PASS PROTOCOL

TITLE:	Plegridy® (peginterferon β-1a) Real World Effectiveness and Safety Observational Program
VERSION:	5.0
DATE OF LAST VERSION OF PROTOCOL:	05 March 2019
EU PAS REGISTER NUMBER:	27459
ACTIVE SUBSTANCE:	L03AB13 peginterferon beta-1a
MEDICINAL PRODUCT:	Plegridy 63 µg, 94 µg, and 125 µg single use pre-filled syringe or pre-filled pen
PRODUCT REFERENCE:	EMEA/H/C/2827
PROCEDURE NUMBER:	Not applicable
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The purpose of this study is to provide long-term safety and effectiveness data in patients with relapsing forms of multiple sclerosis who were prescribed Plegridy in routine clinical practice.
COUNTRIES OF THE STUDY:	Global study including approximately 160 sites in the United States, the European Union, Australia, and sites participating in Study 105MS302 or Study 105MS303 in other countries.
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Protocol 105MS401 was approved by:

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17 Apr 2019

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17 APR 2019

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Date (*DD MMM YYYY*)

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Biogen

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1. LIST OF ABBREVIATIONS

AE	adverse event
ARR	annualized relapse rate
CBC	complete blood count
CI	confidence interval
cNEDA	clinical no evidence of disease activity
CRO	contract research organization
eCRF	electronic case report form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
EQ-5D-3L	EuroQoL EQ-5D, 3-level
ER	emergency room
EU	European Union
FLS	flu-like symptoms
GCP	Good Clinical Practices
GVP	Good Pharmacovigilance Practices
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IFN β	interferon beta
IFN β-1a	interferon beta-1a
IL	interleukin
IRB	Institutional Review Board
ISR	injection site reaction
MedDRA	Medical Dictionary for Regulatory Authorities
MRI	magnetic resonance imaging
MS	multiple sclerosis
[redacted]	[redacted]
[redacted]	[redacted]
PHI	protected health information
POP	Plegridy Real World Effectiveness and Safety Observational Program
Prescribing Physician	The Prescribing Physician is also the Principal Investigator

PRO	patient-reported outcome
RMS	relapsing multiple sclerosis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
US	United States
VAS	visual analog scale

2. RESPONSIBLE PARTIES

A list of all Investigators and their contact information is available upon request.

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Contact Research Organization:

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.

A CRO (IQVIA) will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of serious adverse event (SAE) reports and data management. Before patients are enrolled at each study site, the CRO will review study responsibilities with the Prescribing Physicians and other study site staff, as appropriate.

3. ABSTRACT

Protocol Title:	Plegridy® (peginterferon β-1a) Real World Effectiveness and Safety Observational Program
Version Number:	5.0
Date of Protocol:	16 April 2019
Name and Affiliation of Main Author:	[redacted], PhD [redacted] Biogen
Rationale and Background:	Despite recent approval of several new therapeutic agents for treatment of multiple sclerosis (MS), there continues to be a high unmet medical need in this patient population for effective therapies with an established safety profile that are convenient to use over a long time period. Observational studies are increasingly being used – across many therapeutic areas and chronic diseases, including MS – to study the long term effects of medications and interventions on broad patient populations under real world conditions. Interferon beta-1a (IFN β-1a) therapy has been successfully used as a disease modifying therapy to treat patients with relapsing forms of MS (RMS) for over 15 years. Plegridy®(peginterferon β-1a) has a longer half-life than non-pegylated IFN β-1a. As such, it has been shown to reduce the frequency of administration versus IFN β-1a, thereby increasing treatment convenience. Consequently, we expect that it will improve compliance, while maintaining a safety and efficacy profile at least similar to IFN β-1a. Findings from the pivotal Phase III study (Study 105MS301, 1 year) demonstrated that Plegridy administered at a dose of 125 µg via subcutaneous (SC) injection every two weeks is an effective treatment for RMS. In the clinical trial, treatment with Plegridy has demonstrated to be effective in delaying the progression of disability and in reducing the rate of clinical relapses, but it has also been associated with flu like symptoms (FLS), including muscle aches, fever, fatigue, and chills), and injection site reactions (ISRs), which are typical of IFN products. In clinical practice, pre- and postinjection treatment with acetaminophen or non-steroidal anti-inflammatory drugs for the FLS is common. However, the effects of Plegridy did not have a

	negative effect on patients' health related quality of life (HRQoL) compared with placebo. There is a need to continue to collect long-term data to help optimize patient management and support continued access to Plegridy in the real world setting.
Research Question and Objectives:	The purpose of this study is to provide long-term safety and effectiveness data in patients with RMS who have been prescribed Plegridy in routine clinical practice. **Objectives** The primary objectives of the study are: • To determine the incidence of SAEs in patients with RMS in routine clinical practice; • To assess the overall long-term clinical effectiveness of Plegridy in patients with RMS in routine clinical practice. The secondary objectives of this study are as follows: • To describe Plegridy prescription and utilization patterns in routine clinical practice; • To assess the specific long-term clinical effectiveness of Plegridy in patients with RMS in routine clinical practice; • To monitor the safety and tolerability of Plegridy in routine clinical practice by assessing the incidence of adverse events (AEs) of FLS, ISR, and AEs (including laboratory abnormalities) leading to treatment discontinuation; • To assess the effect of FLS on patient-reported effectiveness of, and satisfaction with, prophylactic management using a FLS-Visual Analog Scale (VAS); • To evaluate the change in HRQoL, FLS, FLS-VAS, healthcare resource consumption, and treatment adherence over time.
Study Design:	This study will be conducted as a prospective, observational study of patients with RMS who are newly or currently prescribed Plegridy in routine clinical practice, including patients who participated in Study 105MS302 (ATTAIN) or Study 105MS303 (ALLOW). Enrolled patients will be followed for a maximum of five years (regardless of treatment discontinuation) or until patient death, withdrawal, or the patient is considered lost to follow-up. Data will be collected from information routinely recorded in the medical record or prospectively collected by the Prescribing

	Physician. Patient-reported outcomes (PROs) will be completed by patients either electronically through a secured, personalized link or on paper at the time of a routine clinic visit. If a patient does not complete his/her PROs during the clinic visit, then he/she can complete the PROs electronically via the secure, personalized link within four weeks of his/her routine clinical visit.
Population:	This study will be conducted in patients with RMS who are newly or currently prescribed Plegridy under routine clinical practice, including patients who participated in Study 105MS302 or Study 105MS303. Detailed criteria are described in the protocol.
Variables:	The data collected at enrollment will coincide with routine visits to the neurological clinic as per local guidelines and label. The following will be collected at enrollment: • Documentation of informed consent • Demographic characteristics • Relevant medical history and co-morbidities • MS disease history • Prior MS treatment history • Prior and concomitant medications and therapies • History of FLS on previous IFN therapy • Ambulation status • Use of assistive devices, if applicable • Magnetic resonance imaging (MRI) results and other laboratory tests, if available • Expanded Disability Status Scale (EDSS) information, if used in routine clinical practice • Neurologic assessment, if EDSS not used in routine clinical practice • [redacted] • PROs [EuroQoL EQ-5D, 3-level (EQ-5D-3L), FLS, FLS-VAS, healthcare resource consumption questionnaire, treatment adherence questionnaire, and [redacted]] • Pregnancy status (female patients) • Nursing status (female patients)

	Subsequent data will also be collected during routine clinical practice visits for up to five years from enrollment. Data will be collected, as per local clinical practice and label, at baseline (month 0), every three months (i.e., 3, 6, 12 months after baseline [± four weeks]) for follow-up Year 1, and every six months (± four weeks) in follow-up Year 2 through Year 5 in accordance with routine clinic visits. The following will be collected during routine clinical practice visits: • Plegridy treatment information • Concomitant medication(s) use • Participant of Study 105MS302 or Study 105MS303 • Complete blood count (CBC) with differential, if consistent with routine clinical practice • Other laboratory tests recommended in the local label, if consistent with routine clinical practice • SAEs • AEs of special interest (FLS, ISRs) • AEs [including laboratory abnormalities] leading to treatment discontinuation • MS relapse information • EDSS information, if used in routine clinical practice • Neurologic assessment, if EDSS not used in routine clinical practice • [redacted] • [redacted] • MS-related hospitalization details • MRI results, if available • Ambulation status • EQ-5D-3L • FLS and FLS-VAS • Healthcare resource consumption questionnaire • Treatment adherence questionnaire

Data Sources:	Data from patients with MS who are newly or currently prescribed Plegridy under routine clinical practice will be collected at baseline and every three months during the first year of follow up, then every six months in Year 2 through Year 5. All clinical assessments are intended to be performed at the time of a routine clinical encounter or by referencing the medical record. Data from all clinical visits will be recorded. MS relapse will be confirmed by the Prescribing Physician. No visits or examinations, laboratory tests or procedures are mandated as part of this study.
Study Size:	In Version 3.0 of this protocol, approximately 1600 patients across approximately 160 participating sites in the United States (US), European Union (EU), Australia, and sites participating in Study 105MS302 and 105MS303 in other countries were planned to be enrolled. In January 2017, following a decision by Biogen to limit enrollment to approximately 1100 patients, a Protocol Clarification Letter was sent to all study sites providing official notification that enrollment into the study should be stopped. The current target sample size is expected to provide acceptable precision around the estimates of the proportion of patients experiencing SAEs and ensure a reasonable likelihood of observing rare AEs over a 5-year period. The target sample size will also provide acceptable precision around the overall effectiveness endpoint of the proportion of patients with no evidence of disease activity clinically (cNEDA), which is defined as having no relapses and no disability progression.
Data Analysis:	Statistical analyses will be based on all patients who enroll in the study and receive at least one within-study dose of Plegridy. Analyses will be conducted separately for patients newly-prescribed Plegridy (Plegridy-naïve) from those who have previous exposure to Plegridy prior to study enrollment (Plegridy-experienced). Statistical analyses will generally be descriptive and exploratory in nature. No formal statistical hypothesis testing is planned. Ninety-five percent confidence intervals (95% CIs) for the incidence and incidence rate point estimates will be calculated using the negative binomial distribution and the Poisson distribution, respectively. Analyses of continuous endpoints may include summaries of values over time, change from baseline over time, shift tables, and/or summaries of worst post-baseline values. The proportion of patients with cNEDA will be calculated over time (e.g., Baseline to Year 1, Baseline to Year 2, etc.) as well as

	for specific time intervals (e.g., from Year 1 to Year 2, etc.) along with 95% CIs for the proportions. Annualized relapse rate (ARR) will be analyzed using a negative binomial model, adjusted for appropriate prognostic factors, and time-to-sustained disease progression for at least six months will be analyzed using Kaplan-Meier estimates. In addition, Poisson regression models and Cox proportional hazard models might be applied to assess the association between ARR/time to sustained disability progression and certain demographic variables, baseline disease characteristics, or medical history variables of interest, respectively. All SAEs will be summarized by listing all standard terms of SAEs occurring during the study with counts and percentages. All AEs including FLS and ISRs will be summarized by listing all standard terms of AEs occurring during the study, along with counts and percentages. FLS scores will also be summarized using mean, standard deviation (SD), median, and maximum and minimum values. Longitudinal evaluation of PROs using a linear regression model may be performed to evaluate patients' long term experience (e.g., change over time).
Milestones:	Start of data collection: 03 December 2014 End of data collection: Q1 2022 (estimated) Study progress reports: Not applicable* Interim reports: Not applicable* Final report of study results: Within 12 months of last data collection (estimated to be June 2022) * No commitment by Biogen to provide study progress reports or interim progress reports to regulators is currently in place.

