the ARR.

The pharmacokinetics (PK) and immunogenicity of DAC HYP 150 mg SC administered every 4 weeks using a prefilled syringe (PFS) is being investigated in 26 subjects in Study 205MS302 (OBSERVE), an ongoing, single-arm, open-label study that has enrolled a total of 113 subjects with RRMS.

Refer to the Investigator's Brochure for additional details.

5.2. Study Rationale

This study will provide subjects who complete Phase 3 Study 205MS301 with the opportunity to receive open-label DAC HYP monotherapy prior to local product marketing approval for evaluation of long-term safety, efficacy, and immunogenicity of DAC HYP in subjects with RRMS. In addition, this study will assess the safety, tolerability, and efficacy of switching to DAC HYP in subjects previously on long-term treatment with interferon β-1a in Study 205MS301.

5.3. Rationale for Dose and Schedule Selection

The existing scientific and clinical experience with DAC HYP supports its further investigation in the management of MS. The DAC HYP dose and schedule in this protocol were used in parent Study 205MS301 (DECIDE), and will be the treatment regimen used in the commercial setting.

A single-use, disposable PFS will be provided to simplify the injection process and thereby reduce the burden of administering a long-term therapy such as DAC HYP in the clinic or at home. At the Sponsor's discretion, single-use autoinjectors containing PFS may be used to administer DAC HYP in 75-100 subjects at selected sites. Autoinjectors will be dispensed to each subject for use on 6 consecutive scheduled dosing days.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

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.

6.1.2. Secondary Objectives

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

- To assess the long-term immunogenicity of DAC HYP administered by PFS
- 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 safety, tolerability, and efficacy of switching to DAC HYP in subjects previously on long-term treatment with interferon β-1a in Study 205MS301
- To evaluate PD parameters that may be associated with treatment response

6.2. Endpoints

6.2.1. Primary Endpoints

- Incidence of AEs including serious AEs (SAEs), discontinuation of DAC HYP due to AEs, and withdrawals due to AEs

6.2.2. Secondary Endpoints

- Shifts in clinical laboratory assessments (hematology and blood chemistry)
- Incidence of depression as assessed by the Beck Depression Inventory, Second Edition (BDI-II)
- Incidence of anti-DAC binding antibodies (ADAbs) over time
- Incidence of anti-DAC HYP neutralizing antibodies (NAbs) over time
- 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 12 weeks, or at least a 1.5-point increase on the EDSS from a baseline EDSS <1.0 that is sustained for 12 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 atrophy on brain MRI (Note: The decision to collect and analyze brain atrophy data will be made after the analysis of Study 205MS301 is complete. Brain atrophy analysis may be omitted.)

- Change in Multiple Sclerosis Functional Composite (MSFC) score
- Change in EDSS score
- Proportion of subjects who are free from disease activity.
- Proportion of subjects with sustained improvement in disability as defined by the number of subjects with baseline EDSS of at least 2.0 who experience ≥1.0 decrease in EDSS that is sustained for 24 weeks.
- 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 (EQ-5D and EQ-VAS)
- Change in direct 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 HRPQ

7. STUDY DESIGN

7.1. Study Overview

Subjects who participate in Study 205MS303 will roll over from parent Study 205MS301 (DECIDE), a multicenter, double-blind, randomized, active-control, parallel-group study designed to evaluate the efficacy and safety of DAC HYP versus IFN β-1a in patients with RRMS. In Study 205MS301 subjects are randomized in a 1:1 ratio into the following groups:

Group 1: Approximately 900 subjects, DAC HYP 150 mg SC once every 4 weeks plus IFN β-1a placebo (A-PLC) IM once weekly for 96 to 144 weeks

Group 2: Approximately 900 subjects, IFN β-1a 30 mcg IM once weekly plus DAC HYP placebo (D-PLC) SC once every 4 weeks for 96 to 144 weeks

This multicenter extension study will provide subjects who complete Study 205MS301 with the opportunity to receive open-label DAC HYP monotherapy for the evaluation of the long-term safety, efficacy, and immunogenicity of DAC HYP in subjects with RRMS. Up to 1841 subjects may participate in this study for up to approximately 3 years or until availability of commercial product (whichever is sooner), and in accordance with applicable laws and regulations. All subjects will receive DAC HYP 150 mg by an SC injection every 4 weeks.

7.2. Overall Study Duration and Follow-Up

The study period will consist of baseline assessments, treatment (for up to approximately 3 years), and post-treatment safety follow-up visits (from approximately 4 to 24 weeks after the last dose of DAC HYP).

7.2.1. Baseline Assessments

With the exception of LFTs, which must be repeated within 7 days prior to each administration of DAC HYP, tests/assessments performed at the subject's last visit in Study 205MS301 and within 28 days of the subject's first dose of DAC HYP (Week 0) in Study 205MS303 will be used as the baseline for Study 205MS303; if final Study 205MS301 tests/assessments are not performed within the 28-day window, they must be repeated upon entry into Study 205MS303 and before the first dose of DAC HYP is administered.

7.2.2. Treatment

All subjects will receive open-label treatment with DAC HYP 150 mg SC using a PFS every 4 weeks for up to approximately 3 years, or until availability of commercial product (whichever is sooner), and in accordance with applicable laws and regulations. At the Sponsor's discretion, 75-100 subjects at selected sites may dose with DAC HYP using a single-use autoinjector that contains a PFS on 6 consecutive scheduled dosing days (Table 4).

Eligible subjects will have clinic visits scheduled every 4 weeks for the first 12 weeks in this study, followed by clinic visits scheduled every 12 weeks for up to approximately 3 years of continuous treatment.

Subjects who are dosing at home must be instructed to not administer their monthly dose of DAC HYP until the study site has contacted them to authorize dosing (after the *Treating Neurologist* or their backup has reviewed LFT results obtained during the previous 7 days).

7.2.3. Post-Treatment Long-Term Follow-Up

Subjects are to return to the study site for follow-up visits at 4, 8, 12, 16, and 24 weeks (±10 days) after the last dose of DAC HYP.

7.3. Study Stopping Rules

Biogen Idec may terminate this study, after informing Investigators, at any time. Investigators will be notified by Biogen Idec or designee if the study is placed on hold, completed, or closed.

Until the analysis of Study 205MS301 is complete, an independent Safety Monitoring Committee (SMC) will make recommendations for continuation of the study based on a review of safety data from this study and from other ongoing trials of DAC HYP in subjects with MS conducted by the Sponsor. Thereafter, the independent SMC will no longer monitor Study 205MS303 and the decision to continue the study will be made the by the Sponsor.

7.4. End of Study

The End of Study is last subject, last visit for final collection of data for the primary outcome.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the 205MS303 Baseline Visit or at the timepoint specified in the individual eligibility criterion listed:

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
2. Must be a subject currently participating in Study 205MS301 who has completed either the Week 144 Visit or the End of Study Visit (Week 96).

   Note: Subjects who are not able to enroll into 205MS303 at the time of their Week 144/End of Study Visit may be eligible to enroll into 205MS303 at a later time if they are still participating in the 6-month follow-up period of 205MS301 at the time of expected rollover into 205MS303.
3. Women of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 4 months after their last dose of study treatment.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the Study 205MS303 Baseline Visit or at the timepoint specified in the individual criterion listed (Note: Day 1 is the day of the first dose in Study 205MS303):

Medical History

1. Any subject who permanently discontinued study treatment in Study 205MS301 prior to the end of the study treatment period, or had an Early Termination visit in Study 205MS301.

   Note: Subjects for whom dosing was temporarily suspended in Study 205MS301 are not excluded from participation in this extension study if the criteria for resuming DAC HYP treatment under the Study 205MS301 protocol have been met at the time of enrollment into Study 205MS303.
2. Any significant change in the subject's medical history that would preclude administration of DAC HYP, including laboratory tests or a current clinically significant condition that, in the opinion of the Investigator, would have excluded the subject's participation in Study 205MS301. The Investigator must re-review the subject's medical fitness for participation and consider any factors that would preclude treatment in Study 205MS303, including:

   - History of any significant cardiac, endocrine, hematological, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal,

neurological (other than MS), and/or other major disease (e.g., malignancy) that would preclude administration of DAC HYP.

- Clinically significant laboratory abnormalities (hematology and blood chemistry) from the most recently available test in Study 205MS301, as determined by the Investigator. Laboratory findings mandating discontinuation of study treatment as defined in Protocol 205MS301 are exclusionary.

3. Any of the following abnormal blood tests within the 7 days prior to Day 1:

   - alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), or gamma-glutamyl-transferase (GGT) >3× the upper limit of normal (ULN)

     Note: Subjects ending 205MS301 on a treatment suspension may not enroll into 205MS303 until ALT/SGPT and AST/SGOT are ≤2× ULN.

   - total bilirubin >2× ULN (subjects with an established diagnosis of Gilbert's syndrome are excluded if total bilirubin is >2.5× ULN)

     Note: Subjects ending 205MS301 on a treatment suspension may not enroll into 205MS303 until total bilirubin ≤1× ULN (subjects with an established diagnosis of Gilbert's syndrome may not enroll into 205MS303 until total bilirubin is ≤1.5× ULN).

4. Other medical reasons that, in the opinion of the Investigator and/or Biogen Idec, make the subject unsuitable for enrollment.

Treatment History

5. Treatment with any prohibited concomitant medication during Study 205MS301.

   Note: Subjects who start an approved, open-label IFN β preparation after completion of dosing in Study 205MS301 are not excluded, but IFN β treatment must be discontinued before the first dose of DAC HYP in Study 205MS303 is given.

