Non-Interventional Study Protocol

Study Protocol Number	MS700568-0150
Title	**C**ladribine tablets in Highly-**a**ctive Relapsing **M**ultiple Sclerosis R**e**a**l**-W**o**rld Effec**t**iveness in UK Clinical Practice (CAMELOT-MS)
Protocol Version Identifier	2.0
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Replaces Version	1.0
Sponsor	Merck Serono Limited An affiliate of Merck KGaA, Darmstadt, Germany 5 New Square Bedfont Lakes Business Park Feltham, Middlesex TW14 8HA, United Kingdom
Research Question and Objectives	Research question: What are the real-world treatment outcomes and patterns in patients with high disease activity relapsing-remitting multiple sclerosis (HDA-RRMS) who have been treated with cladribine tablets in the UK? This study aims to investigate the effectiveness of cladribine tablets in a UK real-world setting. Primary Objective: In patients with HDA-RRMS who initiated on cladribine tablets: • To analyse the annualised relapse rate yearly up to 5 years after cladribine tablet initiation Secondary Objectives: In patients with HDA-RRMS who initiated on cladribine tablets: • To analyse the proportion of patients relapse-free at each year (and up to 5 years) after cladribine tablet initiation • To analyse the time after cladribine tablet initiation to first relapse • To evaluate the proportion of patients who discontinued cladribine tablets and reasons for discontinuation

- To evaluate the subsequent disease-modifying therapies (DMTs) received after cladribine tablets discontinuation up to 5 years after cladribine tablets initiation
- To analyse the proportion of patients with disability progression confirmed over 6 months, 2 years after treatment initiation
- To analyse the incidence rate of selected, identified, and potentially clinically important adverse events

The primary and secondary objectives will be analysed overall and by most recent DMT prior to cladribine tablets initiation (DMT naïve, "platform" treatment, high-efficacy cell-depleting treatment, or high-efficacy non-depleting treatment).

Country(-ies) of Study

United Kingdom

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2 List of Abbreviations

AE	Adverse Event
CI	Confidence Interval
CNS	Central Nervous System
CRO	Contract Research Organization
DMT	Disease-modifying Therapies
eCRF	Electronic Case Report Form
EDSS	Expanded Disease Severity Scale
FAS	Full Analysis Set
GPP	Good Pharmaco-epidemiology Practices
HDA-RRMS	High Disease Activity Relapsing-remitting Multiple Sclerosis
IAP	Integrated Analysis Plan
ICF	Informed Consent Form
IEC	Independent Ethics Committee
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
RRMS	Relapsing-remitting Multiple Sclerosis
SmPC	Summary of Product Characteristics

3 Responsible Parties

Responsible Parties	Contact details
Coordinating Investigator	PPD [redacted]

3.1 Responsibilities of the Investigator

The investigator is responsible for the conduct of the study at his/her site. He/She will ensure that the study is performed in accordance with the protocol and will ensure the quality and integrity of data, following all applicable international and national guidelines.

This non-interventional study will not interfere with treatment prescription by investigators. Accordingly, the investigator will decide in advance the best therapeutic strategy for each patient according to current practice, regardless of the potential participation of this patient in the study. Subsequently, if the prescribed treatment is in line with the study protocol, the investigator will consider the possibility of including the patient in the study.

The investigator is responsible for adverse reaction and/or laboratory abnormalities recording and reporting, as specified in Section 11.

4 Abstract

Title	**C**ladribine tablets in Highly-**a**ctive Relapsing **M**ultiple Sclerosis R**eal**-W**o**rld Effec**t**iveness in UK Clinical Practice (CAMELOT-MS) PPD Merck Serono PPD, Merck Serono
Rationale and Background	Real-world insights, data and experience are increasingly important to inform clinical decisions of treatment choice in multiple sclerosis (MS). In the UK, the first patients to be treated with cladribine tablets were initiated on the treatment soon after the EU marketing authorization in August 2017. The UK currently has a relatively large patient population that has been treated with cladribine tablets. This multicentre chart review study will investigate the medium to long-term treatment outcomes and patterns of cladribine tablets in a real-world setting. In addition, the chart review study provides the opportunity to assess outcomes among patients previously treated with high-efficacy therapies not available at the time of the pivotal clinical trials. Prior therapies can be categorized in three groups: immediate prior treatment with a 'platform' treatment, which include interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate; immediate prior treatment with a high-efficacy cell-depleting treatment, which include alemtuzumab and ocrelizumab; and immediate prior treatment with a high-efficacy non-depleting treatment, which include natalizumab and fingolimod. This list is non-exhaustive and additional regulatory approved medications may be added to complete the list.
Research Question and Objectives	Research question: What are the real-world treatment outcomes and patterns in patients with high disease activity relapsing-remitting multiple sclerosis (HDA-RRMS) who have been treated with cladribine tablets in the UK? This study aims to investigate the effectiveness of cladribine tablets in a UK real-world setting. Primary Objective: In patients with HDA-RRMS who initiated on cladribine tablets: • To analyse the annualised relapse rate yearly up to 5 years after cladribine tablet initiation Secondary Objectives: In patients with HDA-RRMS who initiated on cladribine tablets: • To analyse the proportion of patients relapse-free at each year (and up to 5 years) after cladribine tablet initiation

	• To analyse the time after cladribine tablet initiation to first relapse • To evaluate the proportion of patients who discontinued cladribine tablets and reasons for discontinuation • To evaluate the subsequent disease-modifying therapies (DMTs) received after cladribine tablets discontinuation up to 5 years after cladribine tablets initiation • To analyse the proportion of patients with disability progression confirmed over 6 months, 2 years after treatment initiation • To analyse the incidence rate of selected, identified, and potentially clinically important adverse events (AEs) The primary and secondary objectives will be analysed overall and by most recent DMT prior to cladribine tablets initiation (DMT naïve, "platform" treatment, high-efficacy cell-depleting treatment, or high-efficacy non-depleting treatment).
Study Design	This will be a multicentre chart review, Phase IV study, to be conducted across approximately 7 or 8 sites in the UK, using medical records of patients who initiated cladribine tablet monotherapy for treatment of HDA-RRMS per clinical practice. Patients who initiated treatment with cladribine tablets between 22 August 2017 and at least 3 years before enrolling into the study may be enrolled in the study. After obtaining patients' consent to participate in this study, patient data will be abstracted from the medical chart. The first chart review, at enrolment, will include any relevant medical history, data recorded in the year prior to cladribine tablet initiation, and data recorded between the date of cladribine tablet initiation and the study enrolment date. A second chart review will be conducted approximately 1 year after enrolment. This second data abstraction will collect data recorded between the study enrolment date and the date of the second chart abstraction. The total observation period per patient will vary depending on the period between the date of cladribine tablet initiation and study enrolment date. The observation period per patient, counting from 1 year prior to cladribine tablet initiation until the date of the second chart review, will be at minimum 5 years and at maximum 7 years. The data to be collected are routinely collected information per clinical practice, including demographic data, medical history, disease characteristics (clinician confirmed relapses, Expanded Disease Severity Scale [EDSS] scores, magnetic resonance imaging [MRIs], and

