Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A randomized, double-blind, 2-period, 2-sequence crossover Phase I study with a 1 month run-in period to examine the effect of cladribine tablets on the pharmacokinetics of a monophasic oral contraceptive containing ethinyl estradiol and levonorgestrel (Microgynon®) in pre-menopausal women with relapsing multiple sclerosis (RMS)
Study Number:	MS700568-0031
Protocol Version:	29 July 2021/Version 5.0
Merck Compound Number:	Cladribine
Study Phase:	I
Short Title:	Effects of cladribine tablets on the pharmacokinetics of Microgynon®
Coordinating Investigator:	[redacted]
Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 64293 Darmstadt, Germany
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Medical Monitor Name and Contact Information:	[redacted] Phone: Mobile: Fax: Email:

Protocol Amendment Summary of Changes

Version Number	Type	Version Date
5.0	Global Amendment 4.0 (Substantial)	29 July 2021
4.0	Global Amendment 3.0 (Non-substantial)	20 November 2020
3.0	Global Amendment 2.0 (Non-substantial)	06 April 2020
2.0	Global Amendment 1.0 (Non-substantial)	04 July 2019
1.0	Original Protocol	09 October 2018

Protocol Version 5.0 (29 July 2021)

Overall Rationale for the Amendment

This substantial protocol amendment was required to revise the sample size. CCI [redacted] These changes are considered suitable for proving bioequivalence and achieving the study objectives.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Sample size was reduced.	Recalculation of the statistical analysis.
1.2 Schema	A randomization window of 10 days after Run-In-period Day 21 was added to the study design diagram.	Clarification of process.
1.3 Schedule of activities	A randomization window of 10 days after Run-In-Period Day 21 was added to the table.	Clarification of process.
4.1 Overall Design	Sample size was reduced.	Recalculation of the sample size.
4.4 End of Study Definition	To further clarify explicitly that sites should only initiate clinical routine activities (e.g., blood drawing) after the unblinding process has been completed. To further describe that the end of study is defined as when the end of study blood laboratory testing and all other EOS-visit safety examinations have been collected/received at site and have been reviewed.	Clarification of process.
5.3.4 COVID-19 Vaccination Considerations	To give more guidance in the COVID-19 pandemic situation with regards to the different COVID-19 vaccines	COVID-19 pandemic.

Section # and Name	Description of Change	Brief Rationale
6.1 Study Intervention(s) Administration	Packaging and Labeling: Remove the sentence "The medical care treatment in the second year will be supplied in blisters containing 1, 4 and 6 tablets like the commercial split."	Clarification of process.
6.3.2 Blinding	Unblinding process after end of study for each participant: Removed "immediately".	Clarification of process.
6.7 Study Intervention after the End of the Study	Supply of cladr bine treatment described.	Clarification of process.
6.9 Management of Adverse Events of Interest	Hematological monitoring: Added a sentence on lymphocytes blinding, result review, and adverse event reporting process.	Clarification of process.
7.2 Participant Discontinuation/Withdrawal from the Study	Drop-out rate and number of participants evaluable adapted to recalculated sample size.	Recalculation of the sample size.
8.2.4 Clinical Safety Laboratory Assessment	Reference added to Section 6.9 instead of reference to Medical Monitoring Plan.	Minor correction.
[redacted]	[redacted]	[redacted]
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Adverse events of special interest: Explicitly express that only "lymphopenia" Grade3/4 represents an AESI, not Grade 1 and 2. Align and clarify nonserious AESI reporting process and the AESI Reporting Form (AESIs Grade 3/4 lymphopenia to be reported)	Clarification of process.
Appendix 9 Coordinating Investigator Signature Page	Site number "CCI" added.	Completion of signature page.
Whole document	Correction of typing errors, minor editorial and document formatting revisions	Minor corrections; therefore, have not been summarized.

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A randomized, double-blind, 2-period, 2-sequence crossover Phase I study with a 1 month Run-in-Period to examine the effect of cladribine tablets on the pharmacokinetics of a monophasic oral contraceptive containing ethinyl estradiol and levonorgestrel (Microgynon®) in pre-menopausal women with relapsing multiple sclerosis (RMS).

Short Title: Effects of cladribine tablets on the pharmacokinetics of Microgynon®

Rationale: The primary study rationale is to evaluate the potential effects of cladribine tablets on the pharmacokinetics of an oral contraceptive (Microgynon tablets [ethinyl estradiol (EE) 30 µg, levonorgestrel (LNG) 150 µg]).