Miscellaneous

6. Female subjects who are currently pregnant or breastfeeding, or considering becoming pregnant while in the study.
7. Previous participation in Study 205MS303.
8. History of drug or alcohol abuse (as defined by the Investigator) at any time after the start of Study 205MS301.
9. Unwillingness or inability to comply with the requirements of the protocol, including the presence of any condition (physical, mental, or social) that is likely to affect the subject's ability to comply with the protocol.

9. ENROLLMENT AND REGISTRATION PROCEDURES

9.1. Enrollment and Screening

Subjects must be consented before any procedures are performed. At the time of consent, the subject will be enrolled into the study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the enrollment log. With the exception of LFTs, 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 will be used as the baseline for Study 205MS303 and does not need to be repeated at entry into Study 205MS303. Testing required at Week 0 that is done outside the 28-day window must be repeated upon entry into 205MS303. LFTs must be performed within 7 days prior to administration of DAC HYP.

9.2. Registration of Subjects

Subjects should be registered in the study after the Investigator has verified that they are eligible per the criteria in Sections 8.1 and 8.2 and all baseline assessments have been performed. No subject may begin treatment prior to enrollment and registration. Each subject will be registered in Study 205MS303 under the same identification number assigned to him or her in parent Study 205MS301.

As confirmation, Biogen Idec will provide the Investigator with written verification of the subject's registration by mail or fax.

Refer to the Study Reference Manual for details on registration.

10. STUDY TREATMENT MANAGEMENT

Study treatment (PFS or autoinjectors) must be stored in a secure location. Accountability for study treatment is the responsibility of the Investigator. Study treatment must only be dispensed by a Pharmacist or medically qualified staff, and stored in a secure, monitored, locked location in accordance with the conditions specified in current prescribing information or the Directions for Handling and Administration (DHA) included in the Study Reference Manual.

Study treatment is to be dispensed only to subjects enrolled in this study. Once treatment is dispensed to a subject, it can only be used by that subject.

10.1. DAC HYP

Prefilled Syringe (PFS)

DAC HYP is supplied as a liquid in a 1-mL BD-staked PFS with a 29 gauge × ½ inch needle, comprising 150 mg/mL DAC HYP plus excipient materials (sodium succinate, sodium chloride, and polysorbate 80). At a minimum, the study treatment label will include a study reference code, drug identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. Depending on country requirements, the Investigator's name may also appear on the label. DAC HYP must not be used after the expiration date unless a written notification of an expiration date extension is provided by Biogen Idec.

Autoinjector

The DAC HYP PFS is assembled inside a single-use, disposable autoinjector device.

The autoinjector label will include the DAC HYP product code "BIIB019," conditions for storage, Sponsor, and a caution statement. Depending on country requirements, the Investigator's name may also appear on the label. DAC HYP must not be used after the expiration date unless a written notification of an expiration date extension is provided by Biogen Idec.

10.2. DAC HYP Preparation

Each DAC HYP PFS or autoinjector contains only one dose and is intended for SINGLE USE INJECTION ONLY. Any drug that remains in the PFS after injection must not be used for another dose or another subject.

After Week 12, subjects may choose to administer their DAC HYP dose at home, either by administering the injection themselves or by a designated caregiver. The subject or designated caregiver will be trained by clinic staff on the correct PFS injection technique prior to initiating at-home DAC HYP dosing.

Autoinjectors may be provided to selected sites and will be supplied injection-ready. Study personnel or subjects at these sites do not need to insert the PFS into the device. Study site personnel will receive appropriate autoinjector training from a Sponsor-designated trainer prior to initiation of autoinjector use.

10.3. DAC HYP Accountability

The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), any amount returned by subject, and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all PFS and autoinjectors, both used and unused, must be saved for study treatment accountability. At the end of the study, a final reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed or returned to Biogen Idec.

A written explanation will be provided for any discrepancies. After reconciliation, the Investigator must destroy or return to Biogen Idec all unused study treatment PFS and autoinjectors as instructed by Biogen Idec.

If any study treatment supplies are to be destroyed at the site, the Principal Investigator(s) must obtain prior approval by Biogen Idec. The Principal Investigator(s) must notify Biogen Idec, in writing, of the method, date, and location of destruction.

11. TREATMENT OF SUBJECTS

Biogen Idec will provide DAC HYP (PFS or autoinjectors) to all study sites.

Refer to Section 10 (Study Treatment Management) for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

11.1. Study Treatment Schedule and Administration

Starting at Week 0, all subjects will receive one DAC HYP 150 mg SC injection every 4 weeks for up to approximately 3 years or until availability of commercial product (whichever is sooner), and in accordance with applicable laws and regulations.

DAC HYP will be administered by clinic staff at the monthly visits for the first 12 weeks of this study. After Week 12, administration of DAC HYP may occur in the clinic or at home (by the subject or by a designated caregiver) depending on subject preference. The subject or designated caregiver will be trained by clinic staff on the correct injection technique prior to initiating at-home DAC HYP dosing. **Subjects who are dosing at home must be instructed to not administer their monthly dose of DAC HYP until the study site has contacted them to authorize dosing.**

Following review of LFT results by the *Treating Neurologist* or their backup, study personnel should promptly inform the subject whether the monthly dose of DAC HYP should be administered or whether study treatment is to be withheld based on the dosing criteria defined in Section 11.7.2. Study personnel will document this communication with the subject. Subjects should administer DAC HYP as soon as permission has been given and within 7 days of the LFT.

11.2. Placebo or Reference Product Agents

Not applicable.

11.3. Treatment Precautions

Anaphylactic-like and hypersensitivity reactions following administration of proteins such as DAC HYP can occur. DAC HYP will be administered in the clinic under observation by qualified medical personnel for the first 12 weeks of this study. Subjects will be educated by the *Treating Neurologist* or their back-up on the signs and symptoms of hypersensitivity reactions and instructed to contact the site if they experience any acute or delayed reactions post injection.

11.4. Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by study site staff.

After Week 12, subjects will record treatment in a dosing diary that will be reviewed periodically by study site staff and the Clinical Monitor. Subjects who choose at-home administration will return used PFS or autoinjectors to the clinic at their scheduled clinic visits.

11.5. Concomitant Therapy

A concomitant therapy is any drug or substance administered from the Baseline Visit until completion of the study. A concomitant procedure is defined as any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed from the time the subject is enrolled in the study until the subject's final clinic visit.

Concomitant treatment with any of the following is not allowed during the study, unless approved by the Biogen Idec Medical Director(s) or the Advisory Committee, or as otherwise described in this protocol:

- Any alternative disease modifying MS drug treatment such as chronic immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to: IFN-β, IFN-α, glatiramer acetate, cyclophosphamide, methotrexate, mycophenolate mofetil, mitoxantrone, cyclosporine, azathioprine, 4-aminopyridine or related products), except for subjects who were on a stable dose of commercially available Fampridine-SR prior to study enrollment. Initiation of Fampridine-SR after enrollment is not permitted, with the exception of acute management of protocol-defined relapse (as described in Section 14.6).
- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications.
- Any monoclonal antibodies other than DAC HYP.
- Intravenous immunoglobulin (IVIg), plasmapheresis or cytapheresis, total lymphoid irradiation, or T-cell or T-cell receptor vaccination.
- Any systemic steroid therapy including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IV methylprednisolone (IVMP), except for protocol-defined treatment of relapses as described in Section 14.6 or for limited, acute treatment of general medical conditions. Steroids that are administered by non-systemic routes (e.g., topical, inhaled) are allowed.

  Note: The guidelines for management of cutaneous events allow a limited course of systemic corticosteroids if medically indicated. See Section 22 for full details.
- Antineoplastic or chemotherapeutic agents, including, but not limited to, cyclophosphamide, methotrexate, azathioprine, cladribine, cytarabine, or flutamide.
- Valproic acid, carbamazepine, lamotrigine, or phenytoin. Subjects who have been taking **1** of these medications at a stable dose for at least 6 consecutive months may continue to receive the medication and may continue study treatment under this protocol. However, if any of these medications must be initiated or dose escalated, study treatment must be permanently discontinued as described in Section 11.8.

  Subjects who have been treated with any of these medications for fewer than 6 consecutive months, or who take more than 1 of these medications, or who have had dose escalations within the past 6 months must do 1 of the following:

  - Discontinue the medication (any agent used for <6 consecutive months must be discontinued). Subjects may use an alternative medication allowed by the protocol, if needed.
  - Subjects taking more than 1 agent must reduce to ≤1 agent (any agent that is continued must have been taken for at least 6 consecutive months).
  - In the case of dose escalation, revert to a previous dose that had been used for at least 6 months.
  - Permanently discontinue study treatment.
- Isoniazid, propylthiouracil, or nimesulide. Subjects who currently take any of these medications must either change to an alternative medication allowed by the protocol or permanently discontinue study treatment.

Subjects who receive any of these restricted medications may be required to permanently discontinue study treatment as outlined in Section 11.8. Subjects who permanently discontinue study treatment will be allowed to receive IVMP as treatment for MS relapse while they are participating in the study, as described in Section 11.8.

Use of the following medications is strongly discouraged during the study, although they are permitted if alternative medications are not available:

- Herbal or dietary supplements.
- Agents that have established risks of hepatotoxicity or serious rash according to labeling information (examples include, but are not limited to, amoxicillin/clavulanate, clarithromycin, ketoconazole, minocycline, nitrofurantoin, trimethoprim/sulfamethoxazole, diclofenac, sulfasalazine, amiodarone, methyldopa, nefazodone, and halothane). Alternatives to these therapies should be used whenever possible.

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue is not restricted, but should be optimized as early as possible in an attempt to maintain consistent treatment for the duration of the study.