4. AMENDMENTS AND UPDATES

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect patient 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 patient. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

See Table 1 for a summary of significant amendments to the study protocol.

In the event of a protocol modification, the patient informed consent form (ICF) may require similar modifications (see Section 9.1 and Section 9.2).

Table 1: Changes to Protocol 105MS401

No.	Date	Protocol Section(s)	Amendment	Reason
1	18 Sep 2015	4.2, 7.2.4, 9.1	Version 2	Methods for collecting patient-reported outcomes were clarified to avoid confusion.
2	18 Sep 2015	7.1, 8.1, 9.1, 14.7	Version 2	Clarified that patients newly or currently prescribed Plegridy are eligible to be enrolled.
3	18 Sep 2015	13.2.1, 13.2.2, 13.2.4	Version 2	Clarified that AEs should be reported from the time the patient signs ICF.
4	18 Sep 2015	7.1, 8.1, 9.1, 14.7	Version 2	Clarified that "newly or currently prescribed" patients are eligible to be enrolled to avoid confusion as to whether patients must receive at least 1 dose of Plegridy.
5	18 Sep 2015	13.4.2	Version 2	Clarified that pregnancy in female partners of male patients in study will not be referred to Pregnancy Registry unless Physician becomes aware of unfavorable outcome (e.g., congenital anomaly).
6	18 Sep 2015	12.2, 12.7	Version 2	Clarified that FLS-VAS need not be completed for patients without flu-like symptoms.
7	18 Sep 2015	12.2	Version 2	Clarified that assessments and procedures conducted while patients are enrolled in the study should be as per local guidelines and label, not one or the other.
8	02 Feb 2016	7.1	Version 3	Total number of sites decreased from approximately 300 to 160 sites in the US, EU, and sites participating in Study 105MS302 (ATTAIN) or 105MS303 (ALLOW) in other countries.
9	02 Feb 2016	7.1	Version 3	Duration of patient enrollment revised from 36 months to 33 months with last patient in by July 2017.
10	02 Feb 2016	7.1, 14.7	Version 3	Study sample size reduced from approximately 3000 to 1600 patients.
11	02 Feb 2016	14.6	Version 3	First interim analysis changed from after 500 patients complete 1 year of follow-up to after at least 250 patients complete 1 year of follow-up.
12	05 Mar 2019	All sections	Version 4	Protocol migrated into EMA-compliant PASS template, which involved reorganization of section headings without major revision of associated text. Substantive changes are described below.
13	05 Mar 2019	8.1, 8.6.7	Version 4	Study sample size was reduced from 1600 to 1100 patients, and the enrollment period was reduced from 33 to 27 months. A Protocol Clarification Letter was sent to all study sites in January 2017 officially notifying them to stop enrollment into the study.
14	05 Mar 2019	15.1	Version 4	Pen/syringe collection was discontinued. Official notification of Pen Collection Program discontinuation was provided to all sites in March 2016.
15	16 Apr 2019	13, 14, 15	Version 5	New Section 13 added to incorporate signature page for Prescribing Physician; existing Sections 13-15 were renumbered to Sections 14-16. Version and date information was updated.

AE = adverse event; EMA = European Medicines Agency; EU = European Union; FLS-VAS = flu-like symptoms visual analog scale; ICF = Informed Consent Form; PASS = post-authorization safety study; US = United States.

5. MILESTONES

Table 2: Milestones for Protocol 105MS401

Milestone	Planned Date
Start of data collection	03 December 2014
End of data collection	Q1 2022 (estimated)
Study progress reports	No commitment by Biogen to provide study progress reports to regulators is currently in place.
Interim report(s) of study result	No commitment by Biogen to provide interim study results to regulators is currently in place.
Registration in EU PAS register	January 2019
Final report of study results	Within 12 months of last data collection (estimated to be June 2022).

6. RATIONALE AND BACKGROUND

6.1. Introduction

Plegridy (peginterferon β-1a) is a disease modifying therapy indicated to treat patients with RMS that is administered via SC injection using a pre-filled syringe or pre-filled pen at the recommended dose and frequency in the local label.

The pharmacological properties of Plegridy are consistent with those of non-pegylated IFN β-1a. A definitive mechanism of action of Plegridy in MS is not known. However, the biological effects are consistent with those of non-pegylated IFN β-1a and the mechanism of action is likely to be similar. Plegridy binds to the type 1 IFN receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of IFN-responsive gene expression. These genes, and their gene products, are believed to mediate the efficacy of Plegridy in MS.

As an IFN β, Plegridy modulates immune responses that are believed to play a role in the pathogenesis of MS. While the pathogenesis of the disease is complex and multifaceted, Plegridy may act at several levels, including up-regulation of anti-inflammatory cytokines (e.g., interleukin [IL]-4, IL-10, IL-27), down-regulation of pro-inflammatory cytokines (e.g., IL-2, IL-12, IFN-γ, tumor necrosis factor-alpha), and inhibition of the migration of activated T cells across the blood-brain barrier; however, additional mechanisms have been proposed.

6.2. Profile of Previous Experience

6.2.1. Nonclinical Experience With Plegridy

The nonclinical toxicity testing of Plegridy showed that Plegridy is well tolerated and has identified effects consistent with the known clinical experience with type I IFNs. In a 5-week, repeat-dose toxicology study in rhesus monkeys, no adverse effects were observed at doses up to 100 μg/kg per week. The no-observed-adverse-effect-level provides an approximately 500-fold safety margin over the Phase 3 dose (125 μg) based on a comparison of single dose exposures (AUC_{168h}) between rhesus monkeys and humans. In a 5-week, repeat-dose, hormone study in rhesus monkeys, mild and reversible effects on menstrual cyclicity and serum 17-beta estradiol and progesterone levels were observed at the highest dose tested, 125 μg/kg per wk. Plegridy is unlikely to be carcinogenic in view of the clinical experience with Avonex: IFNs as a class have not been shown to be mutagenic, and pegylation is not expected to alter its genotoxic potential.

6.2.2. Clinical Experience With Plegridy

One year results from a pivotal Phase III, global, multicenter, randomized, double-blind, parallel-group, placebo-controlled study (Study 105MS301, 1 year) in relapsing-remitting MS patients with the aim of determining the safety and efficacy of Plegridy have been reported [Deykin 2014]. When compared with placebo, subcutaneously injected Plegridy

every two or four weeks reduced the ARR by 36% and 28%, respectively; the risk of relapse by 39% and 26%, respectively; and the number of new or newly enlarging thoracic spinal nerve 2 (T2) lesions by 67% and 28%, respectively.

Identified and Potential Risks

The most commonly reported adverse drug reactions observed in the pivotal Phase III study (reported in at least 10% of patients treated with Plegridy, and more frequently compared to placebo) were injection site erythema, influenza like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia.

A higher incidence of influenza-like illness was reported in patients receiving Plegridy every two weeks than those receiving placebo (47% vs. 13%), and the highest incidence of FLS (e.g., influenza-like illness, chills, hyperpyrexia, musculoskeletal pain, myalgia, pain, pyrexia) was reported during Plegridy treatment initiation with a gradual decrease in incidence over the first six months. The majority of patients with FLS (90%) reported FLS as mild to moderate in severity; none were considered serious in nature. Less than 1% of patients who received Plegridy compared to placebo discontinued treatment due to FLS.

ISRs (e.g., injection site erythema, pain, pruritus, or edema) were reported by 66% of patients who received Plegridy every two weeks compared to 11% of patients receiving placebo. Injection site erythema was the most commonly reported ISR. Of the patients who experienced ISRs, 96% reported them as mild or moderate in severity. One patient out of 1468 patients who received Plegridy in clinical studies experienced an injection site necrosis which resolved with standard medical treatment.

In addition to the events observed during clinical development described above, exposure to IFN β in general has been associated with hepatic injury, depression and suicidal ideation, seizures, worsening of cardiac disease and decreased peripheral blood counts, and monitoring is advised for patients, particularly those at increased risk for these events. Additional information may be found in the local labeling for Plegridy.

6.3. Study Rationale

IFN β-1a is a common first-line treatment for RMS and has been used successfully for over 15 years. Plegridy, in its pivotal Phase III study, demonstrated an efficacy and safety profile over two years similar to other IFN β therapies while being dosed less frequently. The profile of Plegridy combined with its dosing regimen may address some of the factors that lead to discontinuation, avoidance of therapy, or poor adherence seen with the shorter-acting IFN β therapies. However, knowledge gaps exist regarding the long-term safety and effectiveness of Plegridy in the real-world setting. Therefore, Biogen is conducting the Plegridy Observational Program (POP), a large prospective, observational, longitudinal study that will monitor the long-term safety, effectiveness, and HRQoL associated with Plegridy in persons with MS in the real-world setting. Of particular interest are evaluations of the tolerability and incidence of FLS and ISRs, the long-term safety profile of Plegridy, the

effectiveness of Plegridy on measures of MS disease activity (relapse activity and disability progression), and the effect of Plegridy on PROs.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Research Question

The purpose of this study is to better characterize the long-term benefit-risk profile of Plegridy in patients with MS who are prescribed Plegridy under routine clinical care.

7.2. Primary Objective

The primary objectives of the study are as follows:

- To determine the incidence of SAEs in patients with RMS in routine clinical practice; and
- To assess the overall long-term clinical effectiveness of Plegridy in patients with RMS in routine clinical practice.

7.3. Secondary Objectives

The secondary objectives of this study are as follows:

- To determine Plegridy prescription and utilization adherence patterns in routine clinical practice;
- To assess the specific long-term clinical effectiveness of Plegridy in patients with RMS in routine clinical practice;
- To monitor the safety and tolerability of Plegridy in routine clinical practice by assessing the incidence of AEs of FLS, ISRs, and AEs (including laboratory abnormalities) leading to treatment discontinuation;
- To assess the effect of FLS on patient-reported effectiveness of and satisfaction with prophylactic management using a FLS-VAS; and
- To evaluate the change in HRQoL, FLS, FLS-VAS, healthcare resource consumption, and treatment adherence over time.