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
Primary		
To examine the effect of repeat-dose cladribine tablets on the repeat-dose pharmacokinetics of the monophasic oral contraceptive Microgynon by assessment of its constituents, ethinyl estradiol (EE; 30 µg/tablet) and levonorgestrel (LNG; 150 µg/tablet)	• Primary PK parameters calculated for EE and LNG from plasma concentrations: Area under the concentration–time curve from zero to tau at steady state ($AUC_{\tau,ss}$), and the maximum plasma concentration at steady state ($C_{max,ss}$). • Secondary PK parameters calculated for EE and LNG: $C_{min,ss}$; C_{trough}; $t_{max,ss}$; $C_{av,ss}$; and peak-to-trough fluctuation (PTF%).	Study Periods 1 and 2 on Days 14/15
Secondary		
To examine the safety and tolerability of Microgynon and cladribine co-administration.	Occurrence of treatment-emergent adverse events (TEAEs), changes in safety laboratory tests, 12-lead electrocardiograms (ECGs) (morphology, and time intervals [PR, QRS, RR, QT and corrected QT intervals [QTc]), and vital signs (PR, SBP, DBP, body temperature)	Time from first treatment to last assessment
To examine cladribine exposure	Cladr bine C_{max} and t_{max}	Cladribine PK sampling in Study Periods 1 and 2 at predose on Days 9, 10, 11, 12 and 13, postdose on Days 10, 11, 12 and 13 at 0.25, 0.5, 1.0, 1.5, 2.0h

$_{ss}$=at steady state; AUC_{τ}=Area under the concentration–time curve from zero to tau; C_{av}=average concentration; C_{max}=maximum plasma concentration; C_{min}=minimum observed concentration during a complete dosing interval; C_{trough}=concentration observed immediately before next dosing; DBP=diastolic blood pressure; ECG=electrocardiogram; EE=ethinyl estradiol; h=hour; LNG=levonorgestrel; PK=pharmacokinetic; PTF%=peak-to-trough fluctuation; PR=pulse rate; QTc=corrected QT intervals; SBP=systolic blood pressure; t_{max}=time to reach the maximum observed concentration collected during a dosing interval; TEAEs=treatment-emergent adverse events

Overall Design: This is a randomized, double-blind, 2-period, 2-sequence crossover study with a 1 month Run-in-Period in pre-menopausal women with active relapsing multiple sclerosis (RMS) requiring a disease-modifying RMS treatment. The study design will comprise a ≤ 21-day Screening period followed by a Microgynon Run-in-Period, followed by 2 sequential treatment periods (Study Periods 1 and 2) of 28 days each. In case the Screening period lasts > 21 days and ≤ 60 days due to a delayed menstrual cycle of the participant (Run-in Day 1), it is acceptable that the participant starts delayed with the Run-in-Period without having re-performed the Screening assessments. In case of the requirement to re-assess one or more Screening laboratory value(s), the Screening period may be prolonged for up to 8 weeks after the last Screening laboratory assessment and it is acceptable that the participant starts with a delayed Run-in-Period without re-assessing the complete set of Screening laboratory assessments.

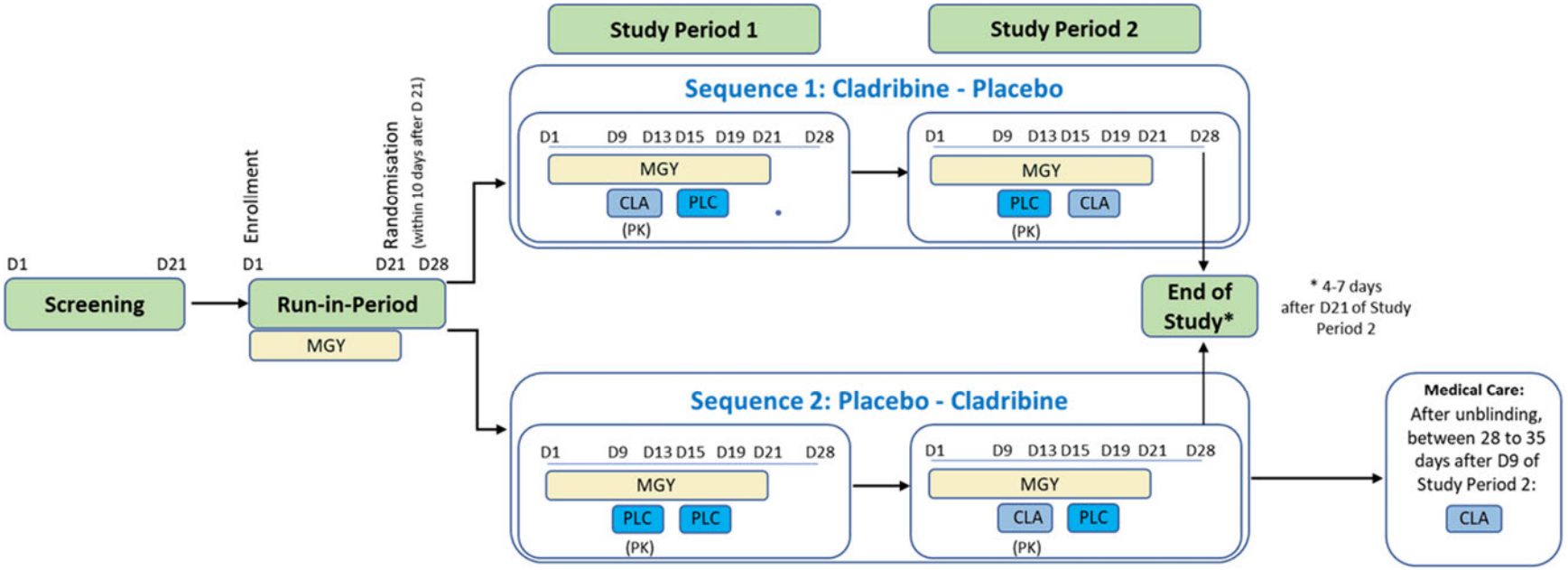
Number of Participants: CCI [redacted]