Subjects should be instructed not to start taking any new medications, including non-prescribed medications, unless they have received permission from the Investigator. The use of live vaccines in humans concurrently treated with daclizumab has not been explored; therefore live vaccines should not be administered to MS subjects who are being treated with DAC HYP.

The use of concomitant therapies or procedures defined in this section must be recorded on the subject's case report form (CRF), according to instructions for CRF completion (Note: concomitant therapies in Study 205MS301 that continued at Study 205MS303 entry must be recorded on the CRF). AEs related to administration of these therapies or procedures must be documented on the appropriate CRF. For subjects who prematurely discontinue study treatment, all concomitant medications should be recorded throughout the remainder of the subject's participation in the study.

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If DAC HYP is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

11.7. Treatment Schedule Modifications

Subjects who experience a significant change in their medical status (e.g., neurological worsening/suspected MS relapse, possible injection-site reaction, infection, cutaneous event fever, abdominal pain, jaundice, nausea, vomiting, pruritus) must contact the *Treating Neurologist* as soon as possible and no more than 48 hours after symptom onset. The subject should then be evaluated by the *Treating Neurologist* within no more than 72 hours for physical and neurological assessments and further treatment recommendations if appropriate. These subjects should not administer additional DAC HYP until they have been evaluated by the *Treating Neurologist* or their backup.

Additional treatment considerations for specific events are described below.

11.7.1. Infections

Subjects who have evidence of a clinically significant infection will be instructed to notify the *Treating Neurologist* or their backup within 48 hours of onset, and scheduled dosing of DAC HYP may be withheld. If the subject's infection resolves within 2 weeks of the scheduled DAC HYP dose, the subject may receive the previously scheduled dose of DAC HYP at that time. If the infection has not resolved within the 2 weeks, dosing of DAC HYP will remain suspended, and the subject will miss a dose.

11.7.2. Elevated Liver Function Tests

Before a monthly dose of DAC HYP is given, LFT results (ALT, AST, and total bilirubin) from a test performed within the previous 7 days must be reviewed by the *Treating Neurologist* or their backup, and must be within the protocol-required limits shown below (LFT procedures are described in Section 14.4.3).

Study treatment must be temporarily suspended if a subject develops any of the following:

- ALT/SGPT or AST/SGOT >3× ULN
- total bilirubin >2× ULN*
- any other clinically significant hepatic test abnormality in the opinion of the Investigator

Confirmatory laboratory testing should be performed as soon as medically indicated to guide subject management, but must also be performed in 1 week to determine whether the subject has met the permanent discontinuation criteria listed in Section 11.8. (Note: All confirmatory LFTs following a treatment suspension must be performed through the central laboratory until the LFT abnormality has resolved.)

Study treatment must be suspended until **all** of the following parameters are met:

- ALT/SGPT **and** AST/SGOT ≤2× ULN

- total bilirubin ≤ULN*

* For subjects with an established diagnosis of Gilbert's syndrome, the total bilirubin suspension criterion is >2.5× ULN; the resolution criterion is ≤1.5× ULN or return to baseline.

Subjects who require suspension of study treatment for ≥8 consecutive weeks will have study treatment permanently discontinued; subjects who require a second suspension of study treatment will also have study treatment permanently discontinued (see Section 11.8).

An Unscheduled Hepatic Assessment Visit is to be performed as soon as possible (but within 1 week) after permanent discontinuation of study treatment for subjects who are required to discontinue dosing due to elevated LFTs as described in Section 11.8.

Resuming study treatment after temporary LFT suspension:

Before resuming study treatment, LFTs must be re-evaluated within 7 days prior to the planned dose. ALT **and** AST must be ≤2× ULN **and** total bilirubin must be ≤ULN for study treatment to continue. If ALT, AST, or total bilirubin exceeds these values at this retest, study treatment must be permanently discontinued (see Section 11.8).

11.8. Discontinuation of Study Treatment

A subject *must* permanently discontinue DAC HYP for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.5.4.
- The subject experiences a hypersensitivity or suspected allergic reaction to study treatment.
- The subject develops a chronic viral infection (e.g., hepatitis C, HIV).
- The subject develops elevated LFTs that meet any of the following criteria:
  - The subject develops an ALT/SGPT or AST/SGOT elevation >5× ULN that is confirmed by an immediate repeat test (preferably within 24 hours). This requires *immediate* discontinuation of DAC HYP, and treatment may not resume unless a laboratory error is documented upon repeat testing.
  - Upon confirmatory tests 1 week apart, the subject has developed elevations of:
    - ALT/SGPT or AST/SGOT >3× ULN or
    - total bilirubin >2× ULN*

      * total bilirubin >2.5× ULN for subjects with an established diagnosis of Gilbert's syndrome
  - LFT abnormalities that have resulted in suspension of study treatment for ≥8 consecutive weeks.
  - For subjects who previously had study treatment suspended for LFT abnormalities (including any suspension that occurred during Study 205MS301) and then

resumed dosing, LFT abnormalities that require a new suspension of study treatment.

- After reinitiation of DAC HYP dosing following a suspension, and within 7 days prior to the next scheduled monthly visit, the subject develops ALT/SGPT or AST/SGOT >2× ULN, or total bilirubin > ULN**

  ** total bilirubin >1.5× ULN or baseline (whichever is higher) for subjects with an established diagnosis of Gilbert's syndrome

- The subject requires treatment with any of the disallowed concomitant medications, unless approval is given by the Advisory Committee. Note: IVMP for treatment of a protocol-defined relapse is allowed as detailed in the protocol. Treatment with valproic acid, carbamazepine, lamotrigine, or phenytoin is only allowed under the conditions detailed in the protocol.
- The subject experiences a medical emergency that necessitates permanent discontinuation of treatment.
- The subject desires to discontinue treatment under this protocol.
- At the discretion of the Investigator for medical reasons or for non-compliance.

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

The LFT abnormality that led to treatment discontinuation should continue to be monitored until resolution is documented.

In addition, a careful review of all concomitant medications must be documented. The Investigator should consider discontinuation of all potential hepatotoxic medications. The subject should be referred to a physician with expertise in the diagnosis and treatment of liver disease, and additional hepatic studies should be performed according to local standard of care. The central laboratory may be utilized for additional hepatic testing per Investigator request.

- Upon confirmatory tests 1 month apart, the subject's hematology results are as follows in the absence of an identified reversible cause by the Investigator (e.g., infection):
  - white blood cell count is <2500 cells/μL, or
  - lymphocyte count is <800 cells/μL, or
  - platelet count is <75,000 cells/μL

  Subjects who meet the above criteria must have study treatment withheld until hematology retest results are available.

Subjects who permanently discontinue DAC HYP treatment should complete all post-treatment safety follow-up evaluations (see Section 13.3).

Subjects who permanently discontinue study treatment may be treated with alternative approved MS therapies according to local practices, and should remain in the study and complete safety follow-up evaluations as described in Sections 4.2 and 13. However, subjects who desire to

discontinue participation in this study or are unwilling or unable to comply with the protocol should be withdrawn from the study and complete an Early Termination Visit.

The reason(s) for discontinuation of treatment must be recorded in the subject's CRF.

11.9. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.

Subjects who withdraw from the study should complete the End of Treatment Visit assessments as described in Section 14.9 (subjects should be encouraged to complete all other post-treatment safety follow-up visits). The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

12. EFFICACY, DAC HYP CONCENTRATION, AND PHARMACODYNAMIC ASSESSMENTS

12.1. Clinical Efficacy Assessments

The following clinical tests/assessments will be performed to assess the efficacy of DAC HYP:

- Relapse Assessment: Subjects who suspect they are experiencing new symptoms or worsening symptoms need to contact the *Treating Neurologist* within 48 hours of the onset of the symptoms.
- Refer also to Section 14.6 Unscheduled Relapse Assessment Visit for additional details.
- EDSS [Kurtzke 1983]: Review of EDSS procedures will be performed prior to study start as necessary for training purposes.
- MSFC [Fischer 1999]: Timed 25-Foot Walk, 9HPT with both upper extremities and PASAT 3
- Brain MRI scan with and without Gd (T2 hyperintense lesions, T1 hypointense lesions, Gd+ lesions, brain atrophy).
- Subjects will complete the following questionnaires at various timepoints specified in Section 4.2:
  - EQ-5D quality of life questionnaire (the EQ-5D descriptive system and the EQ-VAS)
  - MSIS-29 (29-item physical and psychological assessment)
  - HRU (hospitalizations, emergency room visits, and unscheduled neurologist visits)
  - Treatment Satisfaction Questionnaire for Medication (with PFS use) or Treatment Satisfaction Survey (with autoinjector use)
  - HRPQ (productivity questionnaire)

Refer to Section 4.2 for the timing of assessments.

12.2. Pharmacokinetic Assessments

Blood samples will be collected at selected timepoints throughout the study to determine DAC HYP serum concentrations.

Refer to Section 4.2 for the timing of sample collection.

12.3. Pharmacodynamic Assessments

[redacted]

[redacted]

12.4. [redacted]

[redacted]

13. SAFETY ASSESSMENTS

13.1. Clinical Safety Assessments

The following clinical assessments will be performed to determine the safety profile of DAC HYP:

- Medical history
- Physical and neurological examination
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate (subjects must remain in the same body position quietly for 5 minutes prior to having their pulse and blood pressure taken)
- Weight
- Concomitant therapy and procedure recording
- AE and SAE recording
- Beck Depression Inventory, Second Edition (BDI-II)
- Immunogenicity assessments
- Alcohol Use Disorders Identification Test - Consumption Questionnaire (AUDIT-C)

See Section 4.2 for the timing of assessments.

