CLASS STUDY

A 4-year non-interventional, multicentre, prospective study to evaluate effectiveness, adherence and safety of CLAdribine tablets in patients with highly active relapsing multiple Sclerosis in Slovakia

Protocol No.: MS700568-0102

Non-interventional clinical study

Coordinating Investigator

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Sponsor

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Protocol version

1.0. from 13th January 2020

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Coordinating Investigator:

I agree to conduct the study in accordance with this Protocol and in compliance with all applicable Health Authority requirements and national laws.

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Protocol Number: MS700568-0102
Protocol Version: 13 January 2020 / Version 1.0

Principal Investigator:

The signature below constitutes the approval of this protocol and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and ICH guidelines.

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Name

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Signature *Date of signature*

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1 PROTOCOL SUMMARY

Trial Title:	**A 4-year non-interventional, multicentre, prospective study to evaluate effectiveness, adherence and safety of cladribine tablets in patients with highly active relapsing multiple sclerosis in Slovakia**
Protocol No:	MS700568-0102
Sponsor	Nezisková organizácia CARMENTA Agátová 3385/5E 841 01 Bratislava Slovakia
Coordinating Investigator:	Prof. MD. Peter Turčáni PhD. First Department of Neurology, Faculty of Medicine, Comenius University, Nemocnica Stare Mesto, Mickiewiczova 13, 81369 Bratislava, Slovak Republic
Location:	Slovakia
Medicinal Product:	Cladribine (MAVENCLAD®), oral tablets. Decision to initiate treatment with cladribine has to be made before patient is enrolled to the study. Dosing and administration of cladribine will be performed in accordance with MAVENCLAD® Summary of Product Characteristics (SmPC) applicable in Slovakia including management of concomitant medication. Administration and choice of rescue therapy will be fully in discretion of the physician and according to standard of care.
Rationale:	Cladribine is an oral disease modifying drug (DMD) approved for the treatment of adult patients with highly active relapsing multiple sclerosis. Cladribine is a nucleoside analogue of deoxyadenosine that has been shown to exert long-lasting effects by preferentially targeting lymphocytes and the autoimmune processes involved in the pathophysiology of MS. Of note, Cladribine 10 mg tablets treatment consists in 16 to maximum 20 days of oral dosing in the first 2 years with no further treatment required in the next 2 years. The aim of the present study is to evaluate clinical benefits of Cladribine 10 mg tablets treatment in real-life settings of Slovakian standard care as this information is missing to date.
Study Objectives:	**Primary** • To assess the effectiveness of Cladribine 10 mg tablets in the real life settings by the Annualized Relapse Rate (ARR)[1] during the 4-year observational period.

[1] A relapse is defined as meeting the following criteria:

	Secondary • To evaluate disability progression[2] occurrence during the 4-year study observational period. • To evaluate changes of Expanded Disability Status Scale (EDSS) during the 4-year study observational period. • To evaluate the MRI measures performed yearly during the 4-year study observational period. • To evaluate the proportion of patients receiving rescue therapy according to the local standards of care during the 4-year observational period. • To evaluate the patient adherence to Cladribine 10 mg tablets treatment after both dosing periods in year 1 and 2. • To evaluate association of patient adherence to treatment with relapse occurrence during the 4-year study observational period. • To evaluate safety of Cladribine 10 mg tablets treatment during the 4-year study observational period.
Study Design:	This is a non-interventional, multicentre, prospective, study for patients with highly active relapsing MS for whom Cladribine 10 mg tablets therapy was indicated independently before enrolment to the study. Eligible subjects will undergo all visits and procedures before and during the treatment as per local standards and Cladribine 10 mg tablets administration will be in accordance with approved SmPC. Protocol does NOT define any mandatory

1. Neurological abnormality, either newly appearing or re-appearing, with abnormality specified by both
    a. Neurological abnormality separated by at least 30 days from onset of a preceding clinical event
    and
    b. Neurological abnormality lasting for at least 24 hours
2. Absence of fever or known infection (fever with temperature (axillary, orally or intrauriculary) > 37.5°C)
3. Objective neurological impairment, correlating with the subject's reported symptoms, defined as either
    a. Increase in at least one of the functional system (FS) scores of the EDSS
    or
    b. Increase of the total EDSS score

The occurrence of paraesthesia, fatigue, mental symptoms, and/or vegetative symptoms without any additional symptom will not be classified as an MS clinical relapse.

[2] The time to sustained progression of disability is defined as the time to a sustained increase (for at least 3 months) of at least 1 point in the EDSS score compared to baseline for all subjects with an EDSS ≤5.0 or an increase of at least 1.5 points if the baseline EDSS score was 0.

	assessment. Assessments schedule is approximate, all described assessments and events will be collected and finally statistician will analyse them within relevant window for respective visit. According to standard practice in Slovakia, patients treated by DMD visit their physician at MS centre at least once per year (as required by payers) but usually every 3 months. Patients will be followed up to 4 years after the first dose of Cladribine 10 mg tablets. Patients with low lymphocyte count to start Cladribine 10 mg tablets therapy after the first year are allowed to postpone second cycle up to 6 months until lymphocyte count recovers (as per SmPC) and therefore their participation may take up to 4.5 years.
Patient Selection Criteria:	**Total expected number of participating patients: 100** **Inclusion Criteria:** • Age ≥18 years. • Patients for whom start of Cladribine 10 mg tablets therapy for highly active relapsing MS (relapsing-remitting multiple sclerosis – RRMS, or secondary progressive multiple sclerosis - SPMS) has been indicated independently before signing informed consent. • Patient fulfils following local indication criteria for Cladribine 10 mg tablets treatment as applicable in standard of care: ○ 1 severe relapse treated by corticosteroids or EDSS score increase by at least 1 grade during the previous year and at least 1 T1Gd+ lesion or 9 or more T2 lesions during the treatment by at least one other DMD, OR ○ 2 or more disability causing relapses treated by corticosteroids during the previous year and treated or untreated by the other DMD. MS diagnosis has to be confirmed by cerebrospinal fluid examination. • Signed informed consent. • Ability to communicate with investigator and study staff and to comply with their instructions for the entire length of the study participation. **Exclusion criteria:** • Other type of MS than highly active relapsing MS. • Contraindications listed in Cladribine 10 mg tablets