	lymphocyte counts, as available), treatments (cladribine tablets, other DMTs for MS, and COVID-19 vaccines), and selected potentially clinically important AEs.
Population	Inclusion criteria: *1.* At least 18 years of age at cladribine tablet treatment initiation *2.* Physician diagnosis of HDA-RRMS as defined by clinical or radiological features *3.* Treatment initiation with cladribine tablet monotherapy on or after 22 August 2017 and at least 3 years before enrolment *4.* Completion of Year 1 treatment of cladribine tablets (Week 1 and Week 2 treatment, per recommended dose in Year 1: 1.75 mg/kg body weight, cumulatively) *5.* Provide written informed consent to participate in the study Exclusion criteria: *1.* Received cladribine tablet treatment within an interventional clinical trial during the study period *2.* Received treatment with any investigational therapy for RRMS in the 6 months prior to cladribine tablet treatment initiation
Outcomes	Primary outcomes: • Estimated annualised relapse rate in the year prior to treatment initiation with cladribine tablets, and in Years 1, 2, 3, 4 and 5 after initiation Secondary outcomes: • Proportion of patients who remain relapse-free in each year and at 4 and 5 years after initiation of cladribine tablet treatment • Time from cladribine tablet initiation to first relapse • Proportion of patients who discontinued cladribine tablets and reasons for discontinuation • Subsequent DMTs (none or by DMT type) received after cladribine tablets discontinuation/treatment completion up to 5 years after cladribine tablets initiation • Disability assessed by the EDSS at treatment initiation and start of treatment Year 2

	• Proportion of patients with disability progression confirmed over 6 months, assessed by the EDSS, at 2 years after cladribine tablet treatment initiation
	• Rates of selected, identified, and potentially clinically important AEs, including:
	  • grade 3 lymphopenia
	  • grade 4 lymphopenia
	  • herpes infections
	  • serious infections (infections for which a hospitalisation is initiated or extended)
	  • opportunistic infections (new onset or reactivation of latent infection)
	  • malignancies
	
	The primary and secondary outcomes will be analysed overall and stratified by most recent prior DMT subgroups:
	• naïve to DMT
	• prior platform therapy
	• prior high-efficacy cell-depleting treatment
	• prior high-efficacy non-depleting treatment

Variables	• Demographic data at cladribine tablet initiation: Gender, age, height, and weight • Medical history and comorbidities at cladribine tablet initiation: All relevant medical history and comorbidities in the year prior to initiation with cladribine tablets (both past and ongoing comorbidities at date of initiation with cladribine tablets will be collected) • Medication history at cladribine tablet initiation: Relevant medications taken in the year prior to initiation with cladribine tablets • MS disease history: Date of initial MS diagnosis and type of MS at cladribine tablet initiation • Prior DMTs: Any DMTs for MS taken prior to initiating treatment with cladribine tablets, including starting date, end date, and dosage

	• Treatment with cladribine tablets: Date of initiation of each treatment course, dose, potential date of discontinuation of treatment and reason for discontinuation, if applicable
	• Subsequent DMTs: Other DMTs for MS initiated after treatment with cladribine tablets will be recorded, including the date of initiation and potential discontinuation dates and dosage
	• COVID-19 vaccines: Vaccines for coronavirus disease 2019 (COVID-19) attributable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
	• Course of disease
	  • clinician confirmed relapses
	  • annual EDSS scores
	  • MRI data
	• Lymphocyte levels
	• Selected AEs (reported once informed consent has been obtained)

Data Sources	The data will be collected from patient medical records and the patient's general practitioner may be contacted by the principal investigator or a member of the site team regarding medical history and concomitant medications. The data will be transcribed into an electronic case report form (eCRF).
Study Size	Approximately 200 patients (minimum of 90 patients) will be enrolled in this study.
Data Analysis	The estimated annualised relapse rate in the year prior to treatment initiation with cladribine tablets, and in years 1, 2, 3, 4 and 5 (upon availability, depending on the available observation time) after initiation will be summarised using descriptive statistics for continuous variables. The proportion of patients who remain relapse-free in each year (and up to 5 years) after initiation of treatment (among patients active at the start of each year) will be summarised using Kaplan-Meier summary statistics. The Kaplan-Meier survival curve for time from initiation to first relapse will be plotted. Proportion of patients who discontinued cladribine tablets and reasons for discontinuation, proportion of patients with confirmed disability progression, and the subsequent DMTs (none or by DMT type) received after cladribine tablet treatment initiation will be summarised using descriptive statistics. The incidence rates of AEs will be summarised by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

Milestones	Start of data collection: Q3 2021 End of data collection: Q3 2023 Final report of study results: Q2 2024

5 Amendments and Updates

Number	Date	Section of Study Protocol	Amendment or Update
1	25/03/2022	4 Abstract, 9.2.4 Overview of Study Events, 9.3 Variables	Clarification of medical history, comorbidities, medication history, and adverse event variable collection.
		4 Abstract, 9.5 Study Size	Addition of minimum sample size and update of sample size calculation to this minimum sample size.
		4 Abstract, 9.1.1 Design Overview, 9.2.1 Study Population	Increase in approximate number of sites.
		6 Milestones, 9.7.4 Sequence of Analyses, 12.1 Study Report	Removal of interim analysis and interim report.
		4 Abstract, 9.1.1 Design Overview, 9.2.4 Overview of Study Events, 9.4 Data Source	Addition of clarification that the patient's general practitioner may be contacted to obtain information regarding medical history and concomitant medications.
		9.1.1 Design Overview, 9.2.4 Overview of Study Events	Window to enter data in the EDC after enrollment extended to 28 days.
		Multiple sections	Administrative updates (including author).