13.2. Laboratory Safety Assessments

The following laboratory tests will be performed to assess the safety profile of DAC HYP:

- Hematology: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell count, white blood cell count (with differential), and platelet count
- Blood chemistry: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT/SGPT AST/SGOT, lactate dehydrogenase, gamma glutamyl transferase, blood urea nitrogen (BUN), creatinine, and bicarbonate
- Comprehensive hepatic panel (only required for subjects who permanently discontinue dosing due to elevated liver function tests as defined in Section 11.7.2). Testing will include screening for the following:
  - hepatitis A, B, C, and E
  - other viral infections: Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV-6), varicella zoster virus (VZV), herpes simplex virus (HSV), and Parvovirus B19
  - gamma-globulins, including IgE and IgG levels

  - autoantibodies: antinuclear antibody (ANA), anti-smooth muscle antibody (anti-SM), anti-liver/kidney microsome-1 antibody (anti-LKM1), antimitochondrial antibody (AMA), and anti-soluble liver antigen (SLA)
  - metabolic disease: ceruloplasmin
  - toxicology screen: drugs of abuse

  Additional testing may be performed based on results of the above testing or the subject's clinical history. Additional hepatic assessments should be performed according to local standard of care.

- Thyroid function panel, including TSH and T4
- Urinalysis: protein, blood, glucose, ketones, nitrite, leukocytes, pH, specific gravity by dipstick and microscopy
- Urine pregnancy testing

Refer to Section 4.2 for the timing of assessments.

13.3. Study-Specific Safety Assessments

Blood serum collection for binding and neutralizing anti-drug antibody testing will be performed. Note: When necessary, samples drawn for one purpose (e.g., immunogenicity) may be used to meet another protocol-defined objective (e.g., DAC HYP concentration assessment).

14. SCHEDULE OF EVENTS

14.1. Overview

A written, signed Informed Consent Form (ICF) and all authorizations required by local law (e.g., Protected Health Information [PHI] in North America) must be obtained prior to performing any tests or assessments under this protocol.

Test results from the subject's last visit in Study 205MS301 may be used as baseline data for Study 205MS303 if performed within 28 days prior to the first dose in Study 205MS303.

Clinic visits will occur once every 4 weeks for the first 12 weeks, then every 12 weeks thereafter. Monthly LFTs (either at study site or local laboratory) will be performed before each dose (results required for dosing).

On a dosing day, all tests and assessments must be performed prior to DAC HYP administration. When DAC HYP administration and MRI evaluation are required at the same visit, the MRI scan should be performed prior to DAC HYP administration.

After Week 12, subjects will have the option of administering DAC HYP at home following Investigator review of monthly pre-dose LFT results. Subjects who are not able to administer their own dose or prefer not to administer their own dose of DAC HYP will be given the option to choose another individual (caregiver) to administer their treatment at home or to have their treatment administered by staff at the study site.

Follow-up visits will take place at 4, 8, 12, 16, and 24 weeks after each subject's last dose of DAC HYP. Unscheduled Relapse Assessment Visits (if necessary) should be scheduled within 72 hours of the onset of any new neurological symptoms that may indicate neurological worsening or possible clinical relapse. Unscheduled Hepatic Assessment Visits (if necessary) should be scheduled as soon as possible (but within 1 week) following discontinuation of study treatment due to elevated LFTs.

14.2. Site Personnel

For each subject, the Principal Investigator will designate the following study site personnel:

- A primary and backup *Treating Neurologist*
- A primary and backup *Examining Neurologist*
- A primary and backup *Treating Nurse* (or Study Coordinator)
- A primary and backup *Examining Technician*
- An *MRI Technician*
- A *Pharmacist* (or authorized designee)

Both the *Examining Neurologist* and *Treating Neurologist* must have a minimum of 2 years of neurology specialty training and anticipate at least a 3-year commitment to the study, or be approved by the study Advisory Committee. *Examining Neurologists* and *Treating Neurologists*

in parent Study 205MS301 must remain in the same roles in extension Study 205MS303 until completion of Study 205MS301. When possible subjects should be evaluated by the same *Examining Neurologist* assigned to them in Study 205MS301.

The primary *Treating Neurologist* will be responsible for:

- Management of the routine neurological care of the subject
- Assessment (including assignment of causality) and treatment of AEs and MS relapses
- Review of selected hematology and all blood chemistry results from the central laboratory
- Assessment of pre-dose LFT results, as detailed in Section 11.7.2
- Monitoring and follow-up of any abnormal hepatic tests
- Assessment of injection sites, as detailed in Table 4
- Referral of subjects to a dermatologist if that subject experiences a cutaneous event as described in Section 14.7

The *Treating Neurologist* may designate other medical personnel (i.e., the backup *Treating Neurologist* or the *Treating Nurse*) at the study site to perform some of the tests and evaluations that are designated to be performed by the *Treating Neurologist*. If there is more than 1 *Treating Neurologist* available at a given site such that each one is assigned to particular subjects, then these *Treating Neurologists* may act as backup for each other. The same holds true for the *Treating Nurses* and *Examining Technicians*.

Hematology and blood chemistry data will be sent to the investigational sites to aid in management of the subject. As with other laboratory and clinical information, this data should NOT be reviewed by the *Examining Neurologist*, the backup *Examining Neurologist*, the *Examining Technician*, or the backup *Examining Technician*.

The primary *Treating Nurse* or Study Coordinator will be responsible for:

- Assisting the *Treating Neurologist* in subject management, including the treatment of AEs, the treatment and assessment of disease relapses, and the recording of AEs and concomitant medications
- Monitoring the EDSS scores (as determined by the *Examining Neurologist*) and informing the *Treating Neurologist* if a subject experiences at least a 1.0-point increase on the EDSS from a baseline EDSS ≥1.0 that is sustained for 12 weeks, or at least a 1.5-point increase on the EDSS from a baseline EDSS <1.0 that is sustained for 12 weeks
- Administering the Multiple Sclerosis Impact Scale (MSIS-29), patient-reported questionnaires (BDI-II, MSIS-29, EQ-5D), HRU, and subject assessment of injection pain (VAS)
- Collection of blood samples and obtaining vital signs

- Study treatment administration/dispensation/accountability

The *Examining Neurologist* will be responsible for:

- Obtaining an EDSS score based on a detailed neurological examination at the scheduled timepoints required in the protocol, and at every Unscheduled Relapse Assessment Visit

The *Examining Neurologist* must not be involved with any other aspect of subject care and management and must remain blinded to AEs, concomitant medications, laboratory data, MRI data, and any other data that have the potential of revealing the previous treatment assignment in Study 205MS301. Further, the *Examining Neurologist* is not to serve as *Treating Neurologist* for any subjects at a given study site. To ensure consistency across sites, *Examining Neurologists* must have a current EDSS certification prior to obtaining an EDSS from subjects at their site. The backup *Examining Neurologist* will conduct a detailed neurological examination and obtain an EDSS score ONLY if the primary *Examining Neurologist* is unavailable due to illness, vacation, or travel.

If an *Examining Neurologist* has to be replaced, the new *Examining Neurologist* must undergo a training session. The communication of new findings on the neurological examination from the *Examining Neurologist* to the *Treating Neurologist* is permitted (because findings on the neurological examination may be important in the routine care of the subject, e.g., medical management of relapses) and will be provided via source documentation.

The roles of *Treating Neurologist* and *Examining Neurologist* (primary and backup) are NOT interchangeable during this extension study. For consistency in EDSS scoring, all sites should attempt to maintain the same assessor for each subject throughout the study.

The *Examining Neurologist* (or the *Examining Technician*) will be responsible for:

- Administering the components of the MSFC at each scheduled timepoint required in the protocol

The *Examining Technician* must remain blinded to AEs, concomitant medications, laboratory data, MRI data, and any other data that have the potential of revealing the treatment assignment. To ensure consistency across sites, *Examining Technicians* must undergo a standardized training session prior to enrollment of subjects at their site. All sites should attempt to maintain the same *Examining Technician* throughout the study. If an *Examining Technician* has to be replaced, the new *Examining Technician* must undergo a training session. It is not necessary for the *Examining Technician* to be a healthcare professional as long as he/she is qualified, in the opinion of the Principal Investigator, to administer the MSFC.

The *MRI Technician* will be responsible for:

- Performing a brain MRI scan with and without Gd at all protocol-required timepoints. Study-specific MRI scan procedures and protocols, which will be provided prior to study start, must be followed.

The *Pharmacist* (or authorized designee) will be responsible for:

- Storage, distribution, and accountability of study treatment.

14.3. Subject Management

The following restrictions apply to all subjects enrolled into this study:

- Subjects must follow the restrictions for concomitant medications and procedures described in Section 11.5.
- Contraception requirements are to be followed as described in Section 15.5.3.
- Whenever possible, a subject should undergo protocol-required tests and assessments at the same time of day throughout the study.
- Subjects should not donate blood until 4 months after their last dose of DAC HYP.
- Subjects should not receive live or live-attenuated vaccines during DAC HYP treatment or for at least 6 months after treatment with DAC HYP.

14.4. Special Instructions for Tests and Assessments

Note: Information about the tests and assessments to be performed in this study is also provided in Sections 12 and 13, and in the Study Reference Manual.

14.4.1. Rescreening

Subjects who are not eligible for participation at baseline due to a temporary condition (e.g., acute infection) are allowed to be rescreened once the condition has resolved, provided they are rescreened and enrolled within 6 months of completing Study 205MS301.

14.4.2. Pregnancy Testing

- Pregnancy testing is only required for women of childbearing potential. A urine pregnancy test is to be performed at the Baseline Visits and at other timepoints designated in Section 4.2 Schedule of Events. Study treatment will be immediately discontinued if the subject has a positive pregnancy test at any time during the study.
- Results from all urine pregnancy tests must be reviewed by the study site prior to dosing and must be negative.