	SmPC. • Moderate or severe hepatic impairment (Child-Pugh score >6) • Patient (men and women of childbearing potential) is unable or unwilling to practice birth control during Cladribine 10 mg tablets treatment and for at least 6 months after the last dose. • Concurrent participation in any interventional study.
Recruitment modalities:	**Site selection:** 12 centres specialized in the care of patients with MS across Slovakia **Patient selection:** Physician will offer participation to all consecutive patients meeting eligibility criteria during the enrolment period. Competitive enrolment is allowed.
Study endpoints:	**Primary:** • ARR at 48 months **Secondary:** • Proportion of relapse-free patients at 24 and 48 months • ARR at 24 months • The time to sustained progression of disability from baseline up to 24 and 48 months • Time to the first relapse from baseline up to 48 months • Time to the second relapse from baseline up to 48 months • Changes in mean number of T1 Gd+ lesions per MRI scan taken at 12, 24, 36 and 48 months compared to baseline • Changes in mean number of active T2-weighted lesions per MRI scan taken at 12, 24, 36 and 48 months compared to baseline • Changes in level of disability as measured by EDSS at 6, 12, 18, 24, 30, 36, 42 and 48 months compared to baseline • No evidence of disease activity (NEDA-3) at 24 and 48 months • The proportion of patients receiving rescue therapy according to local standards of care from baseline up to 48 months • Patient adherence to Cladribine 10 mg tablets treatment after both dosing periods as assessed at 3 and 15 months (by counting used tablets from original

	packages as patients will be asked to bring them to the site). • Frequency of adverse events (AE) interviewed or reported spontaneously by the patients or as noted on physical, MRI or laboratory examinations up to month 48 • Percentage of patients with at least 1 Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 Lymphocyte Toxicity up to month 48 • Median time to recovery from grade 3 or 4 Lymphocyte Toxicity • Percentage of patients who developed herpes zoster infections or malignancies up to month 48
Collected Data:	**V1 - Pre-dose Year 1 Visit** Date of visit, date of ICF signature (if different), meeting of eligibility criteria (yes/no) Basic demographic data: • Year of birth • Gender Baseline characteristics: • Relevant medical history • Relevant concurrent diseases/concomitant medications Condition of MS: • Date of MS diagnosis • Medical history related to MS • Previous MS therapy • Number of relapses in the last 12 months • Current EDSS score • Current MRI status (within 3 months) Pre-treatment requirements • Is patient eligible to start Cladribine 10 mg tablets therapy as per SmPC? (yes/no) • Patient weight • Lymphocyte count • Number of Cladribine 10 mg tablets to be used in the whole treatment course year 1 **V2 - Visit Month 3 Year 1** (2 months after the first dose of Cladribine 10 mg tablets in Year 1)

	• Visit date • Date of Cladribine 10 mg tablet therapy start Number of Cladribine 10 mg tablets really used the whole treatment course year 1 • Lymphocyte count • Any relapse and rescue therapy from the last visit • Any AE from the last visit • Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit **V3 - Visit Month 7 Year 1** (6 months after the first dose of Cladribine 10 mg tablets in Year 1) • Visit date • Lymphocyte count • EDSS score • Any relapse and rescue therapy from the last visit • Any AE from the last visit • Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit **V4 - Pre-dose Year 2** (12 months after the first dose of Cladribine 10 mg tablets in Year 1; For patients with lymphocyte count bellow 800 cells/mm³ the treatment course in year 2 must be delayed for up to 6 months to allow for recovery of lymphocytes. For these patients will be postponed until recovery - up to maximum of 6 months). • Visit date • Is patient eligible to continue Cladribine 10 mg tablets therapy as per SmPC? (yes/no) • MRI status • EDSS score • Patient weight • Lymphocyte count • Number of Cladribine 10 mg tablets to be used in the whole treatment course year 2 • Any relapse and rescue therapy from the last visit • Any AE from the last visit • Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit

	V5 - Visit Month 3 Year 2 (2 months after the first dose of Cladribine 10 mg tablets in Year 2) • Visit date • Date of Cladribine 10 mg tablet therapy start Number of Cladribine 10 mg tablets really used in the whole treatment course year 2 • Lymphocyte count • Any relapse and rescue therapy from the last visit • Any AE from the last visit • Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit **V6 - Visit Month 7 Year 2** (6 months after the first dose of Cladribine 10 mg tablets in Year 2) • Visit date • Lymphocyte count • EDSS score • Any relapse and rescue therapy from the last visit • Any AE from the last visit • Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit **V7 - Visit Month 12 Year 2/month 1 Year 3** (12 months after the first dose of Cladribine 10 mg tablets in Year 2) • Visit date • MRI status • EDSS score • Any relapse and rescue therapy from the last visit • Any AE from the last visit • Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit **V8 - Visit Month 7 Year 3** (18 months after the first dose of Cladribine 10 mg tablets in Year 2) • Visit date • EDSS score • Any relapse and rescue therapy from the last visit • Any AE from the last visit • Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants,

	anxiolytics) from the last visit **V9 - Visit Month 12 Year3/month 1 Year 4** (24 months after the first dose of Cladribine 10 mg tablets in Year 2) • Visit date • MRI status • EDSS score • Any relapse and rescue therapy from the last visit • Any AE from the last visit • Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit **V10 - Visit Month 7 Year 4** (30 months after the first dose of Cladribine 10 mg tablets in Year 2) • Visit date • EDSS score • Any relapse and rescue therapy from the last visit • Any AE from the last visit • Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit **EOS - Visit Month 12 Year 4** (36 months after the first dose of Cladribine 10 mg tablets in Year 2)/**Premature Withdrawal Visit** • Visit date • MRI status • EDSS score • Any relapse and rescue therapy from the last visit • Any AE from the last visit • Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit • Reasons for premature withdrawal if applicable
Statistical Considerations:	Analysis of collected data is based on descriptive statistics including absolute and relative frequencies of discrete variables. Continuous variables are described by count (without missing), mean and its 95% confidence interval (CI), standard deviation, median, minimum, and maximum. Discrete variables are described by count (absolute frequency), and percentages (relative frequency). Missing data will not be replaced. Analysis of primary endpoint - ARR at 48 months - will be