8. RESEARCH METHODS

8.1. Study Design

POP is a prospective, global, observational study designed to provide long-term effectiveness and safety data in patients with RMS who have been prescribed Plegridy in routine clinical practice.

Plegridy will not be supplied for this study. The study will collect data in an observational manner from patients who are prescribed Plegridy by physicians, according to the approved label in the respective country.

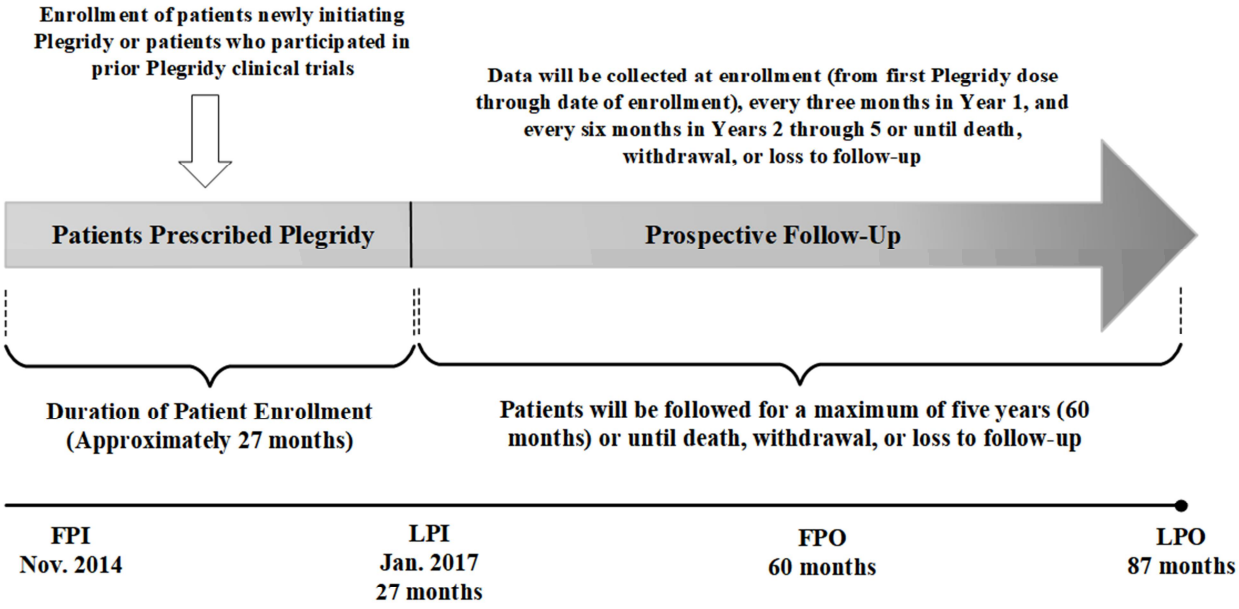
Based on Version 3.0 of this protocol, dated 02 February 2016, enrollment was to be continued until July 2017, when approximately 1600 patients with RMS who are newly or currently prescribed treatment with Plegridy were planned to be enrolled. Approximately 160 sites in multiple regions, including the US, the EU, Australia, and sites participating in Study 105MS302 or 105MS303 in other countries, were to participate. Enrollment was to be competitive to provide for the highest likelihood of enrolling the targeted number of patients in a 33-month period. In January 2017, following a decision by Biogen to limit enrollment to approximately 1100 patients, a Protocol Clarification Letter was sent to all study sites providing official notification that enrollment into the study should be stopped. Enrollment was ended in January 2017 after a 27-month period.

Patients are to be followed (regardless of discontinuation of Plegridy) for a maximum of 60 months or until death, withdrawal from study, or loss of follow-up, whichever occurs first. Data are to be collected at baseline and every three months during the first year of follow-up, then every six months in Year 2 through Year 5.

The POP is a prospective observational study designed with the potential to combine with other similar longitudinal studies of MS. While no such cross-study analysis has been undertaken to date, the POP will provide an additional complementary and supplementary data-set to bolster future studies of MS and its treatment options.

Figure 1 below presents a schematic of the prospective observational study of patients with RMS prescribed Plegridy.

Figure 1: Study Design



FPI = First Patient In; LPI = Last Patient In; FPO = First Patient Out; LPO = Last Patient Out

8.1.1. Primary Endpoints

Safety of Plegridy will be evaluated by assessment of the incidence proportion and incidence rate of SAEs.

Effectiveness of Plegridy on cNEDA will be evaluated by assessment of the proportion of patients with no relapses and no disability progression.

8.1.2. Secondary Endpoints

Secondary endpoints will address non-serious AEs of special interest and other clinical effectiveness and non-safety related objectives as follows:

- Plegridy prescription and utilization patterns will be evaluated by assessment of prescribed dosing frequency, duration of Plegridy use, and primary reason for discontinuation of Plegridy (see Section 8.3.3 "MS Treatments and Concomitant Medications").
- Effectiveness of Plegridy on specific MS clinical disease activity will be evaluated by assessment of relapse-related endpoints (e.g., ARR, time-to-first relapse, proportion of patients with relapse, and distribution of number of relapses and disability progression-related endpoints based on the EDSS (e.g., proportion of patients with progression and time-to-sustained progression for at least six months).

- Safety and tolerability of Plegridy will be assessed by the incidence proportion and incidence rates of non-serious AEs, including but not limited to FLS, ISRs, and AEs (including laboratory abnormalities) leading to treatment discontinuation.
- The impact of the severity of FLS on the ability to successfully manage symptoms via prophylaxis will be evaluated using the patient-reported FLS-VAS.
- Changes in FLS assessment and FLS-VAS over time.
- Changes in HRQoL measures will be evaluated over time using the EQ-5D-3L.
- Healthcare resource consumption will be evaluated by assessment of endpoints such as MS-related and non-MS-related physician visits, specialists' visits, use of physiotherapy, hospitalizations and lengths of stay, and emergency room (ER)/department visits.
- Patient-reported treatment adherence to Plegridy will be assessed using the Treatment Adherence Questionnaire for all patients.

[redacted]

8.2. Setting

8.2.1. Inclusion Criteria

To be eligible to participate in this study, patients must meet the following eligibility criteria at the time of enrollment:

1. Patient and or legal representative is willing and able 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 patient privacy regulations.
2. Patient with MS who is newly, or is currently, prescribed Plegridy according to local label including patients who participated in Study 105MS302 or Study 105MS303.
3. Patient age 18 years or older.
4. Patient willing and able to complete PROs with minimal assistance.

8.2.2. Exclusion Criteria

Patients will be excluded from study entry if the following exclusion criterion exists at the time of enrollment:

1. Concurrent enrollment in any clinical trial of an investigational product. Participation in non-interventional study can be allowed as long as this

participation does not interfere with this protocol or is likely to affect the patient's ability to comply with the protocol.

8.2.3. Study Location

Global study including approximately 160 sites in the US, the EU, Australia, and sites participating in Study 105MS302 or Study 105MS303 in other countries.

8.2.4. Overall Study Duration and Follow-Up

The study period will consist of enrollment and a follow-up period. Patient participation in the study will be for up to five years (60 months) from enrollment. The planned duration of the study is approximately seven years (87 months), which includes over two years (27 months) for patient enrollment and a maximum of five years (60 months) of follow-up per patient. Patients will be followed for up to five years or until death, withdrawal, or loss of follow-up, whichever occurs first. Follow-up is planned regardless of whether patients discontinue treatment with Plegridy.

8.2.4.1. Enrollment

Patients must be consented before any data are collected. At the time of consent, the patient will be enrolled into the study. Participating study sites are required to enroll eligible patients consecutively into this study. If an eligible patient was approached and does not participate in the study, the reason for nonparticipation will be documented in the enrollment log.

Physicians who are routinely involved in the care and treatment of patients with MS will be targeted for recruitment. Efforts will be made to recruit a variety of Prescribing Physicians who are representative of Plegridy prescribers. Site selection criteria will include the projected availability of eligible patients in a 12 month enrollment period and the availability of time for the physician (and other site staff) to complete the electronic case report forms (eCRFs). To the extent possible, representative sites reflective of the treatment patterns within each country will be recruited. Selection criteria and basic site information (e.g., site size, investigator specialty, site type) will be collected via a site qualification questionnaire.

Patients with MS who are newly or currently prescribed Plegridy under routine clinical practice, and according to the local label, or who were previously participating in Study 105MS302 or Study 105MS303 are eligible to participate in this study and will be enrolled at the time of presentation of a routine clinic visit. No clinic visits are required as part of participation in this study. All clinical assessments are intended to be performed at the time of a routine clinical encounter or by referencing the medical record. PROs will be completed by patients either electronically or on paper. Electronic PROs can be accessed via a secure, personalized link either at the time of a routine clinic visit or outside of the clinic within four weeks of the visit. PROs can be completed on paper at the time of a routine clinic visit and responses will be subject to electronic data capture (EDC) by the site. If patients do not complete the PROs during their routine clinic visit, they can complete the PROs electronically through the secure, personalized link within four weeks of their routine clinic visit.

Eligible patients may be naïve to Plegridy at the time of enrollment, but need not be naïve to other MS treatments, and must not currently be enrolled in any other clinical trial of an investigational product, unless according to the study Medical Director it does not conflict with the observational study (e.g., health economic studies). Patients with previous exposure to Plegridy will be evaluated separately from patients who are newly prescribed Plegridy because prevalent Plegridy-users may be more or less likely to experience AEs, may fail to report AEs that occurred before study enrollment, or may have discontinued Plegridy treatment due to an AE. Patients participating in other clinical studies are excluded so as not to unduly confound causality assessments when the safety profile of a concomitant experiment agent has yet to be established and/or the physician is blinded to the patient's treatment assignment.

The decision to enroll a patient in this study must not be made until after the Prescribing Physician and patient decide to begin Plegridy treatment and Plegridy treatment has been prescribed. Patients (or their legally authorized representative) agreeing to participate in the study will read and sign the informed consent and confidentiality statements. Enrollment data will be collected by the Prescribing Physician at the routine clinical visit at which Plegridy is first prescribed. For patients with previous exposure to Plegridy prior to enrollment, data will be collected from the time of first dose of Plegridy through enrollment in this or previous studies (see Section 8.3.1 for details). During enrollment, the Prescribing Physician will also inform female patients of childbearing potential if a pregnancy registry is being conducted independently of this observational study.