14.4.3. Monthly Liver Function Test Assessments Prior to DAC HYP Dosing

Before a monthly dose of DAC HYP is given, LFT results from a test performed within the previous 7 days must be reviewed by the *Treating Neurologist* or their backup, and must be within protocol-required limits as described in Section 11.7.2.

Note: "Scheduled" clinic visits are those visits that must be performed at the study site. Scheduled clinic visits occur every 4 weeks during the first 12 weeks of the study and every 12 weeks thereafter.

LFTs can be performed as follows:

- Samples for LFTs must be drawn within 7 days prior to administration of the monthly DAC HYP dose. These samples may be tested either locally inside or outside of the clinic (e.g., at a local laboratory or by visiting nurses) or at the central laboratory at

the discretion of the Investigator and the results can then be used to determine whether dosing should continue or be suspended at the monthly dosing timepoint (see Section 11.1).

- If the central laboratory is used to test LFTs prior to a scheduled clinic visit, samples for any other laboratory assessments required at that upcoming clinic visit may also be drawn within the 7 days prior to the visit and do not need to be repeated at that scheduled clinic visit.
- 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 that scheduled clinic visit.
- If the subject is administering DAC HYP injections at home, site personnel must contact the subject after review of LFT results to authorize the monthly injection, or if LFT results warrant, to instruct the subject to withhold their injection.
- Confirmatory LFTs following a treatment suspension must be performed through the central laboratory until the LFT abnormality has resolved.

14.4.4. Other Assessments

- Vital signs include supine systolic and diastolic blood pressure, pulse, and body temperature, and should be measured pre-dose. The subject must rest quietly for 5 minutes prior to blood pressure and pulse measurements. Weight will be collected at Baseline and at the time of first autoinjector use at selected sites.
- The MSIS-29 must be administered prior to the subject's visit with the *Treating Neurologist*.
- Subject assessment of injection pain using a visual analog scale (VAS) should be completed as soon as possible after the injection is administered, but no later than 60 minutes post-injection.
- Additional visits to assess elevated LFTs may be required as described in Section 11.8.
- If a subject experiences at least a 1.0-point increase on the EDSS from a baseline EDSS ≥1.0 or a 1.5-point increase on the EDSS from a baseline EDSS <1.0 , then the EDSS must be repeated within 12 weeks to determine whether protocol-defined disability progression has occurred.
- The first 4 DAC HYP injections of the 3-year extension (i.e., Weeks 0 through 12) must be given in the clinic. The first of these injections must be given by study personnel. At subsequent visits, subjects and/or caregivers will be instructed on DAC HYP self-administration and may administer their scheduled dose under staff supervision. After the subject completes the required in-clinic injections (i.e., after Week 12), DAC HYP may be dispensed to subjects for at-home administration if the subject chooses. If necessary, drug dispensation may occur at monthly intervals.

14.5. Definition of MS Relapse and Disability Progression

14.5.1. MS Relapse

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 *Examining Neurologist** or their backup. The subject must have objective signs on the examination confirming the event.

* When possible subjects should be evaluated by the same *Examining Neurologist* assigned to them in Study 205MS301 during this open-label study.

New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse. New or recurrent neurological symptoms that occur less than 30 days following the onset of a protocol-defined relapse should be considered part of the same relapse. Management of MS relapse is described in Section 14.6.

14.5.2. Disability Progression

Disability progression can only be confirmed from the EDSS scores obtained according to the protocol-defined schedule of assessments at regular visits, and is defined as one of the following:

- at least a 1.0-point increase on the EDSS from a baseline EDSS ≥1.0 that is sustained for 12 weeks, or
- at least a 1.5-point increase on the EDSS from a baseline EDSS <1.0 that is sustained for 12 weeks

14.6. Management of MS Relapse

Subjects who experience new or worsening neurological symptoms must contact the *Treating Nurse* or *Treating Neurologist* or their backup within 48 hours after the onset of symptoms. A standardized Suspected Relapse Questionnaire will be completed to determine the necessity of an Unscheduled Relapse Assessment Visit.

If required, the subject will then be evaluated in person by the *Treating Neurologist* not more than 72 hours after the onset of the symptoms. At the Unscheduled Relapse Assessment Visit, the *Examining Neurologist* is to perform a relapse assessment and obtain an EDSS score. New objective findings on neurological examination performed by the *Examining Neurologist** are required to determine if a suspected protocol-defined relapse has occurred. Treatment of an acute relapse event with intravenous methylprednisolone (IVMP) may proceed at the discretion of the *Treating Neurologist* after the examination and will not affect the subject's eligibility to continue in the study.

* When possible subjects should be evaluated by the same *Examining Neurologist* assigned to them in Study 205MS301 during this open-label study.

Subjects who experience a relapse will be required to re-consent for continued study participation at the next scheduled study visit. Subjects who prematurely discontinue study treatment should complete follow-up evaluations (see Sections 4.2 and 13).

Subjects who permanently discontinue DAC HYP treatment should complete the visit schedule described in Section 11.8.

14.7. Cutaneous Events

Subjects who experience a clinically significant cutaneous event (e.g., rash, dermatitis, eczema, acne, folliculitis) should be referred to and evaluated by a local dermatologist. The dermatologist is to document the cutaneous event, take photographs, and if appropriate, obtain a biopsy prior to prescribing treatment. Systemic corticosteroids may be administered if medically indicated.

Subjects presenting with a diffuse cutaneous eruption/rash are to be evaluated and managed as described in Section 22.

If a generalized allergic or hypersensitivity reaction to study treatment is suspected, study treatment must be permanently discontinued as per Section 11.8.

All photographs and biopsy slides will be sent to a central dermatology consultant for further evaluation (see Section 22 and the Study Reference Manual). The incidence and nature of cutaneous events will be monitored by the SMC (see Section 19.2.2).

14.8. Unscheduled Hepatic Assessment Visit

The following tests/assessments will be performed as soon as possible (but within 1 week) after discontinuation of study treatment for subjects who are required to discontinue dosing due to elevated LFTs as described in Section 11.8, unless a definite cause of the LFT abnormality leading to treatment discontinuation has already been established through other testing.

- Vital signs
- Comprehensive hepatic panel
- Recording of concomitant therapy
- Monitor and record AE/SAEs
- Protocol compliance

14.9. Post-Treatment Safety Follow-Up Visit Schedule for All Subjects

All subjects should complete the following schedule of safety follow-up visits after their last dose of DAC HYP:

- End of Treatment Visit (i.e., the assessments required at Week 144). For subjects who prematurely discontinue study treatment before Week 144, these assessments should be performed 4 weeks (±4 days) after the subject's last dose of DAC HYP.
- Post-treatment safety follow-up visits at 8, 12, 16, and 24 weeks after the subject's last dose. The details of these visits are shown in Table 3.

15. SAFETY DEFINITIONS, MONITORING, AND REPORTING

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

At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Serious Pretreatment Event

A serious pretreatment event is any event that meets the criteria for serious adverse event (SAE) reporting (as defined in Section 15.1.3) and occurs after the subject signs the ICF, but before administration of study treatment.

15.1.2. Adverse Event

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

15.1.3. Serious Adverse Event

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

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

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.

15.2. Monitoring and Recording Events

15.2.1. Serious Pretreatment Events

A serious pretreatment event experienced by the subject after signing and dating the ICF, but before administration of study treatment is to be recorded on the SAE Form and faxed to the contract research organization (CRO), [redacted] within 24 hours of the study site staff becoming aware of the event (see Section 15.2.5).

15.2.2. Adverse Events

Any AE experienced by the subject between the time of signing the ICF and subject's final visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

15.2.3. Serious Adverse Events

Any SAE experienced by the subject between the time of the first dose of study treatment and subject's final visit is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to the Sponsor (or designee).

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

Subjects will be followed for all SAEs until the subject's final visit. Thereafter, the event should only be recorded if the Investigator considers it related to study treatment.

15.2.4. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.3.
- The relationship of the event to study treatment as defined in Section 15.3.1.
- The severity of the event as defined in Section 15.3.2.

15.2.5. Immediate Reporting of Serious Adverse Events

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

Reporting Information for SAEs

Any Serious Event that occurs between the time the subject has signed informed consent and subject's final visit must be reported to Biogen Idec SABR or [redacted] within 24 hours of the study site staff becoming aware of the event. **Thereafter, the event should only be recorded if the Investigator considers it related to study treatment**.

A report ***must be submitted*** to [redacted] regardless of the following:

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

To report initial or follow-up information on a Serious Event, fax a completed SAE form to the following:

North America: [redacted]
Latin America: [redacted]
Europe and Asia Pacific: [redacted]

(Country-specific fax numbers are provided in the Study Reference Guide.)

15.2.5.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate CRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen Idec SABR or designee.

15.3. Safety Classifications

15.3.1. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

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

15.3.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.3.3. Expectedness of Events

Expectedness of all AEs will be determined according to the Investigator's Brochure.

15.4. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the

Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.

- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

15.5. Procedures for Handling Special Situations

15.5.1. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed to [redacted] within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded in the CRF; dosing information is recorded on a CRF.

15.5.2. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator or designee should contact the [redacted] Medical Monitor at one of the following phone numbers:

North America (USA and Canada): [redacted]

Latin America: [redacted]

Europe and Asia Pacific: [redacted]

15.5.3. Contraception Requirements

All women of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 4 months after their last dose of study treatment.