6 Milestones

Milestone	Planned date
Start of data collection (First Patient First Visit[a] Date)	Q3 2021
End of data collection (Last Patient Last Visit[a] Date)	Q3 2023
Database lock	Q4 2023
Final report of study results	Q2 2024

[a] Visit in this context refers to the chart abstraction

7 Rationale and Background

7.1 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory neurological disease of the central nervous system (CNS) (Calabresi 2004, Hauser 2008). MS attacks the myelinated axons in the CNS, destroying the myelin and the axons to varying degrees (Weinshenker 1996, Olek 2011). The disease is diagnosed based on clinical findings and supporting evidence from ancillary tests such as magnetic resonance imaging (MRI) of the brain and examination of the cerebrospinal fluid. Multiple sclerosis typically presents in adults 20 to 45 years of age; occasionally, it presents in childhood or late middle age (Cree 2007). The cause of MS is unknown, but it appears to involve a combination of genetic susceptibility and a nongenetic trigger, such as a virus, metabolism, or environmental factors resulting in a self-sustaining autoimmune disorder that leads to recurrent immune attacks on the CNS (Cree 2007).

The course of MS is highly varied and unpredictable. Commonly, the disease is characterized initially by episodes of reversible neurological deficits, which is often followed by progressive neurological deterioration over time. Some patients experience a high disease activity course with rapid and early disability often heralded by high relapse rates and early motor, cerebellar and/or cognitive dysfunction (Hirst 2008). Highly-active relapsing MS is characterized by neurological deterioration causing motor and cognitive dysfunction and impacting health-related quality of life (Jones 2016).

7.2 Mavenclad® (Cladribine Tablets)

Over recent years, there has been an increase in the number of available disease-modifying therapies (DMT) for treatment of MS (Wingerchuk 2014). Despite the recent approvals of such therapies, the treatment burden of MS remains significant. New treatment options are still required to reduce the number of relapses and disease progression that patients experience (Hadjigeorgiou 2013, Tramacere 2015, Tsivgoulis 2015, Lucchetta 2020).

Mavenclad® (cladribine tablets) is approved (European Medicines Agency approval on 25 August 2017) for the treatment of highly-active relapsing MS in adults. These tablets involve a synthetic deoxyadenosine analogue that acts in peripheral tissues and enters the CNS, where it is taken up by lymphocytes and phosphorylated by deoxycytidine kinase. This results in targeted and sustained reductions of the T and B lymphocytes that are implicated in the pathogenesis of MS (Leist 2011).

It has been demonstrated that treatment with cladribine tablets in 2 short courses over 2 consecutive years has consistently shown robust clinically and statistically significant benefits in patients across the spectrum of relapsing MS (early to late stages, treatment naïve or experienced patients) (Giovannoni 2010, Leist 2011). The recommended cumulative dose of cladribine tablets is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year. Detailed information on the chemistry, pharmacology, efficacy, and safety of cladribine tablets is provided in the Summary of Product Characteristics (SmPC). Overall, the most common, clinically relevant adverse reactions

reported among patients treated with cladribine tablets in clinical studies are lymphopenia and herpes zoster.

7.3 Rationale

Real-world insights, data and experience are increasingly important to inform clinical decisions of treatment choice in MS. Confirming the observed evidence from clinical trials with observation of the experience of patients treated in clinical practice is becoming an expected part of the product development programme. These studies complement formal Phase IV studies by contributing evidence in patients treated in clinics rather than trial units, where additional interventions may be applied, and in patients who are not typically enrolled in clinical trials including patients with comorbidities, more advanced disability and ethnic minorities.

The clinical development programme for cladribine tablets provided robust data to confirm its positive risk-benefit profile in patients with MS. The EMA license was granted on the basis of a post-hoc analysis and has created a special need for corroborating real-world evidence in patients who meet the licensed criteria; it is noted that those treated in the post-marketing setting are very different from those included in the pivotal CLARITY trial and followed up in the longer-term in the PREMIERE trial. As such, real-world safety, tolerability, and occurrence of lymphopenia (using re-treatment criteria, and patients previously treated with high-efficacy therapies not available at the time of CLARITY) are open questions noted by UK healthcare professionals.

The structure of the clinical development programme, which does not allow for annual release of longer-term follow-up data from open label extension studies during the launch period, is also a disadvantage compared to other products. The UK provides a unique opportunity for a chart review study to investigate the medium to long-term treatment outcomes and patterns of cladribine tablets in a real-world setting. In the UK, the first patients to be treated with cladribine tablets were initiated on the treatment soon after the EU marketing authorization in August 2017. The UK currently has a relatively large patient population that has been treated with cladribine tablets, including patients already entering the fourth year after treatment initiation. The recruitment of patients who already initiated treatment maximises the follow-up time and minimises the time needed to collect the data.

In addition, this multicentre chart review study provides an opportunity to investigate treatment outcomes among patients previously treated with high-efficacy therapies not available at the time of the pivotal clinical trials. Prior therapies can be categorized in 3 groups: immediate prior treatment with a ‘platform’ treatment, which include interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate; immediate prior treatment with a high-efficacy cell-depleting treatment, which include alemtuzumab and ocrelizumab; and immediate prior treatment with a high-efficacy non-depleting treatment, which include natalizumab and fingolimod. This list is non-exhaustive and additional regulatory approved medications may need to be added to complete the list.

In comparison to the use of registers and databases, collecting data directly from medical records has the advantage of collecting data which are readily available, and provides the ability to follow individual patients who have consented to the study over time. The level of data available will

provide, for example, individuals' lymphocyte counts, reasons for treatment cessation, and effectiveness data on relapse rate and disability.

8 Research Question and Objectives

This study aims to answer the question: What are the real-world treatment outcomes and patterns in patients with high disease activity relapsing-remitting multiple sclerosis (HDA-RRMS) who have been treated with cladribine tablets in the UK? The aim is to investigate the effectiveness of cladribine tablets in a UK real-world setting.