	performed using descriptive statistics: count (without missing), mean and its 95% confidence interval, standard deviation, median, minimum and maximum. Interim analysis will be performed when all patients complete visit at month 25 or withdraw earlier. A sample size of 85 subjects will have more than 80% power to achieve a supposed ARR 0.14 (95 % CI: 0.12–0.17) using a 2-sided significance level of 0.05. Assuming a 15% drop-out rate, a total of 100 patients will be targeted for this study.
Study Timelines:	First patient first visit: April 2020 Last patient first visit: August 2021 End of data collection: October 2025 Enrolment period: 18 months Participation of each patient will take approximately: 4 years (48 months). However, patients who postpone their therapy in year 2 due to low lymphocyte count up to 6 months (as per SmPC) are allowed to take part for up to 4.5 years in this case.

2 LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
ARR	Annualized Relapse Rate
CTCAE	Common Terminology Criteria for Adverse Events
DMD	Disease Modifying Drug
DMT	Disease Modifying Therapy
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
EOS	End of Study Visit
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IEC	Independent Ethics Committee
MAH	Marketing authorization holder
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NEDA	No evidence of disease activity
PML	Progressive Multifocal Leukoencephalopathy
PW	Premature Withdrawal
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SPMS	Secondary Progressive Multiple Sclerosis

3 INTRODUCTION AND RATIONALE

Number of available disease modifying treatments (DMT) for patients with multiple sclerosis (MS) increased considerably in the past decade, however treatment responses are often less than complete, and concern regarding safety and side effect profiles may limit the general use of these drugs. The need for parenteral administration may present relative or absolute barriers to access, limiting treatment adherence and long-term outcomes.

Cladribine 10 mg tablets (MAVENCLAD®) is a novel oral disease modifying drug (DMD) approved in European Union for the treatment of adult patients with highly active relapsing multiple sclerosis.

Cladribine is a nucleoside analogue of deoxyadenosine, which preferentially depletes lymphocytes by exploiting the kinase-to-phosphatase enzyme profile in these cells. This produces moderate and discontinuous reductions in T and B cells with relatively minor and transient effects on innate immune cells, such as neutrophils and monocytes. The dosing regimen of cladribine tablets involves very short treatment periods relative to the length of

clinical effect to moderate lymphopenia, reflecting the cladribine mode of action (Mavenclad Summary of Product Characteristics – SmPC, 2018).

To achieve disease control over 4 years with Cladribine 10 mg tablets (Giovannoni et al., 2018), a maximum of 20 days of oral dosing in the first 2 years is needed with no further treatment required in the next 2 years. 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 treatment year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight (MAVENCLAD SmPC, 2018).

Table 3-1: Schedule of Cladribine 10 mg tablets dosing and lymphocyte count monitoring per SmPC

	Pre-dose	Month 1	Month 2	Month 3	Months 4-6	Month 7	Months 8-12
Year 1	Lymphocyte count	maximum 5 day dosing	maximum 5 day dosing	Lymphocyte count		Lymphocyte count	
Year 2	Lymphocyte count	maximum 5 day dosing	maximum 5 day dosing	Lymphocyte count		Lymphocyte count	
Year 3							
Year 4							

In terms of efficacy, Cladribine 10 mg tablets has consistently shown robust clinically and statistically significant benefits in subjects across the spectrum of RRMS (early to late stages, treatment naïve or experienced subjects) (Giovannoni et al., 2010; Leist et al., 2014) with improvements in both clinical and radiological efficacy outcomes. In particular, it was found that treatment with oral Cladribine 10 mg tablets resulted in significant improvements in the annualized relapse rate (ARR) with significantly more subjects remaining free from relapse, free from 3-month sustained Expanded Disability Status Scale (EDSS) progression and free from magnetic resonance imaging (MRI) lesion activity over 96 weeks compared to placebo (Giovannoni et al., 2010).

Furthermore, safety and tolerability profile of Cladribine 10 mg tablets is favourable and well characterized as resulted from extensive clinical study experience, namely with 3 Phase III studies (CLARITY, ORACLE and ONWARD) and an 8-year safety registry (PREMIERE) (Giovannoni et al., 2010; Comi et al., 2018; Leist et al., 2014; Montalban et al., 2018; Cook et al., 2019).

Since none of cladribine clinical studies has been conducted in Slovakia to date, efficacy and safety data from this country are missing. The aim of the present study is to evaluate clinical benefits of Cladribine 10 mg tablets treatment in real-life settings of Slovakian clinical practice as this information is standard requirement of health authorities and payers and is especially demanded by local medical community. Due to specific prescribing limitation issued by Slovakian Ministry of Health (as described in Inclusion criteria), there is no possibility to extrapolate such data from any other European country. Except relapse and disability progression rate assessment as key effectiveness parameters, change of EDSS, patient adherence and safety data will be evaluated in this CLASS study.

4 STUDY OBJECTIVES

4.1 Primary

- To assess the effectiveness of Cladribine 10 mg tablets in the real life settings by the ARR[3] during the 4-year observational period.

4.2 Secondary

- To evaluate disability progression[4] occurrence during the 4-year study observational period.
- To evaluate changes of EDSS during the 4-year study observational period.
- To evaluate the MRI measures performed yearly during the 4-year study observational period.
- To evaluate the proportion of patients receiving rescue therapy according to the local standards of care during the 4-year observational period.
- To evaluate the patient adherence to Cladribine 10 mg tablets treatment after both dosing periods in year 1 and 2.
- To evaluate association of patient adherence to treatment with relapse occurrence during the 4-year study observational period.
- To evaluate safety of Cladribine 10 mg tablets treatment during the 4-year study observational period.