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

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy

For the purposes of the study, effective contraception is defined as follows:

For females:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with spermicide; diaphragm, sponge, cervical cap)
- Abstinence can be considered an acceptable method of contraception at the discretion of the Investigator. Periodic abstinence (e.g., calendar, ovulation, symptothermal,

post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

15.5.4. Pregnancy

Subjects should not become pregnant during the study. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report the pregnancy by faxing the appropriate form to [redacted] Pharmacovigilance within 24 hours of the study site staff becoming aware of the pregnancy (refer to Section 15.2.5 for reporting information). The Investigator or study site staff must report the outcome of the pregnancy to [redacted] Pharmacovigilance.

Please note that congenital abnormalities/birth defects in the offspring of male or female subjects should be reported when conception occurred during the study treatment period.

15.5.5. Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Biogen Idec Safety and Benefit-Risk Management (SABR) will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

15.6. Investigator Responsibilities

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow-up on the outcome of the pregnancy.
- Complete an SAE form for each serious event and fax it to [redacted] within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to [redacted] within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Report SAEs to local ethics committees, as required by local law.

15.7. Biogen Idec Responsibilities

Biogen Idec's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor or designee is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen Idec is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

16.1. Description of Objectives

See Section 6.1, Objectives.

16.2. Description of Endpoints

See Section 6.2, Endpoints.

16.3. Demography and Baseline Disease Characteristics

Demographic data collected at baseline will be summarized (i.e., age, gender, ethnicity, and weight). Medical history and baseline characteristic data (e.g., EDSS, number of relapses in the previous study, MRI endpoints) will also be summarized.

16.4. Safety and Efficacy

16.4.1. Analysis Population

Safety Population

The safety population will include all subjects who received at least 1 dose of DAC HYP in Study 205MS303. All safety analyses will be completed on the safety population.

Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who received at least 1 dose of DAC HYP in Study 205MS303. This population will be utilized for the efficacy analyses.

16.4.2. General Methods of Analysis

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include the number of subjects with data, mean, standard deviation, median, and range. Categorical endpoints will include the number of subjects with data and the percentage in each category.

The data will be summarized by previous treatment group (Avonex or DAC HYP 150 mg during Study 205MS301). The analysis will focus on Study 205MS303 data although selected analyses will present data after combining data from Studies 205MS301 and 205MS303.

Analyses will generally be descriptive in nature. However, for relevant efficacy analyses, statistical comparisons may be made between efficacy in Study 205MS301 and efficacy in Study 205MS303 among subjects previously randomized to Avonex in Study 205MS301.

Covariates included for inclusion in the statistical models for efficacy analyses for Study 205MS303 will generally be the same as those used for corresponding models in Study 205MS301.

All statistical tests will be 2-sided with an overall Type I error of 5%. Adjustments for multiple comparisons will not be considered.

16.4.3. Primary Endpoints Analysis

Clinical Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. All treatment-emergent events will be included in the evaluation of safety. Treatment emergent includes any event that either occurs or worsens in severity after the onset of study treatment. The incidence of treatment-emergent events will be summarized by treatment group (prior Avonex, prior DAC HYP 150 mg), overall, by severity, and by relationship to study treatment. The summary tables will include incidence estimates for the overall system organ class as well as for preferred terms within each system organ class. In order to assess whether the incidence of events changes over time, the incidence of key events may also be summarized by time period (e.g., 6-month time intervals).

16.4.4. Other Safety Endpoint Analyses

Laboratory Data

Changes in laboratory values will be summarized using shift tables. Shift tables will include hematology, liver function tests, kidney function tests, electrolytes, and other blood chemistry tests. Shifts will be presented from baseline of DAC treatment (Study 205MS303 baseline for subjects randomized to Avonex in Study 205MS301 and Study 205MS301 baseline for subjects randomized to DAC HYP 150 mg in Study 205MS301). Summaries of worst post-baseline laboratory values by clinically relevant categories may also be presented for selected parameters of interest by treatment group. For example, for LFT (alkaline phosphatase, ALT, AST, GGT and total bilirubin), categories may be defined based on cutoff values relative to the ULN.

Vital Signs

Vital signs collected will be examined to determine the incidence of clinically relevant abnormalities. These abnormalities are described in Table 5. For the purpose of the shifts from baseline, the baseline evaluation at the start of DAC HYP treatment will be used.

For each vital sign, the number of subjects evaluated and the number and percentage of subjects with the defined abnormality at any time post dosing will be presented by treatment group.

Table 5: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C or an increase from baseline of ≥1°C
Pulse	>120 beats per minute (bpm) or an increase from baseline of 20 bpm <50 bpm or a decrease from baseline of >20 bpm
Systolic Blood Pressure	>180 mmHg or an increase from baseline of >40 mmHg <90 mmHg or a decrease from baseline of >30 mmHg
Diastolic Blood Pressure	>105 mmHg or an increase from baseline of >30 mmHg <50 mmHg or a decrease from baseline of >20 mmHg

Physical Examination

The physical examination findings will be summarized by treatment group.

16.4.5. Efficacy Endpoints Analyses

Annualized Relapse Rate

Relapses will be summarized by prior treatment group over the 3 years of follow-up in Study 205MS303 as well as over the 5-6 years of the combined study period (Studies 205MS301 and 205MS303).

A negative binomial regression model will be used to estimate the adjusted ARR.

Proportion of Subjects with a Relapse

The proportion of subjects relapsed will be estimated using a Kaplan-Meier curve.

Disability Progression

Sustained disability progression is defined as at least a 1.0 point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS <1.0 that is sustained for 12 weeks. Progression will be assessed relative to the baseline EDSS in Study 205MS303 as well as to baseline scores in the previous study. The proportion of subjects with progression will be summarized using a Kaplan-Meier curve. Progression will be summarized by previous treatment group during the combined study period (Studies 205MS301 and 205MS303) as well as in each study separately. In addition, summary statistics for EDSS and for the change from baseline in EDSS will be presented by visit by previous treatment group.

MSFC

Changes in the MSFC z-score will be summarized by treatment group and study visit. Details on the calculations of the z-score for each component will be described in the statistical analysis plan.

MRI Endpoints

MRI endpoints will be summarized with descriptive statistics overall and over time by treatment group, both as a continuous variable and categorically. A negative binomial regression model will be used for the analysis of new or newly enlarging T2 lesions. The change in volume of lesions and percent change of brain atrophy will be analyzed using an analysis of covariance.

Quality of Life Outcomes

Actual scores and change from baseline in quality of life endpoints will be summarized by visit.

Pharmacodynamics and Pharmacokinetics

The population for DAC HYP concentration and PD analyses will include all subjects who received at least 1 dose of study medication and who have at least 1 sample available for analysis.

Pharmacokinetics

Serum concentration levels will be summarized with descriptive statistics by treatment group and visit. PK data from this study will be used in combination with PK data from other DAC HYP trials for population PK analysis. Details on the analysis will be described in a separate population PK-PD analysis plan.

Pharmacodynamics

Summary statistics for PD variables will be summarized by treatment group and study visit.

Antigenicity/Immunogenicity Data

Immunogenicity (i.e., anti-DAC antibodies) will be assessed on all subjects. Positive samples will be further tested for neutralizing anti-DAC antibodies using a specific neutralizing antibody (NAb) assay. Results will be tabulated by time period, treatment group, and overall.

16.5. Interim Analyses

No formal interim analyses are planned for this study. However, analyses may be performed prior to the end of the study at the discretion of the Sponsor.

16.6. Sample Size Considerations

There is no formal sample size calculation. The number of subjects in this study is determined by the number of subjects who participate in Study 205MS301.

17. ETHICAL REQUIREMENTS

Biogen Idec and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

17.1. Declaration of Helsinki

The Investigator and Biogen Idec must adhere to the principles set forth by the Declaration of Helsinki dated October 2008.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor may submit documents on behalf of the study sites in countries other than the US as applicable.

If the Investigator makes any changes to the ICF, Biogen Idec must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen Idec. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen Idec.

It is the responsibility of the Principal Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

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

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

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

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including baseline tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all subjects participating in a clinical study conducted by Biogen Idec.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including baseline tests and assessments.

Each consent form should contain an authorization allowing the Principal Investigator(s) and Biogen Idec to use and disclose PHI (i.e., subject-identifiable health information) in compliance with local law.

The signed consent form will be retained with the study records.

17.4. Subject Data Protection

Prior to any testing under this protocol, including baseline tests and assessments, candidates must also provide all authorizations required by local law (e.g., PHI authorization in North America).

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen Idec, its partner(s) and designee(s), ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen Idec maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws.

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

Biogen Idec will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not enroll any subjects prior to completion of a study initiation visit, conducted by Biogen Idec or designee. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Principal Investigator(s) must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the course of the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the study site and its facilities.

18.4. Study Funding

Biogen Idec is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen Idec.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

Biogen Idec will be responsible for all administrative aspects of this study including, but not limited to, study initiation, monitoring, management of AEs, and data management.

19.1. External Contract Organizations

19.1.1. Contract Research Organization

[redacted] will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports. Before subjects are screened at each study site, [redacted] will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Electronic or Remote Data Capture

Subject information will be captured and managed by study sites on electronic CRFs via a remote data capture (RDC) developed and supported by [redacted] and configured by Biogen Idec.

19.1.3. Central Laboratories for Laboratory Assessments

[redacted] has been selected by Biogen Idec to analyze all hematology, blood chemistry, and urine samples collected for this study.

LFTs may be assessed locally for dosing decisions. LFTs performed locally must be repeated through the central laboratory at the scheduled monthly visit.

19.1.4. Central Facility for Other Assessments

MRI Reading Center

All scheduled MRI scans with and without Gd will be evaluated at a central MRI reading center. All study sites will be required to send a test scan to the MRI Reading Center for evaluation in order to ensure that the site's scanning techniques are appropriate. This review will take place before the study site is permitted to enroll any subjects into the study.