8.1 Primary Objective

In patients with HDA-RRMS who initiated on cladribine tablets, overall and by most recent DMT prior to cladribine tablets initiation (DMT naïve, "platform" treatment, high-efficacy cell-depleting treatment, or high-efficacy non-depleting treatment):

- To analyse the annualised relapse rate yearly up to 5 years after cladribine tablet initiation

8.2 Secondary Objectives

In patients with HDA-RRMS who initiated on cladribine tablets, overall and by most recent DMT prior to cladribine tablets initiation (DMT naïve, "platform" treatment, high-efficacy cell-depleting treatment, or high-efficacy non-depleting treatment):

- To analyse the proportion of patients relapse-free at each year (and up to 5 years) after cladribine tablet initiation
- To analyse the time after cladribine tablet initiation to first relapse
- To evaluate the proportion of patients who discontinued cladribine tablets and reasons for discontinuation
- To evaluate the subsequent DMT received after cladribine tablets discontinuation up to 5 years after cladribine tablets initiation
- To analyse the proportion of patients with disability progression confirmed over 6 months, 2 years after treatment initiation
- To analyse the incidence rate of selected, identified, and potentially clinically important adverse events (AEs)

8.3 Other Objectives

For patients for whom any MRI data are available:

- To evaluate MS-related lesions as assessed by MRI in patients with HDA-RRMS after cladribine tablet initiation

9 Research Methods

9.1 Study Design

9.1.1 Design Overview

This will be a multicentre chart review, Phase IV study, to be conducted across approximately 7 or 8 sites in the UK, using medical records of patients who initiated cladribine tablet monotherapy for treatment of HDA-RRMS per clinical practice. The observational chart review study design, allowing collection of real-world data dating back to product launch, will maximise the patient observation periods while minimising the burden for the sites and patients.

Patients with HDA-RRMS who initiated treatment with cladribine tablets and are fulfilling the other study eligibility criteria will be identified from patient records and asked to consent to participate in the study. Informed consent may be obtained at the site or remotely (additional details are provided in Section 10.1). Patients should have initiated treatment with cladribine tablets between 22 August 2017 (i.e., date of EU marketing authorisation of cladribine tablets) and at least 3 years before enrolling into the study. In addition, the patient should have completed at least Year 1 of cladribine treatment (i.e., 2 treatment weeks). Sites should aim to enrol patients in chronological order, based on the start date of treatment with cladribine tablets: i.e., patients who initiated cladribine tablets first will be contacted for enrolment first and their data should be abstracted first.

In this observational chart review study, the drug was prescribed before the patient was enrolled in the study as part of routine clinical practice and independent from participation in the current study.

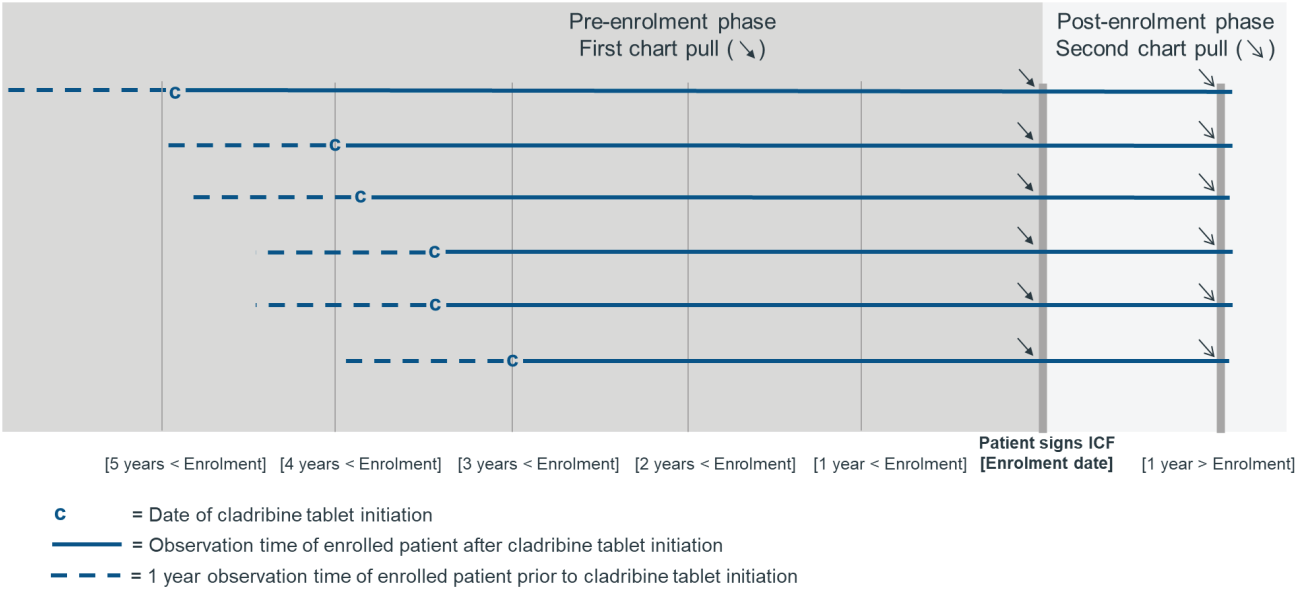
The enrolment date is defined as the date of signing informed consent. Annual chart reviews will be based upon the date of cladribine tablet initiation, which is defined as the start date of Year 1 treatment with cladribine tablets as documented in patients' medical records. This study will involve 2 chart abstractions, with the first chart abstraction at the patient's enrolment and the second chart abstraction approximately 1 year after enrolment (Figure 1).

The first chart review will take place after obtaining patients' consent to participate in this study. Patient data will be abstracted within 28 days after obtaining informed consent. The data will be abstracted from the medical chart and will include relevant medical history, data recorded in the year prior to cladribine tablet initiation, and data recorded between the date of treatment initiation with cladribine tablets and the study enrolment date (Table 1 and Section 9.3). In addition, the patient's general practitioner may be contacted by the principal investigator or a member of the site team to obtain information regarding medical history and concomitant medications.

The second chart review will be conducted approximately 1 year after enrolment (within a window of 14 days from a year after the enrolment date). This second chart abstraction will collect data recorded between the enrolment date and the date of the second data abstraction (Table 1 and Section 9.3).

The data to be collected are routinely collected information per clinical practice, including demographic data, disease characteristics (relapse reports, Expanded Disease Severity Scale [EDSS] scores, MRIs, and lymphocyte counts, as available), treatments (cladribine tablets, other DMTs for MS, and COVID-19 vaccines), medical history, and selected AEs.

Figure 1 **Study Design Schematic**



ICF: Informed Consent Form

9.1.2 Outcomes

The primary and secondary outcomes will be analysed overall and stratified by most recent prior DMT subgroups:

- naïve to DMT
- prior platform therapy
- prior high-efficacy cell-depleting treatment
- prior high-efficacy non-depleting treatment

9.1.2.1 Primary

- Estimated annualised relapse rate in the year prior to treatment initiation with cladribine tablets, and in years 1, 2, 3, 4 and 5 after initiation

  The annualised relapse rate will be calculated from the number of clinician's confirmed relapses that occurred over the respective year.