[3] A relapse is defined as meeting the following criteria:

4. Neurological abnormality, either newly appearing or re-appearing, with abnormality specified by both
    a. Neurological abnormality separated by at least 30 days from onset of a preceding clinical event

    and

    b. Neurological abnormality lasting for at least 24 hours
5. Absence of fever or known infection (fever with temperature (axillary, orally or intrauriculary) > 37.5°C)
6. Objective neurological impairment, correlating with the subject's reported symptoms, defined as either
    a. Increase in at least one of the functional system (FS) scores of the EDSS
    or
    b. Increase of the total EDSS score

The occurrence of paraesthesia, fatigue, mental symptoms, and/or vegetative symptoms without any additional symptom will not be classified as an MS clinical relapse.

[4] The time to sustained progression of disability is defined as the time to a sustained increase (for at least 3 months) of at least 1 point in the EDSS score compared to baseline for all subjects with an EDSS ≤5.0 or an increase of at least 1.5 points if the baseline EDSS score was 0.

5 STUDY DESIGN

5.1 Description of the study design

This is a non-interventional, multicentre, prospective study for patients with highly active relapsing MS for whom Cladribine 10 mg tablets therapy was indicated independently before enrolment to the study. It is planned to enrol about 100 patients in 12 sites specialized for MS treatment in Slovakia (for sample size consideration please see Section 12.1).

Eligible subjects will undergo all visits and procedures before and during the treatment as per local standards and Cladribine 10 mg tablets administration will be in accordance with approved SmPC. There is no assessment mandated per study protocol. Management of disease including administration of rescue therapy and visit schedule are fully at the treating physician's discretion. Data for the study will be extracted from medical charts and entered into the electronic Case Report Forms (eCRF). Study assessments schedule (Table 8-1: Flow chart) is approximate, all described assessments and events will be collected and finally statistician will analyse them within relevant window for respective visit. According to standard practice in Slovakia, patients treated by DMD visit their physician at MS centre at least once per year (as required by payers) but usually every 3 months.

To collect high quality adherence data, patients will be asked to bring used/partially used Cladribine 10 mg tablets packages to the next visit after dosing and physicians will record number of actually used tablets, if Cladribine 10 mg tablets are not administered in the participating site as per standard practice.

Patients will be followed up to 4 years after the first dose of Cladribine 10 mg tablets. Patients with low lymphocyte count to start Cladribine 10 mg tablets therapy after the first year are allowed to postpone second cycle up to 6 months until lymphocyte count recovers (as per SmPC) and therefore their participation may take up to 4.5 years.

5.2 Study Timelines

Table 5-1: Study Timelines

Milestone	Panned date
First patient first visit	April 2020
Last patient first visit	August 2021 (enrolment period 18 months)
Last patient last visit/Data collection completed	October 2025 (participation takes 48 months, however patients who have to delay their treatment in second year due to low lymphocyte count up to 6 months as per SmPC will take part for up to 56 months)

6 SETTINGS

6.1 Site Selection

Centres specialized in the care of patients with MS across Slovakia will be selected for study participation. The planned number of study sites is 12.

6.2 Recruitment Modalities

Physician will offer participation to all consecutive patients meeting eligibility criteria during the enrolment period. Competitive enrolment is allowed.

6.3 Study Population

Planned number of patients in the study is approximately 100.

6.3.1 Inclusion Criteria

- Age ≥18 years.
- Patients for whom start of Cladribine 10 mg tablets therapy for highly active relapsing MS (relapsing-remitting multiple sclerosis – RRMS, or secondary progressive multiple sclerosis - SPMS) has been indicated independently before signing informed consent.
- Patient fulfils following local indication criteria for Cladribine 10 mg tablets treatment as applicable in standard of care:
    - 1 severe relapse treated by corticosteroids or EDSS score increase by at least 1 grade during the previous year and at least 1 T1Gd+ lesion or 9 or more T2 lesions during the treatment by at least one other DMD,

    OR

    - 2 or more disability causing relapses treated by corticosteroids during the previous year and treated or untreated by the other DMD. MS diagnosis has to be confirmed by cerebrospinal fluid examination.
- Signed informed consent.
- Ability to communicate with investigator and study staff and to comply with their instructions for the entire length of the study participation

6.3.2 Exclusion Criteria

- Other type of MS than highly active relapsing MS
- Contraindications listed in Cladribine 10 mg tablets SmPC.
- Moderate or severe hepatic impairment (Child-Pugh score >6).
- Patient (men and women of childbearing potential) is unable or unwilling to practice birth control during Cladribine 10 mg tablets treatment and for at least 6 months after the last dose.
- Concurrent participation in any interventional study.

6.3.3 Withdrawal Criteria

- Withdrawal of patient consent
- Start of a new disease modifying drug
- Lost to follow-up

7 EVALUATION CRITERIA

7.1 Primary endpoint

- ARR at 48 months

7.2 Secondary endpoints

- Proportion of relapse-free patients at 24 and 48 months
- ARR at 24 months
- The time to sustained progression of disability from baseline up to 24 and 48 months
- Time to the first relapse from baseline up to 48 months
- Time to the second relapse from baseline up to 48 months

- Changes in mean number of T1 Gd+ lesions per MRI scan taken at 12, 24, 36 and 48 months compared to baseline
- Changes in mean number of active T2-weighted lesions per MRI scan taken at 12, 24, 36 and 48 months compared to baseline
- Changes in level of disability as measured by EDSS at 6, 12, 18, 24, 30, 36, 42 and 48 months compared to baseline
- No evidence of disease activity (NEDA-3) at 24 and 48 months
- The proportion of patients receiving rescue therapy according to local standards of care from baseline up to 48 months
- Patient adherence to Cladribine 10 mg tablets treatment after both dosing periods as assessed at 3 and 15 months (by counting used tablets from original packages as patients will be asked to bring them to the site).
- Frequency of adverse events interviewed or reported spontaneously by the patients or as noted on physical, MRI or laboratory examinations up to month 48
- Percentage of patients with at least 1 Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 Lymphocyte Toxicity up to month 48
- Median time to recovery from grade 3 or 4 Lymphocyte Toxicity
- Percentage of patients who developed herpes zoster infections or malignancies up to month 48

8 DATA COLLECTION

8.1 Data source

Patients' medical charts, any relevant diagnostic reports including description of MRI scans recorded as part of the standard of care and number of actually used Cladribine 10 mg tablets for adherence evaluation as described in section 5.1 are the source documents for study data collection. Clinical information recorded in patients' medical charts and/or diagnostic reports will be entered into the eCRF (Electronic case report form).