Original MRI images are to be sent to the MRI Reading Center for review (MRI shipping instructions will be provided prior to the start of enrollment at each site).

Additional and more detailed MRI scans with and without Gd procedures and instructions are included in the study MRI manual (to be provided under separate cover prior to start of the study).

19.2. Study Committees

19.2.1. Advisory Committee

The Advisory Committee from parent Study 205MS301 will oversee the administrative progress and provide scientific and medical direction for this study while Study 205MS301 is ongoing. Advisory Committee will monitor subject accrual and compliance with the protocol at individual study sites. The Advisory Committee will determine whether the study should be stopped or amended for reasons other than safety.

Members of the Advisory Committee will include the Medical Director, Clinical Trial Manager, and Project Statistician from Biogen Idec (and/or their designees), and participating Investigators. Biogen Idec will designate one of the participating Investigators to be the Chairperson of the Advisory Committee.

19.2.2. Safety Monitoring Committee

A SMC will be formed to review interim safety data. Safety data will be provided to the SMC for review of all AEs and key laboratory tests for all subjects prior to completion of Study 205MS301.

The Advisory Committee for Study 205MS301 (DECIDE) will also provide scientific and medical direction for Study 205MS303.

19.3. Changes to Final Study Protocol

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

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

In the event of a protocol modification, the subject consent form may require similar modifications (see Sections 17.2 and 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen Idec in writing and

receive written authorization from Biogen Idec to destroy study records. In addition, the Investigator must notify Biogen Idec of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen Idec will designate one of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors, including, but not limited to, the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by Biogen Idec.

Biogen Idec will follow all applicable local regulations pertaining to study report signatories.

20. REFERENCES

Bielekova B, Richert N, Howard T, et al. Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta. Proc Natl Acad Sci U S A. 2004;101(23):8705-8.

Bielekova B, Howard T, Packer AN, et al. Effect of anti-CD25 antibody daclizumab in the inhibition of inflammation and stabilization of disease progression in multiple sclerosis. Arch Neurol. 2009;66(4):483-9.

Fischer JS, LaRocca NG, Miller DM, et al. Recent developments in the assessment of quality of life in multiple sclerosis (MS). Mult Scler. 1999;5(4):251-9.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52.

Rose JW. Treatment of Multiple Sclerosis with a Humanized Monoclonal Antibody Specific for IL-2 Receptor Chain. Neurology. 2003;60(Suppl 1):A478-9.

Rose JW, Watt HE, White AT, et al. Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. Ann Neurol. 2004;56(6):864-7.

Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol. 2010;9(4):381-90.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "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 Who Have Completed Study 205MS301" and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

22. APPENDIX 1: GUIDELINES FOR MANAGEMENT OF CUTANEOUS EVENTS FOR SUBJECTS PARTICIPATING IN BIOGEN IDEC CLINICAL STUDIES OF DAC HYP

The following guidelines apply to subjects receiving open-label treatment with DAC HYP, or subjects potentially receiving DAC HYP treatment in blinded studies.

22.1. Background

Serious adverse events (SAEs) involving cutaneous reactions have been reported in subjects participating in ongoing, blinded MS studies with DAC HYP. All of these events have been reviewed by the 205MS201 (SELECT) study's central dermatologist; some of the events have been characterized as progressive skin eruptions consistent with systemic drug hypersensitivity reactions. Although it is not known whether DAC HYP is the causative agent of these reactions, the following guidelines have been developed for prompt recognition and treatment of these events for subjects who may be participating in DAC HYP clinical studies.

Cases presenting as **diffuse maculopapular eruptions** are considered to be at risk for worsening in severity. Although such eruptions may be of varying severity at presentation, some have become more generalized over a period of weeks to involve >75% of the body surface area and resulted in hospitalization for treatment.

Subjects who have presented with **localized or highly circumscribed rashes** have typically had a favorable course even with continuation of study treatment, but dermatologists and investigators are cautioned that all clinically significant cutaneous events in subjects in DAC HYP clinical studies should be followed closely until resolution.

The relationship between the cutaneous reactions and the duration of study treatment dosing is not established. The onset of the cutaneous eruptions has not been temporally associated with the administration of the SC injection.

In cases of diffuse or severe skin reactions, response to administration of high-dose systemic corticosteroids has generally been favorable, and it is currently believed that this treatment may be able to promote recovery and limit the severity of these events. Unless contraindicated, strong consideration should be given to the use of high-dose systemic glucocorticosteroids (oral or parenteral) for the treatment of widespread, diffuse, maculopapular rashes.

For additional information on the occurrence of cutaneous events in DAC HYP clinical studies, please refer to the Investigator's Brochure.

22.2. General Management of Cutaneous Events

Any subject participating in a DAC HYP clinical study who develops a clinically significant cutaneous event (e.g., rash, dermatitis, eczema, acne, folliculitis) should be evaluated by a dermatologist.

The dermatologist is to document the event, take photographs, and if appropriate, obtain a biopsy prior to prescribing treatment.

Additional diagnostic procedures and careful evaluation for systemic conditions such as infections should be considered as appropriate.

Systemic corticosteroids may be administered if medically indicated (see below).

When the cutaneous event is localized or highly circumscribed, it should be managed according to local practices per the dermatologist. The decision to discontinue study treatment, either temporarily, during the period of evaluation and treatment of the skin event, or permanently should be made by the Principal Investigator in consultation with the dermatologist. If an allergic or hypersensitivity reaction to study treatment is suspected, study treatment must be permanently discontinued.

Subjects presenting with a diffuse cutaneous eruption/rash are to be evaluated and managed as described in Section 22.3.

22.3. Evaluation and Management of Diffuse Cutaneous Eruptions/Rash

22.3.1. Evaluation of Diffuse Cutaneous Eruptions/Rash

Any subject who:

- is currently receiving study treatment (either open label DAC HYP or blinded study treatment), or
- received a dose of study treatment within the last 6 months

and develops a **cutaneous eruption in a diffusely distributed pattern** consistent with a possible drug-hypersensitivity reaction (refer to photographs in Section 22.4) should be evaluated by a dermatologist as soon as possible within 72 hours following event onset. The dermatologist should:

- assess the cutaneous event
- photograph the affected body areas
- perform a skin biopsy (if applicable)
- take a detailed medication history
- determine if there is a contraindication to treatment with corticosteroids

Careful evaluation for systemic conditions such as infections should be considered.

The Adverse Event of Special Interest form should be submitted to the Sponsor as soon as possible within 72 hours following the dermatology evaluation. Photographs of the cutaneous eruption should be included whenever possible. The report should also include the intended treatment plan. If systemic corticosteroids are not administered as described below, the rationale should be provided. If results of the skin biopsy are pending, they can be submitted as a follow-up (submission of the initial report to the Sponsor should not be delayed).

Note: If the event qualifies as an SAE, an SAE report form should be submitted within 24 hours of the staff becoming aware of the event as per the reporting requirements described in the protocol.

Close follow-up (initially within 7 days of evaluation by the dermatologist) should be maintained for all cutaneous events that are not well localized or do not have an otherwise proven etiology and should continue at appropriate intervals until resolution or stabilization.

22.3.2. Management of Diffuse Cutaneous Eruption/Rash

For subjects with a diffuse or severe skin reaction, DAC HYP must be withheld until resolution. The subject should also withhold all other non-essential medications, including protocol-required medications, and non-prescription drugs and supplements, at least until the cutaneous event has resolved. The decision to permanently discontinue study treatment should be made by the Principal Investigator in consultation with the site dermatologist. **If an allergic or hypersensitivity reaction to study treatment is suspected, study treatment must be permanently discontinued.**

If the diffuse rash has <u>any</u> of the following characteristics:

- **is highly inflammatory at presentation**
- **worsens to increasing body surface area, or to mucosal involvement, or to more numerous inflammatory lesions over a period of days to weeks**
- **persists for more than a week without improvement**

and if there is no contraindication to the use of high-dose systemic corticosteroids, it is recommended that the subject receives treatment with a high dose of oral or parenteral corticosteroids (e.g., an equivalent of oral prednisone 60 mg/day or IV methylprednisolone 1 g/day) for a period of approximately 5 days.

It is recommended that systemic corticosteroid therapy be instituted as early in the course of the reaction as possible [Ann Allergy Asthma Immunol. 1999 Dec;83(6 Pt 3):665-700.].

- <u>If the cutaneous event has stabilized or improved after the initial treatment</u>, then it is recommended that the subject tapers the corticosteroids gradually over the next 2 to 3 weeks by reducing the daily dose of oral prednisone per standard medical practice.
- <u>If the cutaneous event worsens during the corticosteroid taper</u>, retreatment with high-dose corticosteroids and a more gradual taper should be considered.
- <u>If the cutaneous event does not improve with corticosteroid treatment</u>, additional treatments should be considered under the guidance of the dermatologist. Additional consultation with the Sponsor should be arranged through the local medical monitor for the clinical study.

If a contraindication to corticosteroids exists, the cutaneous event should be managed according to the local dermatologist. Additional consultation with the central study dermatologist may be arranged through the Sponsor.