9.1.2.2 Secondary

- Proportion of patients who remain relapse-free in each year and at 4 and 5 years after initiation of cladribine tablet treatment
- Time from cladribine tablet initiation to first relapse
- Proportion of patients who discontinued cladribine tablets and reasons for discontinuation
- Subsequent DMTs (none or by DMT type) received after cladribine tablets discontinuation/treatment completion up to 5 years after cladribine tablets initiation
- Disability assessed by the EDSS at treatment initiation and start of treatment Year 2

  The EDSS is a neurological assessment to evaluate disability in patients with MS, performed by the physician. The annual EDSS at cladribine tablet treatment initiation and start of treatment Year 2 will be recorded, where available in the patients' notes. EDSS is routinely collected as part of standard care in the UK as part of the annual assessment required for continuation of treatment.

- Proportion of patients with disability progression confirmed over 6 months, assessed by the EDSS, at 2 years after cladribine tablet treatment initiation

  An EDSS progression is defined as an increase in the EDSS scale as follows:

  - If the EDSS score at cladribine tablet initiation is 0, the increase must be ≥1.5 units
  - If the EDSS score at cladribine tablet initiation is ≥0.5 or ≤4.5, the increase must be ≥1.0 units
  - If the EDSS score at cladribine tablet initiation is ≥5.0, the increase must be ≥0.5 units.

  A confirmed disability progression is defined as EDSS progression (as defined above) confirmed after 6 months.

- Rates of selected, identified, and potentially clinically important AEs, including:
  - grade 3 lymphopenia
  - grade 4 lymphopenia
  - herpes infections
  - serious infections (infections for which a hospitalisation is initiated or extended)
  - opportunistic infections (new onset or reactivation of latent infection)
  - malignancies

These AEs will be reported from the date of cladribine tablet initiation and will be described overall and by most recent prior DMT subgroups (DMT naïve, prior platform treatment, prior high-efficacy cell-depleting treatment, and prior high-efficacy non-depleting treatment).

9.1.2.3 Others

For patients for whom any MRI data are available:

- Number of MRI lesions: T1 gadolinium enhancing lesions, T2 lesions (new/enlarging compared to a previous scan)

  MRI measures of white matter lesional activity (i.e., new/enlarging T2 lesions, T1 hypointense or Gd-enhancing T1 lesions) have shown to be valid surrogate endpoints for clinical outcomes of disease progression (Wattjes MP 2015).

9.2 Setting

9.2.1 Study Population

The study population will be recruited from approximately 7 or 8 sites in the UK and will be identified according to the inclusion and exclusion criteria listed below.

9.2.1.1 Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. At least 18 years of age at cladribine tablet treatment initiation

2. Physician diagnosis of HDA-RRMS as defined by clinical or radiological features

3. Treatment initiation with cladribine tablet monotherapy on or after 22 August 2017 and at least 3 years before enrolment

4. Completion of Year 1 treatment of cladribine tablets (Week 1 and Week 2 treatment, per recommended dose in Year 1: 1.75 mg/kg body weight, cumulatively)

5. Provide written informed consent to participate in the study

9.2.1.2 Exclusion Criteria

Patients are not eligible for this study if they fulfil any of the following exclusion criteria:

1. Received cladribine tablet treatment within an interventional clinical trial during the study period

2. Received treatment with any investigational therapy for RRMS in the 6 months prior to cladribine tablet treatment initiation

9.2.2 Definition of Study Cohorts and Description of Treatments

This is a multicentre chart review study enrolling subjects with HDA-RRMS, who completed at least Year 1 treatment with cladribine tablets in routine clinical practice following the SmPC.

According to the EU SmPC, each treatment year consists of 2 treatment weeks, 1 at the beginning of the first month and 1 at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days on which a subject receives 10 mg or 20 mg (1 or 2 tablets) as a single daily dose, depending on body weight. If necessary, the treatment course in Year 2 can be delayed for up to 6 months (18 months after initiation) to allow for recovery of lymphocytes (at least 800 cells/mm^3). If this recovery takes more than 6 months, the subject should not receive cladribine tablets anymore.

9.2.3 Observation Period

The total observation period per patient will vary, depending on the pre-enrolment time on cladribine tablet treatment (i.e., the period between the date of cladribine tablet initiation and study enrolment date). The observation period per patient, counting from 1 year prior to cladribine tablet initiation until the date of the second chart review, will be at minimum 5 years and at maximum 7 years.

9.2.4 Overview of Study Events

An overview of the planned study events and data collection are provided in Table 1.

At enrolment (i.e., date of signing informed consent form [ICF]), the first chart review should be performed within the following 28 calendar days. The second chart review should be approximately 1 year from enrolment (365 calendar days ± 14 calendar days).

The data have been collected per routine practice at the discretion of the treating physician. In addition, the patient's general practitioner may be contacted by the principal investigator or a member of the site team to obtain information regarding medical history and concomitant medications. All data will be collected upon availability.

Table 1 Schedule of Study Events

Data	Enrolment (Day 1)	Chart Review 1 (Day 1)	Chart Review 2 (Year 1)
Window	-	+28 days	±14 days
Informed consent	X		
Eligibility criteria		X	
Demographic data		X	
Medical history and comorbidities		X	
Medication history		X	
MS disease history		X	

Data	Enrolment (Day 1)	Chart Review 1 (Day 1)	Chart Review 2 (Year 1)
Prior disease-modifying therapies		X	
Treatment with cladribine tablets		X	
Subsequent disease-modifying therapies		X	X
COVID-19 vaccines		X	X
Clinical confirmed relapses		X	X
Annual EDSS scores		X	X
MRI data		X	X
Lymphocyte levels		X	X
Selected adverse events		X	X

EDSS: Expanded Disability Status Scale; MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis

9.2.5 Withdrawal from the Study

Patients are free to discontinue the study at any time without giving their reasons. In addition, patients can be withdrawn from the study for the following reason:

- Enrolment in an investigational clinical trial during the study period

9.3 Variables

- Demographic data at cladribine tablet initiation: Gender, age, height and weight measurements on or nearest to the date of initiating cladribine tablets in the year prior to treatment initiation
- Medical history and comorbidities at cladribine tablet initiation: All relevant medical history and comorbidities in the year prior to initiation with cladribine tablets (both past and ongoing comorbidities at date of initiation with cladribine tablets will be collected)
- Medication history at cladribine tablet initiation: Relevant medications taken in the year prior to initiation with cladribine tablets
- MS disease history: Date of initial MS diagnosis and type of MS at cladribine tablet initiation
- Prior DMTs: Any DMT for MS, taken since initial MS diagnosis and prior to initiating treatment with cladribine tablets, including starting date, end date, and dosage. The most recent DMT taken prior to initiation with cladribine tablets will be categorised in subgroups, as defined in Section 9.7.1.1:
    - naïve to DMT
    - prior platform therapy
    - prior high-efficacy cell-depleting treatment

  - prior high-efficacy non-depleting treatment

- Treatment with cladribine tablets: date of initiation of each treatment course, dose, potential date of discontinuation of treatment and reason for discontinuation, if applicable.