8.2.4.2. Registration of Patients

A patient will be registered at the time of enrollment after the patient (or legally authorized representative) signs the informed consent and after the Prescribing Physician has verified that the patient is eligible per criteria in Section 8.2.1 and Section 8.2.2. No data may be collected prior to registration and assignment of a unique patient identification number. Any patient identification numbers that are assigned will not be reused even if the patient does not receive Plegridy treatment.

An individual patient may only be included once in the study. Patients who prematurely withdraw from the study for any reason will not be eligible to re-enroll.

Patients who withdraw from the study will not be replaced.

Refer to the Study Reference Manual for details on registration.

8.2.4.3. Screening

No specified screening procedures are to be conducted to determine eligibility as screening is not applicable to this observational study.

8.2.4.4. Treatment

Plegridy will be prescribed to patients by their Prescribing Physician under routine clinical practice according to the indication and dosing regimen in the local package insert.

This is an observational study of real-world treatment practices and long-term effectiveness and safety in this population of patients with RMS. This protocol does not recommend the use of any specific treatments. No study medication is provided as a result of participation.

Patients who discontinue treatment with Plegridy will continue to be followed for the duration of the study or until death, withdrawal, or until they are lost to follow-up. The Prescribing Physician will record the primary reason for Plegridy discontinuation, if applicable. Information will be collected at the time of a routine clinical visit following Table 4 and as described in Section 8.3 through 30 days after last dose.

It should be noted that patients who discontinue treatment with Plegridy should continue to be followed in the study. These patients are allowed to restart Plegridy at any time during the study. Once a patient has restarted Plegridy, the information collected should follow Table 4 and as described in Section 8.3.3.

8.2.4.5. Post-Treatment

For patients who discontinue treatment with Plegridy, all follow-up visits will be conducted according to local clinical practice. Patients' participation in the study is independent of potential stopping treatment with Plegridy. Analysis of this patient data will be part of the exploratory analysis.

8.2.4.6. Concomitant Medications

A concomitant medication is any drug or substance administered after the first recorded dose of Plegridy.

As a long-term, observational study to evaluate effectiveness and safety in patients treated in the postmarketing setting, no restrictions on concomitant medications are associated with this study.

All concomitant medications will be recorded in the patient's eCRF according to instructions for eCRF completion. Concomitant medications will be recorded at baseline and at each data collection period until the end of follow-up in order to evaluate their potential influence on the outcomes of interest.

8.2.4.7. Long-Term Follow-Up

After enrollment, the Prescribing Physician will collect patient information during routine clinical visits as described in Section 8.3. For the purposes of this study, routine clinical visits are defined as any visit scheduled per local standard of care. The collected information for each patient will be sent to the CRO managing the study (IQVIA, see Section 8.5) through the EDC system at baseline, approximately every three months (± four weeks) for the first year of follow-up and approximately every six months (± four weeks) for Year 2 through Year 5 of follow-up after enrollment. If the CRO does not receive completed data from the physician on a patient for whom follow-up is expected, the CRO will contact the site to remind them to complete the required data.

PROs may be completed by patients either electronically or on paper. PROs can be accessed electronically via a secure, personalized link either at the time of a routine clinic visit or outside of the clinic within four weeks of the routine visit. Alternatively, the PROs can be completed on paper at the time of a routine clinic visit. PROs will be collected at baseline (enrollment), approximately every three months for the first year of follow-up, and approximately every six months for Year 2 through Year 5 of follow-up after enrollment. If a patient does not complete the PROs during a routine clinic visit, the patient will be asked to complete the PROs within four weeks of each routine visit, if consistent with local regulations.

All information will be sent to the CRO electronically. The information received by the CRO will be stored in a secure database.

8.2.4.8. Non-initiation of Plegridy and Continued Participation in the Study

Consenting patients who are prescribed Plegridy, but do not take at least one dose of Plegridy after enrollment into the study, will continue to be followed for up to 60 months after enrollment, unless death, withdrawal, or loss to follow-up occurs.

Patients who do not initiate treatment with Plegridy can start Plegridy treatment as part of routine clinical practice at any time.

8.2.4.9. Discontinuation of Plegridy

Patients who discontinue treatment with Plegridy will continue to be followed for the duration of the study or until death, withdrawal, or until they are lost to follow-up. The Prescribing Physician will record the primary reason for Plegridy discontinuation, if applicable. Information will be collected at the time of a routine clinical visit following Table 4 and as described in Section 8.3.4 through 30 days after last dose.

It should be noted that patients who discontinue treatment with Plegridy should continue to be followed in the study. These patients are allowed to restart Plegridy at any time during the study. Once a patient has restarted Plegridy, the information collected should follow Table 4 and as described in Section 8.3.3.

8.2.4.10. Withdrawal of Subjects from the Study

Patients must be withdrawn from the study for either of the following reasons:

- The patient withdraws consent.
- The patient is unwilling or unable to comply with the protocol.

The reason for the patient's withdrawal from the study must be recorded in the patient's eCRF.

8.2.4.11. Premature Withdrawal From Study

Patients may withdraw consent to participate in the study at any time with no effect on their medical care or access to treatment. If a patient is withdrawn prior to completing the study follow-up period, any known reason for withdrawal should be documented in the eCRF. All information already collected as part of the study will be retained for the

analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

8.2.4.12. Lost to Follow-Up

If a patient has not been in contact with the Prescribing Physician for 12 months following his or her last routine visit, the site will contact the patient by telephone to assess the patient's interest in continuing study participation. If the site is unable to contact the patient, a follow-up attempt must be made. A site may consider a patient lost to follow-up after three failed and documented contact attempts. If a patient's status is determined to be lost to follow-up, this must be recorded on the eCRF. If a physician ascertains a patient has died, the death should be recorded and reported as described in Section 10.2.4.1.

8.2.4.13. Subject Transfers

In the event that a patient wishes to transfer to a different physician, Biogen will attempt to find another site at which the patient can continue to participate in the study. If the patient continues care with a physician who is not participating in the POP study, Biogen may choose to include the new site in the observational study program, if feasible.

8.2.4.14. Study Stopping Rules

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

8.2.4.15. End of Study

The end of study is last patient, last visit for final collection of data for the primary outcome. The end of study will occur a maximum of five years (60 months) after the last patient is enrolled into the study.

8.2.5. Description of Source Population (new subheading)

The source population for this study includes patients with MS who are newly or currently prescribed Plegridy under routine clinical practice, and according to the local label, or who were previously participating in Study 105MS302 or Study 105MS303.

8.3. Variables

8.3.1. Site and Prescribing Physician Characteristics

The following data will be collected from the site and Prescribing Physician:

- Site characteristics (e.g., community or academic/institutional center, size, geography)
- Prescribing Physician characteristics (e.g., specialty, years in practice, current EDSS certification)

Refer to Section 16 for the timing of assessments.

Refer to the Study Reference Manual for details regarding EDSS certification.

8.3.2. Demographics, Baseline Disease Characteristics, and Treatment History

The following data will be collected at baseline for all enrolled patients:

- Documentation of signed informed consent.
- Demographic: age at enrollment (years), sex, race (where allowed by local regulation).
- Relevant medical history and co-morbidities: assessment of clinically significant medical and surgical history and concomitant diseases, and known cardiovascular risk factors (e.g., smoking, alcohol consumption, patient and family history of high cholesterol, high blood pressure, cardiac disease, peripheral artery disease, arrhythmia, cerebrovascular disease, and diabetes mellitus).
- MS disease history (type of MS, relapse history, and the latest EDSS score based on last neurologic examination conducted prior to enrollment) and the results of the latest brain MRI scan, which may include lesion count (if available).
- Prior use and duration of therapies for MS (if any; e.g., start and stop dates, initial dose, dose reductions or escalations, prescribed dosing frequency, reason for discontinuation).
- Prior use and duration of immunomodulatory, immunosuppressive (including corticosteroids), and anti-neoplastic agents (if any; e.g., start and stop dates, initial dose, dose reductions or escalations, prescribed dosing frequency, reason for discontinuation).
- Prior use and duration of all other concomitant medications (e.g., start and stop dates, initial dose, dose reductions or escalations, prescribed dosing frequency, reason for discontinuation).
- History of FLS on previous IFN therapy (e.g., history of chills, body aches, pyrexia, myalgia, or muscle aches).
- Ambulation status at time of initiating Plegridy.
- MRI results (e.g., lesion counts), if available.
- CBC with differential, if consistent with routine clinical practice and local regulations.
- Other laboratory tests recommended in local label (e.g., liver and renal function tests, urinalysis) if consistent with routine clinical practice and local regulations.
- Concomitant use (i.e., at enrollment) of immunomodulatory, immunosuppressive (including corticosteroids), and anti-neoplastic agents, and other approved MS therapies (if any).
- Concomitant use (i.e., at enrollment) of non-MS therapy medications (if any).

- EDSS information (including Functional System Scores and Ambulation scores), based on neurological examination at enrollment, when collected as part of routine clinical practice (i.e., not specifically performed for the study).
- Neurologic assessment (as per local practice and regulation) if EDSS is not used in routine clinical practice.
- [redacted]
- Patient assessment of the following outcome measures, if consistent with local regulations:
    - EQ-5D-3L: Refer to Section 16.2 , Appendix 1.
    - FLS Assessment: Refer to, Appendix 2.
    - Healthcare resource consumption questionnaire: Refer to Section 16.4, Appendix 3.
    - Treatment adherence questionnaire: Refer to Section 16.5 and Section 16.6, Appendices 4 and 5.
    - FLS-VAS*: Refer to Section 16.7, Appendix 6.
    - [redacted]

    ** Note: If a patient selects "Absent" for Question 1 of the FLS Assessment, then the FLS-VAS does not need to be completed for that patient.*
- Pregnancy status (female patients)
- Nursing status (female patients)
- Participant of Study 105MS302 or Study 105MS303.

Refer to Section 16.1 for the timing of assessments.

8.3.3. MS Treatments and Concomitant Medications

- Plegridy prescription information, including prescribed dose, dosing frequency, start and stop dates, reason for discontinuation (if applicable).
- Use of all concomitant medications (e.g., prescription information, including prescribed dose, dosing frequency, start and stop dates, reason for discontinuation [if applicable]) during follow up.

Refer to Section 16.1 for the timing of assessments.

8.3.4. Laboratory Assessments

The following laboratory assessments will be collected, if performed consistent with routine clinical practice:

- CBC with differential

- Other laboratory tests recommended in local label (e.g., liver and renal function tests, urinalysis)

Refer to Section 16.1 for the timing of assessments.

8.3.5. Safety

The following assessments will be collected to evaluate the safety of Plegridy:

- SAEs
- AEs of special interest
  - FLS (e.g., chills, body aches, pyrexia, myalgia, or muscle aches)
  - ISRs (e.g., injection site erythema, pain, pruritus, or edema)
- AEs, including laboratory abnormalities, leading to treatment discontinuation

Refer to Section 16.1 for the timing of assessments.