8.2 Collected Data

V1 - Pre-dose Year 1 Visit

Date of visit, date of ICF signature (if different), meeting of eligibility criteria (yes/no)

Basic demographic data:

- Year of birth
- Gender

Baseline characteristics:

- Relevant medical history
- Relevant concurrent diseases/concomitant medications

Condition of MS:

- Date of MS diagnosis
- Medical history related to MS
- Previous MS therapy
- Number of relapses in the last 12 months
- Current EDSS score
- Current MRI status (within 3 months)

Pre-treatment requirements

- Is patient eligible to start Cladribine 10 mg tablets therapy as per SmPC? (yes/no)

  Contraindications (all answers have to be no):

  - Hypersensitivity to the active substance or to any of the excipients (yes/no)
  - Infection with human immunodeficiency virus (HIV) (yes/no)
  - Active chronic infection (tuberculosis or hepatitis) (yes/no)
  - Initiation of cladribine treatment in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy (yes/no)
  - Active malignancy (yes/no)
  - Moderate or severe renal impairment (creatinine clearance <60 mL/min) (yes/no)
  - Pregnancy and breast-feeding (yes/no)

  Recommended screening for infections (all answers have to be yes) - A delay in initiation of Cladribine 10 mg tablets should also be considered in patients with an acute infection until the infection is fully controlled.

  - Active or latent tuberculosis excluded (yes/no)
  - Active infection with hepatitis B virus (HBV) excluded (yes/no)
  - Active infection with hepatitis C (HCV) excluded (yes/no)

  Vaccination – If vaccination is needed, initiation of treatment with Cladribine 10 mg tablets must be postponed for 4 to 6 weeks to allow for the full effect of vaccination to occur

  - Vaccination of patients who are varicella zoster virus antibody-negative within 4–6 weeks before initiation of Cladribine 10 mg tablets (yes/no)
  - Vaccination with live or attenuated live vaccines within 4–6 weeks before initiation of Cladribine 10 mg tablets (yes/no)

  Pregnancy and contraception (all answers have to be yes)

  - Pregnancy excluded in women of childbearing potential (yes/no)
  - Women of childbearing potential must agree to prevent pregnancy by use of effective contraception during Cladribine 10 mg tablets treatment and for at least 6 months after the last dose. Women using systemically acting hormonal contraceptives should add a barrier method during Cladribine 10 mg tablets treatment and for at least 4 weeks after the last dose in each treatment year. Women who become pregnant under therapy with Cladribine 10 mg tablets should discontinue treatment. (yes/no)
  - Male patients must agree to take precautions to prevent pregnancy of their partner during Cladribine 10 mg tablets treatment and for at least 6 months after the last dose. (yes/no)

  Assessment before therapy initiation (all answers have to be yes)

  - Lymphocyte count must be normal before initiating Cladribine 10 mg tablets in year 1
  - MRI should be performed before initiating Cladribine 10 mg tablets (usually within 3 months) to exclude progressive multifocal leukoencephalopathy (PML)
- Patient weight
- Lymphocyte count
- Number of Cladribine 10 mg tablets to be used in the whole treatment course year 1

V2 - Visit Month 3 Year 1 (2 months after the first dose of Cladribine 10 mg tablets in Year 1)

- Visit date
- Date of Cladribine 10 mg tablet therapy start
- Number of Cladribine 10 mg tablets really used in the whole treatment course year 1
- Lymphocyte count
- Any relapse and rescue therapy from the last visit
- Any AE from the last visit
- Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit

V3 - Visit Month 7 Year 1 (6 months after the first dose of Cladribine 10 mg tablets in Year 1)

- Visit date
- Lymphocyte count
- EDSS score
- Any relapse and rescue therapy from the last visit
- Any AE from the last visit
- Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit

V4 - Pre-dose Year 2 (12 months after the first dose of Cladribine 10 mg tablets in Year 1; For patients with lymphocyte count bellow 800 cells/mm³ the treatment course in year 2 must be delayed for up to 6 months to allow for recovery of lymphocytes as per SmPC. For these patients V4 will be postponed until recovery - up to maximum of 6 months).

- Visit date
- Is patient eligible to continue Cladribine 10 mg tablets therapy as per SmPC? (yes/no)

  Contraindications (all answers have to be no):
  - Hypersensitivity to the active substance or to any of the excipients (yes/no)
  - Infection with human immunodeficiency virus (HIV) (yes/no)
  - Active chronic infection (tuberculosis or hepatitis) (yes/no)
  - Initiation of cladribine treatment in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy (yes/no)
  - Active malignancy (yes/no)
  - Moderate or severe renal impairment (creatinine clearance <60 mL/min) (yes/no)
  - Pregnancy and breast-feeding (yes/no)

  Recommended screening for infections (all answers have to be yes) - A delay in initiation of Cladribine 10 mg tablets should also be considered in patients with an acute infection until the infection is fully controlled.
  - Active or latent tuberculosis excluded (yes/no)
  - Active infection with hepatitis B virus (HBV) excluded (yes/no)
  - Active infection with hepatitis C (HCV) excluded (yes/no)

  Vaccination – If vaccination is needed, initiation of treatment with Cladribine 10 mg tablets must be postponed for 4 to 6 weeks to allow for the full effect of vaccination to occur

- Vaccination with live or attenuated live vaccines within 4–6 weeks before initiation of Cladribine 10 mg tablets (yes/no)

Pregnancy and contraception (all answers have to be yes)

- Pregnancy excluded in women of childbearing potential (yes/no)
- Women of childbearing potential must agree to prevent pregnancy by use of effective contraception during Cladribine 10 mg tablets treatment and for at least 6 months after the last dose. Women using systemically acting hormonal contraceptives should add a barrier method during Cladribine 10 mg tablets treatment and for at least 4 weeks after the last dose in each treatment year. Women who become pregnant under therapy with Cladribine 10 mg tablets should discontinue treatment. (yes/no)
- Male patients must agree to take precautions to prevent pregnancy of their partner during Cladribine 10 mg tablets treatment and for at least 6 months after the last dose. (yes/no)