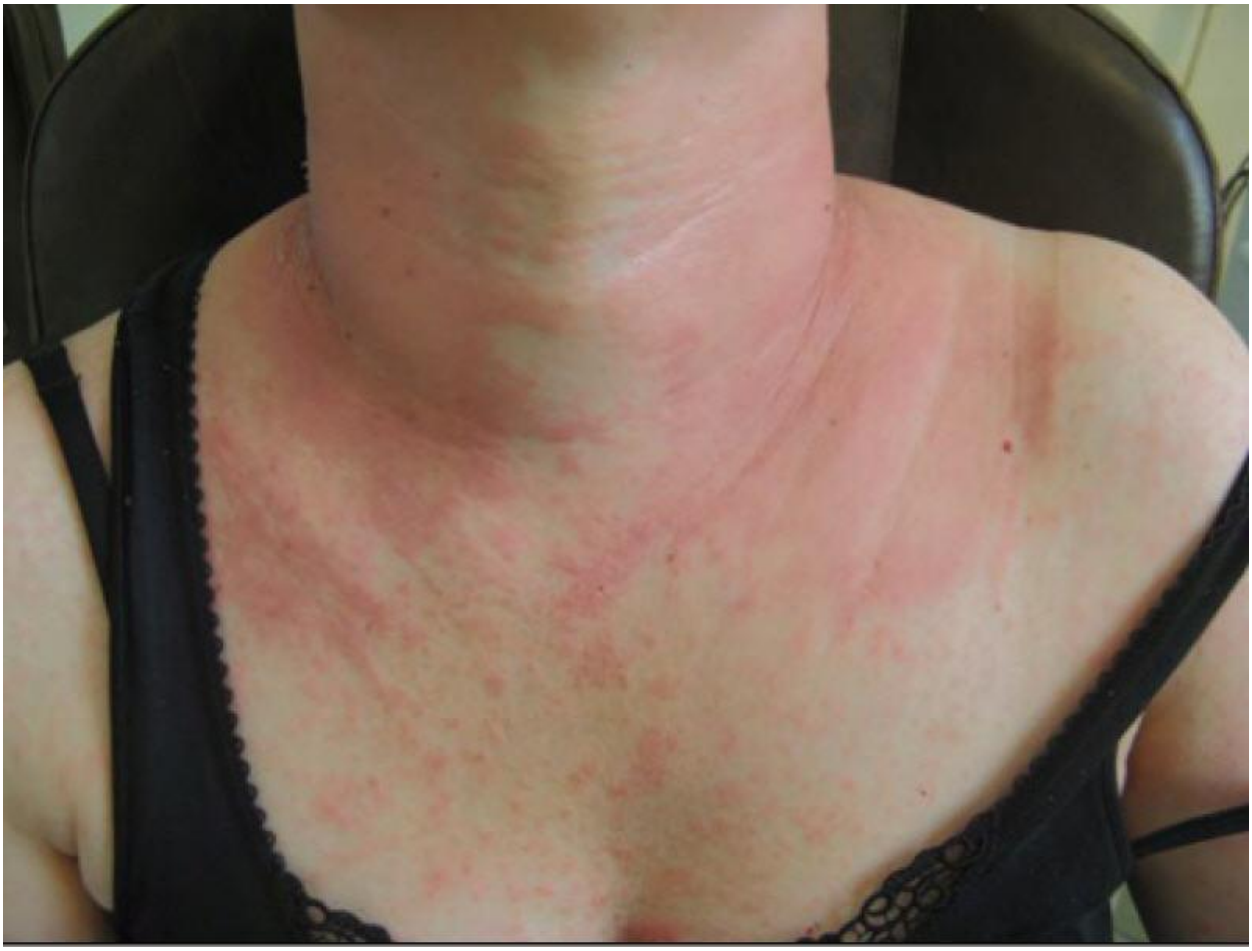
Note: A schematic of the evaluation and management process for subjects presenting with a diffuse cutaneous eruption is presented in Section 22.5.

22.4. Examples of Diffuse Maculopapular Eruptions/Rash in DAC HYP Clinical Studies

Following are examples of the diffuse maculopapular eruptions (with and without urtication) that have occurred in subjects who experienced serious systemic drug hypersensitivity-like reactions in clinical studies of DAC HYP.

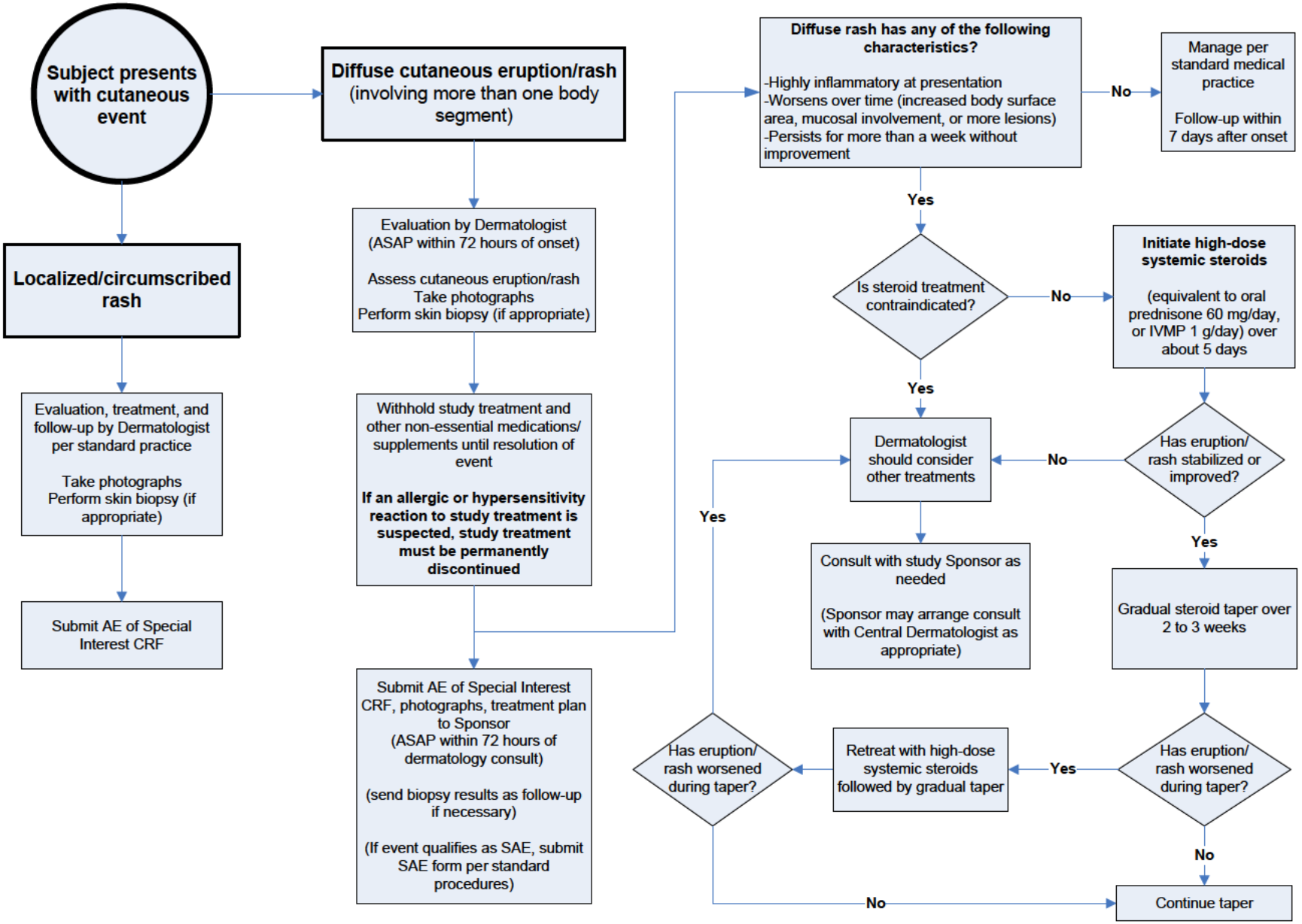
These maculopapular eruptions were diffuse at presentation, or shortly after presentation, with involvement of face, trunk, and extremities.

Treatment guidelines are as described in Section 22.3.



22.5. Treatment Algorithm for Subjects Presenting with Diffuse Cutaneous Eruption/Rash

A schematic for evaluation and treatment of subjects presenting with a diffuse cutaneous eruption/rash is presented on the next page.


Subject presents with cutaneous event
Localized/circumscribed rash
Evaluation, treatment, and follow-up by Dermatologist per standard practice
Take photographs
Perform skin biopsy (if appropriate)
Submit AE of Special Interest CRF
Diffuse cutaneous eruption/rash (involving more than one body segment)
Evaluation by Dermatologist (ASAP within 72 hours of onset)
Assess cutaneous eruption/rash
Take photographs
Perform skin biopsy (if appropriate)
Withhold study treatment and other non-essential medications/ supplements until resolution of event
If an allergic or hypersensitivity reaction to study treatment is suspected, study treatment must be permanently discontinued
Submit AE of Special Interest CRF, photographs, treatment plan to Sponsor (ASAP within 72 hours of dermatology consult)
(send biopsy results as follow-up if necessary)
(If event qualifies as SAE, submit SAE form per standard procedures)
Diffuse rash has any of the following characteristics?
-Highly inflammatory at presentation
-Worsens over time (increased body surface area, mucosal involvement, or more lesions)
-Persists for more than a week without improvement
No
Manage per standard medical practice
Follow-up within 7 days after onset
Yes
Is steroid treatment contraindicated?
No
Initiate high-dose systemic steroids
(equivalent to oral prednisone 60 mg/day, or IVMP 1 g/day) over about 5 days
Yes
Dermatologist should consider other treatments
No
Has eruption/ rash stabilized or improved?
Yes
Consult with study Sponsor as needed
(Sponsor may arrange consult with Central Dermatologist as appropriate)
Gradual steroid taper over 2 to 3 weeks
Yes
Has eruption/ rash worsened during taper?
Yes
Retreat with high-dose systemic steroids followed by gradual taper
Has eruption/ rash worsened during taper?
No
Continue taper
No