8.3.6. Effectiveness

The following clinical tests/assessments will be collected to evaluate the effectiveness of Plegridy, if performed under routine clinical practice:

- MS relapse information (e.g., date of onset, date of visit, neurologic examination, duration, new and/or recurrent neurologic symptoms, hospitalization, treatments including steroids), if applicable. For the purposes of this study, relapse is defined as new or recurrent neurologic symptoms not associated with fever, lasting at least 24 hours. New or recurrent neurologic symptoms that evolve gradually over months are to be considered disease progression, not an acute relapse. New or recurrent neurological symptoms that occur fewer than 30 days following the onset of a relapse as defined above are to be considered part of the same relapse.
- EDSS information (including Functional System Scores and Ambulation scores), based on neurological examination, when collected as part of routine clinical practice (i.e. not specifically performed for the study).
- Neurologic assessment, if EDSS is not used in routine clinical practice.
- [redacted]
- [redacted]
- Details of MS-related hospitalizations (e.g., dates of admission and discharge, reason for admission)
- MRI results (e.g., lesion counts, new lesions/ no new lesions), if available
- Ambulation status during follow-up

Refer to Section 16.1 for the timing of assessments.

8.3.7. Patient-Reported and Health Economics Outcomes

Patient assessment of the following outcome measures will be collected, if consistent with local regulations:

- Impression of functional health and well-being using the EQ-5D-3L index score and the five individual component scores. Refer to Section 16.2, Appendix 1.
- FLS Assessment: Patients will assign a score from "0" to "3" to their muscle aches, chills, fatigue, and body temperature as follows: "0" for absent; "1" for mild, did not interfere with daily activities; "2" for moderate, sufficient to interfere with daily activities; and "3" for severe, bed rest required. Refer to Section 16.3, Appendix 2.

  FLS-VAS: This patient-reported assessment includes two VAS ratings and will be performed to evaluate any prophylactic regimen such as acetaminophen, ibuprofen, aspirin, or naproxen used to alleviate FLS. The first VAS will assess the effectiveness of the prophylactic regimen used by the patient to control FLS. Patients will rate their prophylactic regimen to control FLS between "not effective" to "very effective". The second VAS will evaluate the patient's satisfaction with the effectiveness of the prescribed regimen to control FLS. Patients will rate their satisfaction from "not satisfied" to "very satisfied." Refer to Section 16.7 , Appendix 6.

  Note: If a patient selects "Absent" for Question 1 of the FLS Assessment, then the FLS-VAS does not need to be completed for that patient.
- Healthcare resource consumption questionnaire: This patient-reported questionnaire will ask patients to report the frequency of MS-related, non-MS-related, relapse-related hospitalizations, MS-related neurological visits, MS-related ER visits, and visits to other health care professionals for MS-related and other reasons. Refer to Section 16.4, Appendix 3.
- Treatment adherence questionnaire: This is a patient-reported questionnaire that measures adherence to Plegridy treatment in the past 28 days, the number of missed injections, and reasons for discontinuation, if applicable. Refer to Section 16.5 and Section 16.6, Appendices 4 and 5.

Refer to Section 16.1 for the timing of assessments.

8.4. Data Sources

Except for instances where patient reported outcomes are entered directly into the EDC system by the patient, all data entered into the EDC system should be supported by source documentation maintained within the clinical site records.

8.5. Data Management

A CRO (IQVIA; Danbury, CT and Research Triangle Park, NC) will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports and data management. Before patients are

enrolled at each study site, the CRO will review study responsibilities with the Prescribing Physicians and other study site staff, as appropriate.

Patient information will be captured and managed by study sites on eCRFs by a web-based EDC tool developed and supported by IQVIA. All data will be collected and entered directly into IQVIA's EDC system. All participating sites will have access to the data entered regarding the individual site's own enrolled patients. All sites will be fully trained on using the EDC system, including eCRF completion guidelines and help files. Sites will be responsible for entering extracted patient data into a secure Internet-based EDC registry database via the eCRF. Investigators and site personnel will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. The eCRF should be reviewed, electronically signed, and dated by the Principal Investigator or designee. All changes or corrections to eCRFs should be documented in an audit trail and an adequate explanation required.

8.6. Data Analysis

8.6.1. Description of Objectives

8.6.1.1. Primary Objective

The primary objective is described in Section 7.2.

8.6.1.2. Secondary Objectives

The secondary objectives are described in Section 7.3.

8.6.2. Description of Endpoints

8.6.2.1. Primary Endpoint

The primary endpoints are described in Section 8.1.1.

8.6.2.2. Secondary Endpoints

The secondary endpoints are described in Section 8.1.2.

[redacted]

8.6.3. Demography and Baseline Disease Characteristics

Demographic and baseline disease characteristics will be summarized overall. The demographic profile (age, sex, and race [where legally allowed]), relevant medical history, MS disease history, MS treatment prior to start of Plegridy, and concomitant medications and therapies used will be listed and summarized using appropriate descriptive statistics for categorical and continuous variables. Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using mean, SD, median, and maximum and minimum values. Two-sided

95% CIs will be used. In general, categorical data will be summarized using frequency and percentage, and continuous variables will be summarized using descriptive statistics (number, mean, SD, median, minimum, and maximum). For continuous variables, if the data are approximately normally distributed, then a 95% CI for the mean change will be calculated. If the data are not normally distributed, then the interquartile range will be presented with the median. All analyses will be conducted using a two-sided test and a significance level of 0.05. Due to the inherent differences in Plegridy-naïve patients and those who had exposure to Plegridy prior to study enrollment, analyses will be conducted separately for these two groups. The definition of Plegridy-naïve will be described in the SAP.

8.6.4. Safety

8.6.4.1. Analysis Population

Statistical analyses will be based on all patients who enroll in the study (defined as having an available date of informed consent) and receive at least one within-study dose of Plegridy. Safety analyses will be conducted separately between Plegridy-naïve patients and those who had exposure to Plegridy prior to study enrollment. The definitions will be further described in the SAP.

8.6.4.2. Methods of Analysis

The incidence and incidence rate of all reported SAEs and AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Incidence is defined as the proportion of patients with a given event out of the number of patients in the analysis population. Incidence rate is defined as the number of patients with a given event adjusted for the duration of follow-up for the particular event (e.g., incidence rate per 100,000 per years). Ninety-five percent CIs for incidence and incidence-rate point estimates will be calculated using the binomial distribution and the Poisson distribution, respectively.

Incidence of SAEs and AEs will be stratified by event severity and by relationship to treatment with Plegridy. AEs leading to discontinuation of Plegridy will be summarized separately. Analyses of SAEs and AEs may also be described by characteristics of the sites, Prescribing Physicians, and/or patient subgroups defined by appropriate demographic and/or baseline prognostic factors, and/or concomitant medication exposure (e.g., concomitant MS therapies). Analyses may also be stratified by duration of Plegridy treatment or study duration. Specific subgroup analyses will be described in the SAP.

8.6.5. Effectiveness

8.6.5.1. Analysis Population

The population for analysis includes all enrolled patients with informed consent who meet the eligibility criteria and receive at least one within-study dose of Plegridy.

8.6.5.2. General Methods of Analysis

All computations and generation of tables, listings, and data for figures will be performed using SAS® version 9.3 or higher (SAS Institute; Cary, NC).

The SAP will be fully described in a written and approved document. In general, descriptive analyses will be performed to gain a better understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Categorical variables will be summarized as number and proportion of the total study population and by subgroups where appropriate. Continuous variables will be reported as mean (and SD) or median and range, where appropriate. Additional exploratory analyses may be performed and will be outlined in the SAP prior to analysis.

Full details on handling of all missing data, which are common in observational studies, will be described separately in the SAP. In general, missing data will not be imputed and the data will be analyzed as they are recorded in the eCRFs. However, if more than 10% of data is missing for one or more key variables, the impact of missing data on the analysis will be discussed, and the pattern of missing data will be explored.

8.6.5.3. Primary Endpoint Analysis

cNEDA will be assessed by the proportion of patients free from measured clinical disease activity (no relapses and no disability progression) and will be summarized over time (e.g., baseline to year 1, baseline to year 2, etc.) as well as from specific time intervals (e.g., from year 1 to year 2, etc.) along with 95% CIs for the proportion.

Analyses of cNEDA may also be described by characteristics of the sites, Prescribing Physicians and among patient subgroups defined by appropriate demographic and/or baseline disease characteristics and prognostic factors. Specific subgroup analyses will be described in the SAP.

8.6.5.4. Secondary Endpoints Analysis

Plegridy prescription and utilization

Duration of Plegridy use and prescribed dosing frequency will be summarized both descriptively and categorically, as appropriate. Primary reasons for discontinuation of Plegridy will be tabulated. Plegridy use will also be described by concomitant medications.

Clinical disease activity (relapse activity and disability progression)

Relapse activity will be assessed by evaluating by relapse-related endpoints. These analyses will include the following parameters:

- ARR: defined as the total number of relapses divided by the number of patient-years on study divided by 12 months.
- Time to first relapse: defined as time (in days) between the date of initiating Plegridy to date of onset of first relapse following Plegridy initiation. Please refer to Section 8.3.6 for the definition of relapse.

- Proportion of patients with relapse: The proportion of patients with relapse will be described by counts and percent.
- Distribution of the number of relapses: The distribution of the number of relapses will be summarized using mean (SD) and median (minimum and maximum).

Disability progression will be assessed by evaluating disability progression-related endpoints. These analyses will include the following parameters:

- Proportion of patients with sustained progression for at least six months. For the purposes of this study, progression is defined as at least a 1.0 point increase from baseline in EDSS ≥1.0 or at least a 1.5 point increase from a baseline EDSS = 0.
- Time to sustained progression for at least six months.

ARR will be analyzed using a negative binomial model, adjusted for appropriate prognostic factors. If the data are under-dispersed or if the negative binomial regression model does not converge, a Poisson regression model with the same covariates will be used instead. Time to sustained progression will be analyzed using Kaplan-Meier estimates.

In addition, Poisson regression model and Cox proportional hazard model might be applied to assess the association between certain demographic variables, baseline disease characteristics, or medical history variables of interest and ARR/time to sustained disability progression, respectively.

Analyses of relapse activity and disability progression endpoints may also be described by characteristics of the sites, Prescribing Physicians and among patient subgroups defined by appropriate demographic and/or baseline disease characteristics, or prognostics factors (e.g., baseline EDSS score). Specific subgroup analyses will be described in the SAP.