Assessment before therapy initiation (all answers have to be yes)

- Lymphocyte count must be at least 800 cells/mm³ before initiating Cladribine 10 mg tablets in year 2
- MRI should be performed before continuing Cladribine 10 mg tablets to exclude PML (within 3 months)

- MRI status
- EDSS score
- Patient weight
- Lymphocyte count
- Number of Cladribine 10 mg tablets to be used in the whole treatment course year 2
- Any relapse and rescue therapy from the last visit
- Any AE from the last visit
- Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit

V5 - Visit Month 3 Year 2 (2 months after the first dose of Cladribine 10 mg tablets in Year 2)

- Visit date
- Date of Cladribine 10 mg tablet therapy start
- Number of Cladribine 10 mg tablets really used in the whole treatment course year 2
- Lymphocyte count
- Any relapse and rescue therapy from the last visit
- Any AE from the last visit
- Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit

V6 - Visit Month 7 Year 2 (6 months after the first dose of Cladribine 10 mg tablets in Year 2)

- Visit date
- Lymphocyte count
- EDSS score
- Any relapse and rescue therapy from the last visit
- Any AE from the last visit

- Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit

V7 - Visit Month 12 Year 2/Month 1 Year 3 (12 months after the first dose of Cladribine 10 mg tablets in Year 2)

- Visit date
- MRI status
- EDSS score
- Any relapse and rescue therapy from the last visit
- Any AE from the last visit
- Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit

V8 - Visit Month 7 Year 3 (18 months after the first dose of Cladribine 10 mg tablets in Year 2)

- Visit date
- EDSS score
- Any relapse and rescue therapy from the last visit
- Any AE from the last visit
- Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit

V9 - Visit Month 12 Year 3/Month 1 Year 4 (24 months after the first dose of Cladribine 10 mg tablets in Year 2)

- Visit date
- MRI status
- EDSS score
- Any relapse and rescue therapy from the last visit
- Any AE from the last visit
- Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit

V10 - Visit Month 7 Year 4 (30 months after the first dose of Cladribine 10 mg tablets in Year 2)

- Visit date
- EDSS score
- Any relapse and rescue therapy from the last visit
- Any AE from the last visit
- Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit

EOS - Visit Month 12 Year 4 (36 months after the first dose of Cladribine 10 mg tablets in Year 2)/Premature Withdrawal Visit

- Visit date
- MRI status
- EDSS score
- Any relapse and rescue therapy from the last visit
- Any AE from the last visit

Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit

Table 8-1: Flow chart

Year	**Year 1**			**Year 2**			**Year 3**		**Year 4**		
Timing (month if applicable)	**pre-dose**	**3**	**7**	**pre-dose**	**3**	**7**	**1**	**7**	**1**	**7**	**12**
Visits	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**EOS /PW***
Informed consent	X										
Inclusion/Exclusion criteria	X										
Baseline characteristics (patient and disease)	X										
Patient weight	X			X							
Is patient eligible to start Cladribine 10 mg tablets therapy?	X			X							
MRI status	X			X			X		X		X
Lymphocyte count (or Blood count)	X	X	X	X	X	X					
Number of Cladribine 10 mg tablets to be used	X			X							
Date of Cladribine 10 mg tablet therapy start and number of Cladribine 10 mg tablets really used (as counted from original packages brought back to the site)		X			X						
EDSS	X		X	X		X	X	X	X	X	X
Any relapse and rescue therapy from the last visit		X	X	X	X	X	X	X	X	X	X
Any AE from the last visit		X	X	X	X	X	X	X	X	X	X
Concomitant medication (only corticosteroids, myorelaxants, analgesics, antidepressants, anxiolytics) from the last visit		X	X	X	X	X	X	X	X	X	X
Reasons for premature withdrawal, if applicable											X

*PW – Premature Withdrawal Visit in case of patient premature withdrawal

8.3 Lost to follow-up patients

If a patient is lost to follow-up (they fail to appear for visits without stating an intention to discontinue or withdraw), the site will attempt to communicate with the patient. Sites will be requested to spare no effort in contacting patients at various times of the day and evening, and on different days of the week to verify health status of a patient.

9 DATA MANAGEMENT

9.1 Data Capture

The participating physician will fill all required data in the eCRFs for each patient anonymously within 10 working days from performed relevant visit. Only the participating physician will be able to identify the patient in question.

Prior to granting access to the eCRF, the physician will be trained. Instructions for filling in the eCRF will be provided in a separate document.

The participating physician will ensure that the information contained in patient records is complete, accurate and correct.

9.2 Site and Patient Numbering

Project Data Management will assign a specific number to each centre and a unique identification number to each patient. All participating sites will only have access to view and enter the data for their own patients.

9.3 Data Validation

Data processing may open additional questions to which the participating physician is required to respond by confirming or modifying the data. Response questions will be attached to records that will be archived by the participating physician and the Sponsor.

The procedures for data collection and validation will be detailed in the relevant working documents.

10 QUALITY CONTROL AND QUALITY ASSURANCE

Quality Assurance representative(s) of Sponsor (or their designee) may conduct audit visits at any time during the study period. All necessary related data and documents will be made available for inspection.

10.1 Site Training and Initiation

A meeting will be held to train the Investigators (participating physicians) and their site staff on the study requirements and use of the eCRF. Sponsor (or their designee) will contact each site to review site initiation procedures. Ongoing site management will occur throughout the entire duration of the study. Additional outreach and training including on-site visits will occur for sites (Investigators and staff) needing remedial training and to address quality control concerns prior to analysis.

10.2 Site Monitoring

In-house site management and site monitoring will be used to manage sites during the study

conduct. Random control of data quality will be performed at minimum 10% of active sites with at least one enrolled patient. Records will be checked for data completeness and accuracy by qualified Sponsor representative (or their designee) who will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this study.

If specific problems are identified in some centres, the percentages of quality control checks in a given centre will be appropriately increased and corrective actions will be taken.