- Subsequent DMTs: Other DMTs for MS initiated after treatment with cladribine tablets will be recorded, including the date of initiation, potential discontinuation date, and dosage.

- COVID-19 vaccines: Vaccines for coronavirus disease 2019 (COVID-19) attributable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) administered in the years after initiation of cladribine tablets (until end of observation period) will be recorded.

- Course of disease:
  - clinician confirmed relapses: Each relapse that occurred in the year prior to treatment initiation with cladribine tablets and each year after will be recorded with the onset date (at least month and year)
  - annual EDSS scores: At start of cladribine tablet treatment Year 1, at the start of cladribine tablet treatment Year 2, and 2 years after cladribine tablet treatment initiation
  - MRI data (upon availability): T1 gadolinium enhancing lesions, T2 lesions (new/enlarging compared to a previous scan)

- Lymphocyte levels: At initiation of cladribine tablet treatment and during the years after, where available.

- Selected adverse events: Reporting of AEs once informed consent has been obtained (as described in Section 11), with special focus on:
  - grade 3 lymphopenia
  - grade 4 lymphopenia
  - herpes infections
  - serious infections (infections for which a hospitalisation is initiated or extended), opportunistic infections (new onset or reactivation of latent infection)
  - malignancies.

  For each AE, the start date, end date, classification of serious or non-serious, and outcome should be reported.

Derived and transformed data needed for the analysis are described in Section 9.7.2.

9.4 Data Source

Data for this study will be abstracted from patients' medical records. The investigator or appropriately delegated personnel will transcribe data from medical records into an electronic case

report form (eCRF). In addition, the patient's general practitioner may be contacted by the principal investigator or a member of the site team to obtain information regarding medical history and concomitant medications. The data in the eCRF should be consistent with the relevant source documents. Site staff will be entering data.

Data collected from the patient's medical records will include demographics, MRI scan reports, medical and medication history, comorbidities, cladribine tablet treatment, concomitant medications, and AEs. All data will be reviewed and potentially queried for clarifications and/or corrections of inconsistent or missing data. Further details are provided in Section 9.6.

9.5 Study Size

Approximately 200 patients will be enrolled in this study, with a minimum of 90 patients. This sample size is based on an estimation of what is feasible during the study period. The study will not be powered to detect or report statistical differences and has no comparator group. It will be qualitative and descriptive in nature.

With an expected annualised relapse rate of 0.14 over 2 years (Giovannoni 2010), the distance from proportion to limit of the corresponding 95% confidence interval (CI) will be 0.072 based on available data for 90 patients.

9.6 Data Management

The main purpose of the eCRF is to obtain data required by the non-interventional study protocol in a complete, accurate, legible, and timely manner. The data in the eCRF should be consistent with the relevant source documents.

The investigator or designee is responsible for ensuring that the data collected in the course of this study is accurate and documented appropriately on all applicable forms. Data will then be processed, evaluated, and stored in pseudo-anonymous form in accordance with applicable data protection regulations. The investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any patient names.

The data will be entered into a GCP Compliant and validated database. The Sponsor/Contract Research Organization (CRO) or its designee will be responsible for data processing, in accordance with the Sponsor's/CRO's data management procedures. Database lock will occur once quality control and quality assurance procedures and coding activities have been completed. PDF files of the eCRFs will be provided to the investigators at the completion of the study.

The eCRFs are essential study documents and must be suitable for regulatory inspections and submissions.

9.7 Data Analysis

Further details will be provided in an integrated analysis plan (IAP). The IAP will be finalized prior to any planned analysis, but latest before database lock and will be included in the clinical study report for this protocol. The final IAP will consider any amendment to the protocol.

9.7.1 Analysis Sets

Full Analysis Set

The Full Analysis Set (FAS) is defined as all enrolled patients who were treated with at least one course of treatment with cladribine tablets.

Additional analysis sets may be described in the IAP.

9.7.1.1 Analysis Subgroups

The analysis of the primary and secondary outcomes will be performed among the following subgroups of the most recent DMT taken prior to initiation with cladribine tablets. A non-exhaustive list of such regulatory approved DMTs by subgroup is provided in Table 2.

Table 2 Subgroups by Most Recent prior disease-modifying therapy

Previous disease-modifying therapy class	Therapies
Naïve to disease-modifying therapies	-
Prior platform therapy	Interferon beta; teriflunomide; dimethyl fumarate; glatiramer acetate
Prior high-efficacy cell-depleting treatment	Alemtuzumab; ocrelizumab
Prior high-efficacy non-depleting treatment	Natalizumab; fingolimod

Patients will be classified in only one of the subgroups. For patients who have taken more than one prior DMT, the drug which was taken most recently prior to treatment initiation with cladribine tablets (i.e., the last prior DMT) will be used for categorisation. Patients who had a gap period between the most recent prior DMT and the initiation with cladribine tablets will be classified in the subgroup according to their last prior therapy.

The medications will be coded using WHO Drug Dictionary. A list of the medication codes that qualify for enrolment in each subgroup will be provided in the IAP.

9.7.2 Derived and Transformed Data

Details on the eventual derivation/transformation of the analysis variables will be given in the IAP.

In general, no imputation of missing data will be done.

9.7.3 Statistical Methods

No formal statistical hypothesis will be tested, given the descriptive nature of the study.

Descriptive statistics will be used to summarize data. Quantitative (continuous) variables will be summarised using descriptive statistics, i.e., the number of patients with non-missing value, the number of patients with missing value, the mean, SD, median, minimum, and maximum, and first and third quartile. Qualitative (categorical) variables will be displayed as frequency counts and percentages (n, %).

If CIs are to be calculated, these will be 2-sided with a confidence probability of 95%, unless otherwise specified. For continuous data, CIs for the mean will be calculated assuming a normal distribution of the data. The CIs for binary outcomes will be presented using the Clopper-Pearson method.