Patient-Reported and Health Economic Outcomes

Summary statistics over time, as well as changes from baseline over time, will be presented for the following outcome measures:

- EQ-5D-3L index score, as well as five individual component scores.
- FLS Assessment: The total FLS score (sum of the four symptom scores and fever score) for all of the time points will be calculated. At each assessment time point, the maximum total FLS score that one patient may have is 12 points and the minimum is 0. A total score of two points or higher above the baseline score will be considered positive for the presence of FLS.
- FLS-VAS: The patient-reported FLS-VAS effectiveness of and satisfaction with prophylactic regimens to control FLS ratings will be summarized by mean (SD) and median (maximum and minimum) overall.
- Healthcare Resource Consumption Questionnaire: The number of hospitalizations (MS-related, non-MS-related, relapse-related, resulting in steroid use), MS-related ER visits, MS-related neurologist visits, visits to other healthcare professionals for

MS-related and other reasons will be summarized over time with frequency distribution and/or descriptive statistics.

- Treatment Adherence Questionnaire: The proportion of patients who report taking the recommended dose of Plegridy and prescribed dosing frequency will be summarized both descriptively and categorically, as appropriate. Primary reasons for discontinuation of Plegridy will be tabulated.
- [redacted]

Longitudinal evaluation of continuously measured secondary endpoints (e.g., EQ-5D-3L and FLS) may be performed using a linear regression model to evaluate the long term experience (e.g. change over time) of patients regarding these measures while on Plegridy. Categorical outcomes on healthcare resource consumption, treatment adherence, [redacted] and Plegridy prescription and utilization patterns will be summarized using frequencies and percentages. If necessary, a 95% CI based on binomial distribution might be provided for some of the categorical variables like patient adherence.

FLS-VAS includes the patients' ratings of effectiveness and satisfaction of controlling FLS with prophylactic regimens. The ratings will be summarized by mean (SD) and median (maximum and minimum). Changes of FLS-VAS ratings over time will also be summarized by mean (SD) and median (maximum and minimum). The changes of FLS-VAS ratings over time will be tested using a Wilcoxon rank-sum test. Longitudinal evaluation of FLS-VAS ratings using a linear regression model may be performed to evaluate patients' long-term experience (e.g., change over time) with the effectiveness and satisfaction of prophylactic regimens to control FLS while receiving Plegridy.

[redacted]

8.6.6. Interim Analyses

At a minimum, interim analyses are planned after at least 250 patients have completed one year of follow-up and annually thereafter.

Data from interim analyses will be submitted, at minimum, as abstracts to relevant congresses.

8.6.7. Sample Size Considerations

While no formal statistical hypotheses are being tested in this descriptive observational study, 1100 patients newly or currently prescribed with Plegridy are being targeted for enrollment. All patients will be followed for up to five years, and follow-up is planned regardless of whether patients discontinue treatment with Plegridy. Because this is a long-term observational program, a sample size of 1100 patients was chosen to ensure a reasonable likelihood of observing rare AE events over a 5-year period and to provide informative CIs for SAE incidence and incidence rate point estimates. Based on the withdrawal/discontinuation rates observed in the Plegridy Phase III clinical trial (Study

105MS301, 1-year) and prior Biogen observational studies, it is expected that approximately 3520–3960 person-years of follow-up will accrue.

With a sample size of 1100 patients, the probability of observing an event with an incidence rate of 0.10% (1/1000 persons) will be approximately 67%; the probability of observing an event with an incidence rate of 0.09% (90/100,000 persons, or 1/1111 persons) will be approximately 63%; the probability of observing an event with an incidence rate of 0.08% (80/100,000 persons, or 1/1250 persons) will be approximately 59%; and the probability of observing an event with an incidence rate of 0.054% (54/100,000 persons, or 1/1851 persons) will be approximately 48%.

For the co-primary endpoint of cNEDA, assuming a dropout rate up to 20%, a sample size of 1100 patients, and an expected 68.4% of patients free from clinical disease activity at the end of one year (Study 105MS301, 1-year), a two-sided 95% CI for the observed proportion of patients free from measured clinical disease activity at the end of one year using large sample normal approximation will extend 0.027 to 0.031 from the observed proportion for an expected proportion of 0.684.

8.7. Quality Control

A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented.

8.7.1. Study Site Initiation

The Prescribing Physician must not enroll any patients in this study prior to completion of a study initiation visit, conducted by Biogen or designee. During the site initiation visit, the monitor will provide training on the protocol and conduct of the study to the Prescribing Physician and all site staff involved in the study.

8.7.2. Quality Assurance

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

8.7.3. Monitoring of the Study

In order to ensure the integrity of the data, sites will be monitored. Site monitoring will be performed by IQVIA clinical research associates to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. The monitor will perform source data verification by review of original patient records.

The monitor will close out each site remotely after the last patient's final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures and frequency of monitoring

visits will be described in a Monitoring Plan. Monitor contact details for each participating site will be maintained in the Investigator Site File.

Biogen or its designee representatives and competent regulatory authorities may conduct onsite visits at the study facilities for the purpose of monitoring various aspects of the study, including all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data. The Prescribing Physician must agree to Biogen-authorized personnel having direct access to patient (or associated) files for the purpose of verifying entries made in the eCRF, and assist with their activities, if requested. Adequate space and time for monitoring visits should be made available by the Prescribing Physician or study staff. The site must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the study team.

8.7.4. 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 Prescribing Physician must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Prescribing Physician must notify Biogen of any changes in the archival arrangements including, but not limited to, archiving at an off-site facility or transfer of ownership if the Prescribing Physician leaves the site.

8.8. Limitations of the Research Methods

Additional confounders may not be fully captured in an observational study due to limitation of resources. Patient-reported outcomes are subject to information bias such as recall bias. Sites with smaller numbers of patients enrolled have fewer AE events reported, leading to seemingly decreased AE rates.

8.9. Other Aspects

8.9.1. 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, Prescribing Physician, and Biogen.

8.9.2. Publications

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

Any publication of the results from this study must be consistent with Biogen's publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors, updated April 2010 [International Committee of Medical Journal Editors 2010]. The rights of the Investigator and of

Biogen with regard to publication of the results of this study/registry are described in the Investigator contract.

All reporting will be consistent with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Initiative checklist for cohort studies [von Elm 2008].

9. PROTECTION OF HUMAN SUBJECTS

Biogen and the participating physicians must comply with this protocol and applicable International Conference on Harmonisation (ICH), Good Clinical Practices (GCP), and Good Pharmacovigilance Practices (GVP) guidelines and conduct the study according to local regulations. The patient's privacy; physical, mental, and social integrity; and the confidentiality of his or her personal information will be strictly respected in accordance with the World Medical Association Declaration of Helsinki.

The study will be conducted in compliance with the US Food and Drug Administration Title 21 Code of Federal Regulations Part 50 – Protection of Human Patients and/or Part 56 – Institutional Review Boards (IRBs); the ICH Good Clinical Practice guidelines (May 9, 1997) as they apply to postmarketing observational studies; the Declaration of Helsinki and its amendments; and the Health Insurance Portability and Accountability Act of 1996.

9.1. Institutional Review Board and Independent Ethics Committee

Participating physicians must obtain IRB or independent ethics committee (IEC) approval or favorable opinion, respectively, of the protocol, ICF, and other required study documents prior to starting the study, as required per local regulations. Patient enrollment will not start before Biogen has obtained written confirmation of an approval or favorable opinion from the relevant central or local IRB or IEC, as required per local regulations.

If the Prescribing Physician 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. Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB/IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the study in accordance with local regulations and requirements.

It is the responsibility of the Prescribing Physician to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations. It is the responsibility of the Prescribing Physician to have prospective approval of the study protocol, protocol amendments, and ICFs, and other relevant documents, if applicable, from their local IRB/IEC and provide documentation of approval to the CRO. All correspondence should be retained in the Investigator File.

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 investigational site must submit a close-out letter to the ethics committee and Biogen. Should the study be terminated for

any unanticipated reason, the Prescribing Physician will be responsible for informing the IRB/IEC of the early termination.

9.2. Subject Information and Consent

Prior to any data collection under this protocol, written informed consent with the approved ICF must be obtained from the patient or patient's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all patients participating in a clinical study conducted by Biogen.

Information about the study and the voluntary nature of participation must be explained to the patient, if applicable. The patient must be given sufficient time to consider whether to participate in the study. A copy of the ICF, signed and dated by the patient, must be given to the patient. Confirmation of a patient's informed consent must also be documented in the patient's study file prior to any data collection under this protocol.

Each ICF should contain an authorization allowing the Prescribing Physician and Biogen to use and disclose PHI in compliance with local law.

The signed ICF will be retained with the study records.

Written informed consent must be obtained from patients who participated in Study 105MS302 or Study 105MS303 to link their data collected from Study 105MS302 and Study 105MS303, respectively, with the data for this study by unique identifier.

9.3. 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 patient 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 patient. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the patient ICF may require similar modifications (see Sections 9.1 and 9.2).

9.4. Subject Data Protection

Prior to any data collection under this protocol, eligible patients must also provide all authorizations required by local law (e.g., PHI authorization in North America).

The patient 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 patient's personal medical data confidential.

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier upon study enrollment. This patient identifier will be used in place of patient name for the purpose of data analysis and reporting. For patients who participated in Study 105MS302 or Study 105MS303, the unique identifier assigned to the patient for the trials will be used to link data collected as part of this study with data from Study 105MS302 and Study 105MS303.

Medical record number or other local reference identifiers are not collected as part of the database. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the registry countries, patients will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality according to the Directive 95/46/EC on the protection of individuals, and in compliance with Safe Harbor privacy principles.

The database will be housed at IQVIA in a physically and logically secure computer system maintained by IQVIA in accordance with a written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of ICH guidelines E6R1 regarding the handling of electronic study data and is available for audit upon request. Patient confidentiality will be strictly maintained.

9.5. Internal Safety Review

Applicable personnel at Biogen will review all SAEs on a regular basis.

9.6. Compensation for Injury

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

9.7. Conflict of Interest

The Prescribing Physicians should address any potential conflicts of interest (e.g., financial interest in Biogen) with the patient before the patient makes a decision to participate in the study.

10. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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 patient. If necessary, appropriate medical intervention should be provided.

Each patient or their legally authorized representative and/or main caregiver must be given the names and telephone numbers of site staff for reporting AEs and medical emergencies.

10.1. Definitions

10.1.1. Adverse Event

An AE is any undesirable experience associated with the use of a medical product in a patient. 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 product, whether or not related to the medicinal product. A pre-existing condition that worsens in severity would also be considered an AE.

10.1.2. Serious Adverse Event

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

- results in death
- in the view of the Prescribing Physician, places the patient 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.

All malignancies should be considered serious and reported as SAEs.

An SAE may also be any other medically important event that, in the opinion of the Prescribing Physician, may jeopardize the patient 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 ER or convulsions occurring at home that do not require an inpatient hospitalization.)