11 PHARMACOVIGILANCE

Physicians have to collect all adverse events during the whole study – from the Visit V1 - Pre-dose Year 1 to the EOS/PW without regard to their severity or relationship with Cladribine 10 mg tablets and record them (including follow-up information if applicable) in the respective eCRFs. Reports of Special Situations (see definition bellow) are also to be recorded in the eCRFs following the AE procedure, even if occurring without AE.

Physician has to take all appropriate measures to ensure patient safety as per standard of care. Treatment of any adverse event is left at discretion of the physician who has to follow Cladribine 10 mg tablets SmPC and standard clinical practice.

11.1 Definitions

An Adverse Event (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.

An Adverse Reaction (AR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

ARs may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include **Special Situations** as following:

- Use of a medicinal product during pregnancy or breastfeeding: reports where embryo, foetus or child may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure);
- Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure;
- Lack of therapeutic efficacy;
- Prescription error/dispensing error, e.g., due to confusion of invented names of the medicinal products;
- Drug interaction;
- Suspected transmission of an infectious agent via a medicinal product; or
- Product complaints (incl. falsified products or counterfeit products).

Special Situations will be considered in the Final Study Report or any interim reports, as applicable.

A Serious Adverse Event ("SAE")/Serious Adverse Reaction ("SAR") is any AE/AR as defined above, which also fulfils at least one of the seriousness criteria below:

- results in death,

- is life-threatening[1)],
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/ incapacity,
- is a congenital anomaly/ birth defect, or
- 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 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 intervention to prevent one of the other outcomes listed above. 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.

Note: Event term 'Death', 'Disability' and 'Hospitalization'

Death, disability, and hospitalization are considered outcomes in the context of safety reporting and not usually considered ARs/AEs. Therefore, the primary cause of death, disability or hospitalization should be recorded and reported as an SAE/AR, and the outcome should be recorded in a separate data field. However, a term for the outcome will be selected if it is the only information reported or provides significant clinical information.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the OUTCOME of this respective event and not be as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might then be reported as an SAE.

Adverse Events of Special Interest (AESI) are those events thought to be potentially associated with Cladribine 10 mg tablets or disease under study. Reporting on Adverse Events of Special Interest is an emerging and ever more critical aspect related to characterizing the safety profile of a compound.

In this study AESIs are:

- Lymphocyte toxicity grade 3 and 4 per CTCAE
- Herpes zoster infection
- Malignancy

Events NOT to be considered AEs in this study:

- Medical conditions present in a patient and documented at the time of enrolment of the Non-Interventional Study, and that do not worsen in severity or frequency during the Non-Interventional Study, are defined as baseline medical conditions, and are NOT to be considered AE.
- Symptoms and signs of relapse or worsening of MS will usually be captured in the context of the efficacy assessment and recorded on the relapse module of the eCRF. Therefore, symptoms, relapses or worsening of MS will not be considered as AEs nor captured on the AE module of the eCRF unless considered possibly or probably related to the Cladribine 10 mg tablets (i.e. worsening is not consistent with the anticipated natural progression of the disease).
- Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the

subjects' general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the AE reporting period (from ICF signature to the last study visit).

AE Severity and Causality Assessment:

Physicians 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 other usual level of activity.
- **Severe:** Significant impairment of functioning: the subject is unable to carry out usual activities.

Physicians must assess the causal relationship between AEs and study drug considering temporal relationship between the AE onset and study drug administration, safety profile of study drug (known ARs), the patient's condition (medical history, underlying disease), concomitant medication, and study procedures.

- **Related:** Suspected to be reasonably related to any study medication.
- **Not related:** Not suspected to be reasonably related to any study medication. A reasonable alternative explanation must be provided.

11.22. Recording and Transmission of Safety Events

11.2.1 Responsibilities

Participating physicians will be responsible for the recording and handling of safety information, including, without limitation, AEs and ARs reported as part of the study, including a causality assessment. Participating physician shall ensure that information on any AE is recorded comprehensively and in high quality. Marketing authorization holder (MAH) of the Cladribine 10 mg tablets shall be responsible for the regulatory reporting of safety events to competent health authorities in accordance with Applicable Laws and Codes.

Participating physicians shall comply with the adverse event reporting and safety data exchange requirements set forth in protocol sections 11.2.2 and 11.2.3 bellow and any other such obligation required by Applicable Laws and Codes. ARs related to pharmaceutical products other than the Cladribine 10 mg tablets should be notified to the respective marketing authorization holder or competent health authorities in accordance with Applicable Laws and Codes.

Participating physicians shall fully cooperate with Cladribine 10 mg tablets MAH to enable MAH to meet its safety-related reporting obligations in relation to events or findings associated with the study, inter alia by providing comprehensive, high quality information and support in the follow-up on any safety data.

11.2.2 Safety Events Reporting

For recording in the safety data base, all SAEs (related and non-related, including all fatal outcomes), related non-serious AEs* (ARs), AESIs, Special Situations and other safety events not classified under any of the above mentioned categories which might be emerging safety issues shall be sent to MAH in English language. The information shall be sent via facsimile or email listed below within one (1) business day or three (3) calendar days, whatever comes first, after becoming aware of the event. Contact details are as follows:

- ICSR_CT_GPS@merckgroup.com

- Fax: +49 (0) 6151 72 6914

It is recommended to use MAH's safety data collection forms for non-interventional studies.

* Non-serious AR reports shall be sent within four (4) calendar days via individual report form or in agreed alternative way.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. Continuing at the end of the study).

The data entered on the safety data collection forms must be consistent with the information recorded in the eCRFs. If some data are missing, the form should be completed with the available data and a follow-up report should be sent as soon as possible. The minimum information to be included in the initial report is the following:

- Investigator name and contact details
- Subject identification (e.g., ID number, gender, age)
- Product (including lot/ batch number)
- Description of SAE/AR/ fatal case/ Special situation

The report should contain causality and seriousness information (for AEs) and must be signed off by the physician.

All follow-up information for the AEs including information on complications, progression of the initial AE and recurrent episodes must be reported as follow-up to the original episode within the timeframe applicable to the event category as specified above. An AE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

After submission of the initial report, participating physician and/or Coordinating Investigator may be contacted by the drug safety department of MAH or the study Data Management to obtain follow-up or additional information on the event or for data clarification. Participating physician and/or Coordinating Investigator shall make best effort to obtain the requested information.