The primary, secondary, and other analyses will be performed on the FAS.

Primary Outcome Analysis

The annualised relapse rate for a patient is defined as the number of clinician's confirmed relapses that occurred in the year prior to the date of cladribine tablet initiation, and in Years 1, 2, 3, 4 and 5 after treatment initiation with cladribine tablets (upon availability, depending on the available observation time):

- Year prior to date of cladribine tablet initiation: Month -12 to the day before the date of cladribine tablet initiation (Start Month 1)
- Year 1: Start Month 1 to End of Month 12
- Year 2: Start Month 13 to End of Month 24
- Year 3: Start Month 25 to End of Month 36
- Year 4: Start Month 37 to End of Month 48
- Year 5: Start Month 49 to End of Month 60

Relapses will be counted for the defined time period if the date of onset of the relapse is within the defined time period. In the analyses defined in the IAP, an "induction period" after treatment initiation may be considered for the annualised relapse rate in Year 1.

The annualised relapse rate for a patient will be calculated by dividing the number of clinician confirmed relapses during the period by the person-years of the patient (i.e., the period [in days] that a patient was observed in the study divided by 365.25).

The estimated annualised relapse rate in each of the defined years above will be summarised using descriptive statistics for continuous variables.

The annualised relapse rate will be described overall and among the subgroups by most recent prior DMT, as defined in Table 2.

Secondary Outcome Analysis

The proportion of patients who remain relapse-free in each year after treatment initiation (among patients active at start of each year), at 4 years after treatment initiation and at 5 years after treatment initiation (among patients with 5 years observation time available), and the time from cladribine tablet initiation to first relapse will be described using Kaplan-Meier method. Kaplan-Meier survival curve will be plotted (overall and by most recent prior DMT subgroup) and a table with the probabilities of remaining relapse-free in each year after initiation of treatment will be produced.

The proportion of patients who discontinued cladribine tablets and reasons for discontinuation will be summarised using descriptive statistics.

Subsequent DMTs (none or by DMT type) received after treatment with cladribine tablets will be described up to 5 years after cladribine tablet initiation. The proportion of patients who did not receive any other DMT up to a total of 4 years and up to a total of 5 years (among patients with 5 years observation time available) after cladribine tablet treatment initiation will be analysed using descriptive statistics. Depending on the availability of data and the missing data pattern, a survival analysis may be performed to account for loss to follow-up patterns.

The annual EDSS scores at treatment initiation and start of cladribine tablet treatment at Year 2 will be summarised using descriptive statistics. The proportion of patients with disability progression confirmed over 6 months at 2 years after cladribine tablet initiation will be summarised using descriptive statistics.

The number and percentages of patients with AEs will be reported, and the number of AEs itself. The incidence rates of AEs will be summarised by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Additional summaries will be presented by severity. The AEs will be reported overall, and as stratified in the last prior MS DMT subgroups (as defined in Table 2).

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9.7.4 Sequence of Analyses

The main analysis will be performed once the study is completed with the purpose of evaluating all outcomes and database is locked.

9.8 Quality Control

Quality control activities will include verification of data and ensure the data collected in the eCRF is accurate, valid and in accordance with the protocol. Only authorized staff will have access to the Electronic Data Capture system via a secure website and will receive training regarding data entering in the eCRF.

Representatives of Sponsor and/or its delegates must be allowed to visit all study site locations to assess the data quality and study integrity. On site, they will review study files and, if allowed by local laws and regulations, subject medical charts to compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by Sponsor internal auditors and government inspectors who must be allowed access to case report forms (CRFs), source documents, other study files, and study facilities. The investigator must notify Sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor.

9.9 Limitations of the Research Methods

This study is open label and observational, and data are abstracted from medical records. There is limited control over patient assessment as patient monitoring and diagnostics are per standard of care. This may result in missing data. In addition, variability in the treatments received may limit interpretation of the results (e.g., decreased adherence to, or early discontinuation of cladribine tablet treatment courses, or potential interaction with medication for other conditions). Patient specific methodological challenges such as potential biases from patient selection and loss to follow-up of patients through study attrition are also other limitations. Furthermore, the inclusion/exclusion criteria of the study limit the study population to patients who are alive at least 3 years after cladribine tablet treatment initiation and are able to provide informed consent; consequently, patients who have passed away after cladribine tablet treatment initiation are excluded. In addition, the first-year treatment course must have been completed by the patients, thus patients who discontinued treatment due to, for instance, an immediate adverse drug reaction will be excluded from participation.

9.10 Other Aspects

9.10.1 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the study at a given site, the protocol will be submitted together with its associated documents (specify which documents, e.g., consent form) to the responsible Independent Ethics Committee (IEC) for its favourable opinion/approval. The written favourable opinion/approval of the IEC will be filed by the investigator and a copy will be sent to the Sponsor.

The study must not start at a site before the Sponsor has obtained written confirmation of favourable opinion/approval from the concerned IEC and R&D approval is in place at the site level. The IEC will be asked to provide documentation of the date of the meeting at which the favourable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favourable opinion/approval that clearly identifies the study, the protocol version, and the Patient Information and Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the protocol will also be submitted to the concerned IEC/IRB before implementation in case of substantial changes.

9.10.2 Monitoring

This trial will be monitored in accordance with the ICH GCP, and any other applicable regulations. The site Monitor will perform study visits to the trial site or remotely at regular intervals.

9.10.3 Health Authorities

As chart review study, no approval is required from the National Health Authorities, as in accordance with the regulations of the UK.

9.10.4 Quality Assurance

In compliance with regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies, or IECs may conduct quality assurance audits/inspections at any time during or following a study. The investigator must agree to allow auditors/inspectors direct access to all study-related documents, including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors/inspectors in order to discuss findings and issues.

The protocol, each step of the data capture procedure, and the handling of the data, as well as the study report, may be subject to independent Clinical Quality Assurance. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.10.5 Archiving

The archive should be maintained for the period specified by local regulations, where applicable. All original patient files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations. In the absence of applicable regulations, the archive should be maintained for at least 5 years after the final study report or the first publication of study results, whichever comes later. In any case, the investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10 Protection of Human Subjects

10.1 Subject Information and Informed Consent

An unconditional prerequisite for a patient's participation in the study is his/her written informed consent. The patient's written informed consent to participate in the study must be given before any study-related activities are carried out.