10.2. Monitoring and Recording Events

10.2.1. Adverse Events

The Prescribing Physician should review all AEs experienced by a patient from the time the patient signs the ICF and record the following events in the eCRF:

- SAEs
- AEs (including laboratory abnormalities) leading to discontinuation of Plegridy treatment
- AEs of special interest (FLS, ISRs)

All other non-serious AEs will not be collected as part of this study. The process for reporting these non-serious AEs should follow spontaneous postmarketing rules as per local regulations.

10.2.2. Serious Adverse Events

Any SAE experienced by a patient between the time the patient signs the ICF and before study completion or premature study withdrawal, or within 30 days of discontinuation of Plegridy, is to be recorded on an SAE Form, regardless of the event's relationship to Plegridy. It is the responsibility of the Prescribing Physician to report pharmacovigilance information for other MS products per local regulations. For patients who discontinue treatment but continue to participate in the study, any serious events, including malignancies that occur within 30 days after the last dose of Plegridy will be treated as SAEs and reported on an SAE form. For reporting timelines and procedures, see Section 10.2.4.

MS relapses will not be automatically reported as an SAE unless the relapse was fatal or, in the opinion of the Prescribing Physician, the relapse was complicated by other SAEs.

10.2.3. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 10.1.2.
- The relationship of the event to study treatment as defined in Section 10.3.1.

10.2.4. 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 IQVIA within 24 hours of becoming aware of the SAE. It is the Prescribing Physician's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time the patient signs the ICF and study completion or premature study withdrawal must be reported to IQVIA within 24 hours of the study site becoming aware of the event. For patients who discontinue treatment but continue to participate in the study, any SAE occurring within 30 days after the last dose of Plegridy will be treated as an SAE and reported within 24 hours of the study site becoming aware of the event.

A report ***must be submitted*** to IQVIA regardless of the relationship to Plegridy. It is the

responsibility of the Prescribing Physician to report pharmacovigilance information for other MS products per local regulations.

To report initial or follow-up information on an SAE, please refer to the Study Reference Manual for information on faxing the completed SAE form.

10.2.4.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate CRF within 24 hours of the study site becoming aware of the event. All causes of death must be reported as SAEs. The Prescribing Physician should make every effort to obtain and send death certificates and autopsy reports to IQVIA.

10.3. Safety Classifications

10.3.1. Relationship of Events to Plegridy

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

Relationship of Event to Commercial Drug	
Not related	An adverse event will be considered "not related" to the use of Plegridy if there is not a possibility that the event has been caused by it. 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 Plegridy if there is a possibility that the event may have been caused by it. 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.

10.3.2. 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) causes 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.

10.4. Procedures for Handling Special Situations

10.4.1. Overdose

An overdose is any dose of Plegridy given to a patient or taken by a patient that exceeds the dose described in the local label. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed to IQVIA within 24 hours. An overdose should be reported even if it does not result in an AE.

10.4.2. Reporting Pregnancy and Coordination With the Pregnancy Registry

The Prescribing Physician should refer to the approved local label for guidance if female patients become pregnant or are considering becoming pregnant during the study.

At each routine visit, female patients of childbearing potential will be asked about their pregnancy status and possible pregnancies/spontaneous abortions since the last visit or contact. Spontaneous abortions are considered to be SAEs and must be reported as such. Additionally, congenital abnormalities and/or birth defects in the offspring of male or female patients should be reported as an SAE if the patient was receiving treatment with Plegridy since the first day of her (or in the case of a male patient, his partner's) last menstrual period prior to conception or at any time during pregnancy. Any non-Plegridy related SAEs or pregnancies should be reported according to local pharmacovigilance regulations.

If a Pregnancy Registry is being conducted independently of this observational study, then all pregnant women taking Plegridy (regardless of participation in any studies) will be offered participation in the Pregnancy Registry. Pregnant women may be dually enrolled into this observational study and one or more of the pregnancy registries.

If a pregnant female patient received Plegridy since the first day of her last menstrual period prior to conception or at any time during pregnancy, the Prescribing Physician

should report the pregnancy to IQVIA by faxing the appropriate form within 24 hours of the site becoming aware of the pregnancy. Please refer to the Study Reference Manual for details on reporting the pregnancy and to initiate the enrollment process by IQVIA.

If a pregnant female patient declines participation in the Pregnancy Registry, information on pregnancy outcomes will be collected under this protocol 105MS401. The Prescribing Physician should follow the outcome (including congenital abnormalities/birth defects) of the pregnancy and provide the outcome to IQVIA.

Female partners of male patients who are pregnant at the time a male patient starts receiving Plegridy, or who become pregnant while the male patient is participating in the study, will not be referred to the Pregnancy Registry. Pregnancy reports related to paternal exposure will not be captured as part of this study, unless the Prescribing Physician becomes aware of an unfavorable outcome (e.g., congenital anomalies).

10.5. Medical Emergency

In a medical emergency requiring immediate attention, relevant personnel will apply appropriate medical intervention, according to current standards of care.

10.6. Prescribing Physician Responsibilities

The Prescribing Physician's responsibilities include the following:

- Review all AEs to determine seriousness and fulfillment of collection criteria defined in Section 10.2.1.
- Monitor and record all SAEs (and AEs defined in Section 10.2.1), regardless of the relationship to Plegridy.
- Determine the relationship of each SAE (and AEs defined in Section 10.2.1) to Plegridy.
- Determine the onset and resolution dates of each SAE (and AEs defined in Section 10.2.1).
- Record all pregnancies and refer all pregnant women taking Plegridy to the Pregnancy Registry.
- Complete the appropriate form for each SAE, overdose, and pregnancy and fax it to IQVIA 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 IQVIA within 24 hours of the study site staff becoming aware of new information.
- Ensure all SAE reports are supported by documentation in the patients' medical records.
- Report SAEs (and AEs defined in Section 10.2.1) to local ethics committees, as required by local law.

10.7. Biogen Responsibilities

Biogen's responsibilities include the following:

- Before site activation and patient enrollment, the Clinical Monitor or designee is responsible for reviewing with site staff the definition of an SAE, as well as the instructions for monitoring, recording, and reporting SAEs (and AEs defined in Section 10.2.1).
- Determine the expectedness of all SAEs.
- Notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final study report will be sent to regulators within 12 months of the end of data collection.

11.1. 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.

11.2. 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.

11.3. 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 Prescribing Physician must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Prescribing Physician must notify Biogen of any changes in the archival arrangements including, but not limited to, archiving at an off-site facility or transfer of ownership if the Prescribing Physician leaves the site.

12. REFERENCES

Deykin A, Arnold D, Hung S, et al. Interim analysis of 2-year clinical efficacy and safety of peginterferon beta-1a in patients with relapsing-remitting multiple sclerosis: data from the pivotal phase 3 ADVANCE study [abstract]. Neurology. 2014;82(Meeting Abstracts):S4.005.

International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication [Internet]. 2010. Available from: http://www.ICMJE.org.

von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9. Epub 2008/03/04.

13. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "Plegridy™ Real World Effectiveness and Safety Observational Study (POP)" and agree to conduct the study according to the protocol and the applicable ICH, GCP, and GVP guidelines, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Prescribing Physician's Signature Date (*DD MMM YYYY*)

_____

Prescribing Physician's Name (Print)

_____

Study Site (Print)

14. ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

Table 3: List of Stand-Alone Documents for Protocol 105MS401

Number	Document Reference Number	Date of Document	Title or Content of Document
None			

15. ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS (REVISION 3)

Study title: Plegridy® (peginterferon β-1a) Real World Effectiveness and Safety Observational Program

Study reference number: 105MS401

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				5
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

End of data collection and Final report of study results dates are estimated in Section 5.

The Sponsor will notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs and applicable AEs, as required by local law, within required time frames. A final clinical study report will be submitted to regulators within 12 months of the end of data collection. No commitment by the Sponsor to provide study progress reports or interim progress reports to regulators are currently in place.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.1
2.1.2 The objective(s) of the study?	☒	☐	☐	7.2

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	8.6.5.3, 8.6.5.4
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	6.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.7
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	8.7.4.2
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	8.7.5.4
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.2.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	8.2.3
4.2.2 Age and sex?	☒	☐	☐	8.2.1.1
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	8.2.1.1
4.2.5 Duration of follow-up?	☒	☐	☐	8.2.3

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.1.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	8.2
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	8.2
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.1.1 and 8.1.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.7.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	8.7
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	8.7.5.4

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	8.7
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	8.7

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.3.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.3
9.1.3 Covariates?	☐	☒	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	10
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.7.3
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.7.4.2
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	8.7
10.2 Are descriptive analyses included?	☒	☐	☐	8.7
10.3 Are stratified analyses included?	☐	☒	☐	
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	8.7
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.5.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	8.7.7

Comments:

Detailed description of analysis plan will be provided in a separate Statistical Analysis Plan.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.8.4
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8.2
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8.5 8.7.3

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	8.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.1, 8.2

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.1
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9.1
13.3 Have data protection requirements been described?	☒	☐	☐	9.4

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Deviations will be described in the clinical study report.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11.2

Comments:

Name of the main author of the protocol: [redacted] PhD

Date: dd/Month/year 17/APR/2019

Signature: [redacted]

16. ANNEX 3: ADDITIONAL INFORMATION

16.1. Schedule of Events

Relevant data time points for the study are presented in the Schedule of Events provided in Table 4 below. All data elements will be collected from information routinely recorded in the medical record, or will be prospectively recorded by the Prescribing Physician for the purposes of the study. No visits or examinations, laboratory tests or procedures are mandated as part of this study. Patient-reported outcomes (PROs) will be collected directly from the patient either electronically via secure, personalized link or on paper at the time of a routine clinic visit. If a patient does not complete his/her PROs during the clinic visit then he/she can complete the PROs electronically via the secure, personalized link within four weeks of his/her routine clinical visit. Refer to Section 8.2.4.7 for details regarding PRO collection, and Section 8.3 for details regarding the data elements to be collected. After enrollment in the study, all clinical data are captured in accordance with routine visits per local clinical practice and label regardless of treatment choice.