MAH will perform a company medical assessment for the purpose of signal detection and cumulative reporting of safety information.

MAH of the Cladribine 10 mg tablets is responsible to report all suspected adverse drug reactions and individual case safety reports for expedited reporting arising in the study to the competent health authorities in accordance with Applicable Laws and Codes.

Safety data will be coded by using the MedDRA Coding Terminology in study database by authorized CRO.

MAH will perform regular signal detection on the Cladribine 10 mg tablets in its global safety database. In case of any action arising from such signal detection activities which is relevant for the conduct of the study, MAH will inform participating physicians and Coordinating Investigator in a timely manner.

As part of the monthly reporting, participating physician shall provide MAH with a monthly list of all safety reports, sent to MAH in order to verify that MAH has received all reported cases. MAH will timely check the list and request missing cases, if any.

MAH shall be responsible for compilation and submission to competent authorities of all periodic safety update reports in accordance with Applicable Laws and Codes.

Complete data on AEs (including Special Situations) shall be collected and provided to MAH at the end of the study as part of the final study report, or during the course of the study upon special written request by MAH. All safety data sets shall be provided in an internationally accepted format which allows integration into the global clinical database for the product of MAH.

11.2.3 Reporting of Pregnancies in the Study

In case of pregnancy, physician has to follow Cladribine 10 mg tablets SmPC for treatment management.

Physician shall inform MAH of any pregnancy occurring in a subject exposed with the Cladribine 10 mg tablets during the course of the study by using separate paper data collection forms for pregnancy, independent if an AE was reported or not. Physician shall ensure that the case is followed up to the end of the pregnancy and provide all relevant documentation and a final report on the outcome including health status of a newborn to MAH.

In addition, pregnancy information has to be recorded in the relevant eCRF too.

12 STATISTICAL METHODOLOGY

Based on this part of the protocol, a statistical analysis plan (SAP) will be created. The statistical analysis plan will be processed and approved before closing the database. Possible changes in the evaluated parameters or in the methods of analysis against the protocol will be described and justified in SAP. The statistical analysis is performed in IBM SPSS software.

12.1 Sample Size

A sample size of 85 subjects will have more than 80% power to achieve a supposed ARR 0.14 (95 % CI: 0.12–0.17) using a 2-sided significance level of 0.05. Assuming a 15% drop-out rate, a total of 100 patients will be targeted for this study.

12.2 Data Analysis

Analysis of collected data is based on descriptive statistics including absolute and relative frequencies of discrete variables. Continuous variables are described by count (without missing), mean and its 95% confidence interval (CI), standard deviation, median, minimum, and maximum. Discrete variables are described by count (absolute frequency), and percentages (relative frequency).

Missing data will not be replaced.

12.3 Interim analysis

Interim analysis will be performed when all patients complete visit V7 or withdraw earlier.

13 ETHICAL ASPECTS

This project will be carried out in accordance with the principles set out at the 18th Meeting of the World Health Organization (Helsinki, 2013) and in all Appendices thereto and in accordance with the applicable legislation of the Slovak republic.

The Sponsor will provide all necessary registrations in compliance with the regulations, including data protection rules.

13.1 Informed Consent

Prior to any data collection under this protocol, the Informed Consent Form (ICF) must be signed by the patient, in accordance with local practice and regulations. Information about the study will be explained to the patient by the participating physician. 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 medical records prior to any data collection under this protocol.

The ICF must not be altered without the prior agreement of the relevant independent ethics committee (IEC) and Sponsor.

In order to ensure patient confidentiality, patients will be assigned a unique study number. The key, matching study numbers with patient names will be maintained by the site, and only the study numbers will be recorded on the data collection forms. The Investigator and local site staff will securely store information separately from other study information and it will not be provided to third parties.

13.2 Ethics Committee Approval

Prior to the collection of any study related data, IEC approval of the protocol and ICF and will be obtained as applicable.

13.3 Compensation to Coordinating Investigator

Coordinating Investigator will not receive any remuneration or compensation for work performed and time spent during the study conduct.

14 OTHER ASPECTS

14.1 Record Archiving

The participating physicians shall arrange for the retention of study documentation until the end of the study. In addition, the participating physicians will comply with specific local regulations/ recommendations with regards to patient record retention

It is recommended that the participating physician retains the study documents at least fifteen years (15) after the completion or discontinuation of the study, unless otherwise specified in the Investigator Agreement in line with additional standards and/or local laws.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

14.2 Data Protection and Confidentiality

The patient's personal data and participating physicians' personal data which may be included in Sponsor database shall be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the participating physicians and/or to the patients, Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

In any presentations or in publications of the results of the study, the patients' identities will remain anonymous and confidential. Sponsor, its designee(s), and various government health agencies may inspect the records of the study. Every effort will be made to keep the patients' personal medical data confidential.

All materials, information (oral or written) and unpublished documents provided to the participating physician, including the current protocol and patient records, are the sole property of the Sponsor. These materials and information may not be provided or disclosed by the participating physicians or any person on their team to unauthorized persons without the prior written consent of the Sponsor.

The participating physician considers all information received, obtained or derived during the project to be confidential and will take all necessary steps to ensure that there is no breach of confidentiality, except for the information to be provided according to law.

14.3 Data Ownership and Publication Policy

All data generated from this study are the property of Sponsor who will establish a uniform procedure for analysing, publishing, and disseminating findings from this study.

No use of the data including any presentation or publication will be possible without the authorisation of Sponsor conducting the study.

14.4 Protocol Amendment

Amendments to the protocol can only be made by Sponsor in the written form. All protocol amendments must be signed and dated by the Coordinating Investigator and approved by IEC as applicable prior their implementation.

14.5 Premature Discontinuation of the Study

Sponsor can decide at any time and for any reason to prematurely stop or to interrupt the study; the decision will be communicated in writing to the Investigators.

Similarly, should the Coordinating Investigator decide to withdraw from the study, he will have to immediately inform Sponsor in writing.

In case of study premature discontinuation, all national applicable regulatory procedures will be followed.

15 REFERENCES

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