Adequate information must therefore be given to the patient by the investigator before informed consent is obtained (a person designated by the investigator may give the information, if permitted by local regulations). A patient information sheet in the local language will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential participant, the investigator or his/her designee will inform the patient verbally of all pertinent aspects of the study *(the language used in doing so must be chosen so that*

the information can be fully and readily understood by laypersons). Depending on national regulations, a delegate assigned by the investigator may inform the subject and sign the Informed Consent Form.

The Informed Consent Form must be signed and personally dated by the patient and the investigator. The signed and dated declaration of informed consent will remain at the investigator's site and must be safely archived by the investigator. A copy of the signed and dated information and consent form should be provided to the patient prior to participation.

In case of remote consent, the site will contact the patient by phone to explain the study and will send the Information sheet and Informed Consent Form to the patients who have interest to participate. Patients will have the opportunity to ask questions over the phone and will be given sufficient time to decide whether they would like to participate. It will be clear that participation is voluntary, and the patients will be able to decide freely if they wish to participate. If the patient is willing to participate, informed consent will be provided by phone and by written consent. The medical records of the patients will need a statement that informed consent was obtained before starting the data collection. The informed consent procedure will meet requirements of local regulations.

Whenever important new information becomes available that may be relevant to the patient's consent, the written patient information sheet and any other written information provided to patients will be revised by the Sponsor and be submitted again to the IEC for review and favourable opinion. The agreed, revised information will be forwarded to each patient in the study. The investigator will explain the changes to the previous version.

10.2 Subject Identification and Privacy

When a patient is enrolled (i.e., informed consent is provided), the investigator will assign a unique subject number. This number will serve as the patient's identifier in the study as well in the study database.

Only authorized persons will have access to identifiable personal details, if required for data verification. The patient's original medical data that are reviewed at the site during source data verification by the Monitor, audits, and Health Authority inspections will be kept strictly confidential. The investigator agrees to provide direct access to these documents to the Sponsor and to Health Authority representatives. The investigator is responsible for retrieving information from personal medical records.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Patients will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

11 Adverse Events

11.1 Definitions

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

Investigators should assess the severity/intensity of any AE as follows:

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the subject is unable to carry out usual activities.

A serious adverse event is any AE as defined above, which also fulfils at least one of the seriousness criteria below:

- Results in death
- Is life-threatening[1)]
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered as medically important[2)]

[1)] Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

[2)] Medical and scientific judgement should be exercised in deciding whether other situations should be considered as serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require an intervention to prevent one of the other outcomes listed above. Such important medical events should be considered as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. As a guidance, the important medical event terms list is intended to be used for assessment of suspected adverse reactions (see EMA/207865/2017).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

11.2 Management and Reporting of Adverse Events

In this study, safety data collection is based on secondary use of pseudo-anonymised data from existing patient records. Any AEs will be abstracted from the patient records, regardless of seriousness or relationship to cladribine tablets, from the date of initiation of treatment with cladribine tablets until the end of the study period.

Reports of the selected AEs (as listed in Section 9.1.2.2) will be summarised in the final study report(s).

The investigator will comply with UK pharmacovigilance requirements as defined by HMR (Part-11) to spontaneously report appropriate safety data to the Medicines and Healthcare products Regulatory Agency (MHRA) (e.g., Yellow Card Scheme) as applicable or directly to Merck Serono Ltd.

12 Plans for Disseminating and Communicating Study Results

12.1 Study Report

The completed study will be summarised in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings.

12.2 Publication

The first publication will be a publication of the results of the analysis of the primary outcomes that will include data from all study sites.

The investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by investigators or their representatives will require pre-submission review and approval by the Sponsor.

The Sponsor will not suppress or veto publications but maintains the right to delay publication in order to protect intellectual property rights.

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14 Appendices

14.1 Signature Pages and Responsible Persons for the Study

Signature Page – Protocol Lead

Study Title:	**C**ladribine tablets in Highly-**a**ctive Relapsing **M**ultiple Sclerosis - R**ea**l-W**o**rld Effec**t**iveness in UK Clinical Practice (CAMELOT-MS)
Study Protocol Date / Version:	25 March 2022, Version 2.0

Protocol Lead responsible for designing the non-interventional study:

I approve the design of the non-interventional study:

PPD

Signature

29/03/2022

Date of Signature

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	Merck Serono
Address:	5 New Square, Bedfont Lakes Business Park Feltham, Middlesex TW14 8HA, United Kingdom
Telephone number:	PPD
Fax number:	
E-mail address:	PPD

Signature Page – Protocol Lead

Study Title:	**C**ladribine tablets in Highly-**a**ctive Relapsing **M**ultiple Sclerosis - **R**ea**l**-W**o**rld Effec**t**iveness in UK Clinical Practice (CAMELOT-MS)
Study Protocol Date / Version:	25 March 2022, Version 2.0

Protocol Lead responsible for designing the non-interventional study:

I approve the design of the non-interventional study:

PPD

_____ _____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	Merck Serono
Address:	5 New Square, Bedfont Lakes Business Park Feltham, Middlesex TW14 8HA, United Kingdom
Telephone number:	PPD
E-mail address:	PPD

Signature Page – Coordinating Investigator

Study Title	**C**ladribine tablets in Highly-**a**ctive Relapsing **M**ultiple Sclerosis - R**ea**l-W**o**rld Effec**t**iveness in UK Clinical Practice (CAMELOT-MS)
Study Protocol Date / Version	25 March 2022, Version 2.0

I approve the design of the non-interventional study and I understand and will conduct the study according to the study protocol, any approved protocol amendments, Good Pharmaco-epidemiology Practices (GPP) and all applicable Health Authority requirements and national laws.

PPD

29/03/2022

Signature

Date of Signature

Name, academic degree: PPD

Function / Title: PPD

Institution: PPD

Address: PPD

Telephone number: PPD

E-mail address: PPD

Signature Page – Principal Investigator

Study Title	**C**ladribine tablets in Highly-**a**ctive Relapsing **M**ultiple Sclerosis - R**e**a**l**-W**o**rld Effec**t**iveness in UK Clinical Practice (CAMELOT-MS)
Study Protocol Date / Version	25 March 2022, Version 2.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the study at this site and affirm that I understand and will conduct the study according to the study protocol, any approved protocol amendments, Good Pharmaco-epidemiology Practices (GPP) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Sponsor Responsible Persons not Named on the Cover Page

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	Merck
Address:	Merck 21F, Nuo Center Office, No.2A, Jiangtai Road, Chaoyang District, 100016, Beijing, China
Telephone number:	PPD
Fax number:	
E-mail address:	PPD