Table 4: Schedule of Events: POP 105MS401

Assessments[1]	Baseline[2]	Every 3 months (±4 weeks) in follow-up Year 1	Every 6 months (±4 weeks) in follow-up Years 2-5	Study Discontinuation[3]
Date of Signed Informed Consent	X			
Site and Prescribing Physician Characteristics	X			
Demographic characteristics	X			
Relevant medical history and co-morbidities	X			
MS disease history	X			
History of FLS on previous IFN therapy	X			
Results of latest brain MRI scan	X	X	X	
Prior use and duration of immunomodulatory, immunosuppressive (including corticosteroids), and anti-neoplastic agents, and other approved MS therapies	X			
Prior use and duration of all other concomitant medications	X			
Participant in Study105MS302 or Study 105MS303	X			

Assessments[1]	Baseline[2]	Every 3 months (±4 weeks) in follow-up Year 1	Every 6 months (±4 weeks) in follow-up Years 2-5	Study Discontinuation[3]
Plegridy prescription information: start and stop dates, initial dose, dose reductions or escalations, prescribed dosing frequency, duration of use, reason for discontinuation, if applicable	X	X	X	X
CBC with differential, if consistent with local practice	X	X	X	X
Other laboratory tests recommended in local label	X	X	X	X
Concomitant use of medications	X	X	X	X
EDSS information (Functional System Scores and Ambulation Scores), based on neurological examination, if consistent with local practice	X	X	X	X
Neurological assessment, if not EDSS	X	X	X	X
[redacted]				
MS relapse information, if applicable	X	X	X	X
Use of immunomodulatory, immunosuppressive (including corticosteroids), and anti-neoplastic agents, and other approved MS therapies after discontinuing Plegridy, if applicable		X	X	X
Pregnancy status and nursing status (female patients)	X	X	X	X
PROs[4]: EQ-5D-3L, FLS, healthcare resource consumption questionnaire, treatment adherence questionnaire,[5] FLS-VAS[6]	X[4]	X	X	X
AEs of special interest (FLS, ISR)	X ---------->			
AEs [including laboratory abnormalities] leading to treatment discontinuation)	X ---------->			
SAEs	X ---------->			

1. Data are to be collected according to local clinical practice, preferably within four weeks (before or after) the time of a clinic visit. Data collection will be inclusive of healthcare visits (e.g., clinic, emergency room, etc.) resulting in a diagnosis of MS relapse that occurs within the three-month (Year 1) or six-month (Year 2 through Year 5) data collection period. MS relapse will be confirmed by the Prescribing Physician (see Section 8.3.6 for the relapse definition). No visits or examinations, laboratory tests or procedures are mandated as part of this study.
2. Baseline is defined as the date of enrollment. Data will be collected from the time of first dose through enrollment for patients who had exposure to Plegridy prior to study enrollment.
3. If a patient withdraws prior to completing the study, all information already collected as part of the study will be retained for the analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.
4. PROs may be completed electronically or on paper at a routine visit if consistent with local regulations. If a patient does not complete his/her PROs during the clinic visit then he/she can complete the PROs electronically via the secure, personalized link within four weeks of his/her routine clinical visit. PROs completed on paper will be entered into the EDC by the site.
5. Treatment adherence questionnaire at baseline is only for patients who have received MS therapies prior to enrollment. Patients prescribed their first MS therapy at the time of enrollment will not complete the baseline treatment adherence questionnaire.
6. If a patient selects “Absent” for Question 1 of the FLS Assessment, then the FLS-VAS does not need to be completed for that patient.

16.2. EUROQOL EQ-5D, 3-LEVEL (EQ-5D-3L)

Health Questionnaire
(English version for the US)

Health Questionnaire
(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

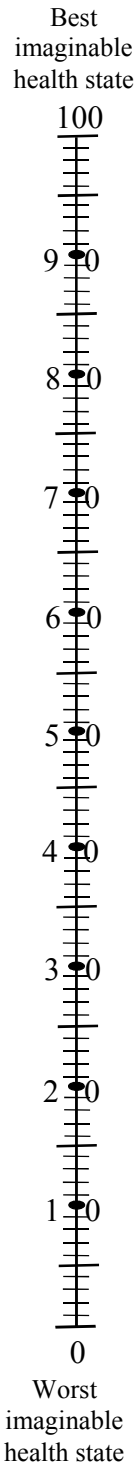
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



16.3. FLU-LIKE SYMPTOMS (FLS) ASSESSMENT

Select the statement which best describes your MUSCLE ACHES, CHILLS and FATIGUE after your most recent injection.

□ absent

□ mild, did not interfere with daily activities

□ moderate, interfered with daily activities

□ severe, bed rest required

If you used any medication to reduce your Flu-Like Symptoms, please select the statement which best describes your MUSCLE ACHES, CHILLS and FATIGUE after taking the medication.

□ absent

□ mild, did not interfere with daily activities

□ moderate, interfered with daily activities

□ severe, bed rest required

If you experienced Flu-Like symptoms, did your symptoms last.

□ 24 hours or less

□ Greater than 24 hours

16.4. Healthcare Resource Consumption Questionnaire

PATIENT ID:

QUESTIONNAIRE DATE:

VISIT TIMEPOINT:

Patient Questionnaire – Resource Utilization

A. This questionnaire was filled out by: (mark only one response)
- ☐ Patient alone with no assistance
- ☐ Patient with assistance
- ☐ Family member / Friend / Family caregiver
- ☐ Paid caregiver

B. What is your living situation
- ☐ Private home, alone or with family or friends, but able to take care of myself
- ☐ Private home with family or friend as caregiver
- ☐ Private home with home health aide support
- ☐ Assisted living

This survey asks how Multiple Sclerosis (MS) affects your use of healthcare services and the impact it has on particular areas of your life. This is not a test. There are no right or wrong answers. If you are unsure how to answer any question, please give the best answer you can.

Please include the healthcare services you have received at any MS center, office or clinic, and hospital, including the facility at which you were recruited for this study.

Questions 1 to 3 refer to the period of time *since your last visit* before the completing this questionnaire.

1. How many times have you visited these healthcare professionals (HCP) in an '*Outpatient Department*' of a clinic or hospital for managing your MS?

HCP	Number of Visits	HCP	Number of Visits
Neurologist – MS Specialist		Physical therapist / Physiotherapist	
Neurologist – not an MS Specialist		Occupational therapist	

General Practitioner / Primary Care Provider / Internist		Rehabilitation therapist	
Physician assistant		Speech therapist	
Nurse – MS Specialist		Psychiatrist/Psychologist	
Nurse – not an MS specialist		Urologist	
Visiting nurse (visited you)		Gynecologist	
Chiropractor		Counselor	

Other HCP: _____ Number of visits: _____

Other HCP: _____ Number of visits: _____

Other HCP: _____ Number of visits: _____

☐ I did not make any visits: _____

2. Have you been admitted to any of the following facilities due to MS? ☐ Yes ☐ No
   - Nursing home
   - Home or residential hospice or MS centers

3. If you answered 'Yes' to question 2, please fill out the following table for details on the admissions. Please fill out each admission on a separate row.

Which facility were you admitted to?	Were you admitted due to relapse?	How many days were you admitted?
☐ Nursing home ☐ Home/residential hospice or MS centers	☐ Yes ☐ No	
☐ Nursing home ☐ Home/residential hospice or MS centers	☐ Yes ☐ No	
☐ Nursing home ☐ Home/residential hospice or MS centers	☐ Yes ☐ No	
☐ Nursing home ☐ Home/residential hospice or MS centers	☐ Yes ☐ No	
☐ Nursing home ☐ Home/residential hospice or MS centers	☐ Yes ☐ No	

Caregiver Services

4. Do you have a family caregiver (a family member or friend) who helps you because of problems due to MS?
   - ☐ Yes (If yes, please continue to question 5)
   - ☐ No (If no, please do not answer the questions below and skip to the next section)

5. Do any of the following apply to your family/friend caregiver?
   - ☐ Caregiver works full-time (Employed outside the home) (if yes, please answer questions 6-8)
   - ☐ Caregiver works part-time (Employed outside the home) (if yes, please answer questions 6-8)
   - ☐ Caregiver works in the home only
   - ☐ Caregiver does volunteer work
   - ☐ Caregiver is retired
   - ☐ None of the above

6. If the caregiver is employed, how many days per week does he/she usually work? ____

7. If the caregiver is employed, in the *past 2 weeks*, how many days did he/she miss work because of helping you because of the problems you experience with MS? _____

8. Has care giving for you caused the caregiver to… (select all that apply)
   - ☐ Cut back on his/her hours at work?
   - ☐ Leave his/her job?
   - ☐ Hire other caregivers by paying out of pocket?
   - ☐ Seek government-funded chore services (e.g., home help)?
   - ☐ Other, specify_____
   - ☐ None of the above

16.5. Treatment Adherence Questionnaire – Baseline

Below are some questions regarding your use of your previous MS therapy prior to Plegridy. Please answer these questions as best as you can in reference to the last 28 days on your previous treatment

You can also seek help from a caregiver (anyone who usually provides care to you at home) to answer these questions.

1. During the last 28 days on your prior treatment, did you take all of your recommended doses of your MS treatment? ☐ Yes ☐ No

2. List all the reasons for not taking entire recommended dose. Please check the responses that apply.

   - ☐ Injection Anxiety
   - ☐ Skin Reaction
   - ☐ Forgot to take
   - ☐ Financial (I could not afford my medication)
   - ☐ Pain at injection site
   - ☐ Depression
   - ☐ Headache
   - ☐ Fatigue
   - ☐ Weakness
   - ☐ Flu-like
   - ☐ Didn't feel like it
   - ☐ Didn't refill
   - ☐ Not sure of the benefits
   - ☐ Tired of injections
   - ☐ No one available to give
   - ☐ Dosing inconvenient
   - ☐ Pregnant or planning
   - ☐ Other

16.6. Treatment Adherence Questionnaire – Follow-up

Below are some questions regarding your use of Plegridy during the past 28 days. Please answer these questions as best as you can.

You can also seek help from a caregiver (anyone who usually provides care to you at home) to answer these questions.

1. During the past 28 days, did you take your recommended doses of Plegridy (125 mcg / every 14 days) in total? ☐ Yes ☐ No

2. If you answered "No" to question #1, how many injections did you not take during the past 28 days?
   _____

3. List all the reasons for not taking entire recommended dose. Please check the responses that apply.

   - ☐ Injection Anxiety
   - ☐ Skin Reaction
   - ☐ Forgot to take
   - ☐ Financial (I could not afford my medication)
   - ☐ Pain at injection site
   - ☐ Depression
   - ☐ Headache
   - ☐ Fatigue
   - ☐ Weakness
   - ☐ Flu-like
   - ☐ Didn't feel like it
   - ☐ Didn't refill
   - ☐ Not sure of the benefits
   - ☐ Tired of injections
   - ☐ No one available to give
   - ☐ Dosing inconvenient
   - ☐ Pregnant or planning
   - ☐ Other

16.7. Flu-Like Symptoms-Visual Analog Scale (FLS-VAS)

Since your last injection, how effective was the medication you took to reduce your flu-like symptoms

Not Effective ---------- Very Effective
0 1 2 3 4 5 6 7 8 9 10

Since your last injection, how satisfied were you with the effectiveness of the medication you took to reduce your flu-like symptoms

Not Satisfied----------Very Satisfied
0 1 2 3 4 5 6 7 8 9 10