Study Intervention Groups and Duration: In the Run-in-Period as well as during both treatment periods, Microgynon will be administered for 21 days, followed by 7 days off-treatment. In Study Periods 1 and 2 Microgynon will continue to be administered together with randomized treatment sequences of a 5-day once-daily cladribine treatment in Study Period 1 followed by a 5-day placebo treatment in Study Period 2, or vice versa; i.e., participants will be randomized to 1 of 2 double-blind treatment sequences, either cladribine-placebo or placebo-cladribine.

Involvement of Special Committee(s): No.

1.2 Schema

Figure 1 **Study Design Diagram**



CLA=Cladribine tablets, 10 mg; MGY=Microgynon tablets (Ethinylestradiol 30 µg, Levonogestrel 150 µg); PLC=Cladribine Placebo tablets; D=day; PK=blood sampling for pharmacokinetics.

1.3 Schedule of Activities

- The Schedule of Activities (SoA) is provided below.

Schedule of Activities – Screening, Run-in-Period and Study Period 1

Assessments & Procedures	Screening (up to 21 days before Day 1)[b]	Run-in-Period	Intervention Study Period 1 (Days)									Notes
		D 1 to 28	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 15	D 21	
Residency			X	X	X	X	X	X	X	X		In individual cases Investigator may allow participants to stay overnight at home from Day 8 to Day 12. In-patient stay is required from the evening of Day 13 until discharge on Day 15 after completion of all planned study assessments.
Ambulatory Visit	X	X									X	Run-in-Period: ambulatory visits on Days 7, 14 and 21
Written Informed Consent	X											Prior to any screening procedures
Inclusion and Exclusion Criteria review	X		X[a]									a Re-check before administration on: contraception method, blood loss and lifestyle considerations. Results of safety laboratory on Day 21 of Run-in-Period (Baseline).
Demographic Data	X											
Physical Examination	X											
Herpes Zoster Serology	X											Serology diagnosis, if ABS negative vaccination and at least 4 weeks before cladribine administration
Medical History / Concomitant Disease	X											
Prior and Concomitant Treatment	X	X	X	X	X	X	X	X	X	X	X	

Assessments & Procedures (cont'd, Study Period 1)	Screening (up to 21 days before Day 1)[b]	Run-in-Period	Intervention Study Period 1 (Days)									Notes
		D 1 to 28	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 15	D 21	
Hematology, Clinical Chemistry & Urine Analysis	X	X							X			Run-in-Period on Day 21 (Baseline)
QuantiFERON®-TB Test	X											Done in local laboratory
Serum Pregnancy Test	X											
Urine Pregnancy Test		X	X									A negative urine pregnancy test must be in place at Day 7 of Run-in-Period and on Day 8 of Study Period 1.
Alcohol Breath Test / Drugs of Abuse	X		X									See Appendix 5. On Day 8 urine drug screen is done locally
Height / Weight / Body Mass Index (BMI)	X	X									X	Additional weight control: Run-in-Period on Day 21 and on Day 21 Study Period 1
Vital Signs	X	X		X	X	X	X	X	X			Run-in-Period on Days 7, 14 and 21. Days 9-13 predose and 1 h postdose; on Day 14 at 24 h and 25.5 h postdose (Day 13) of cladr bine/placebo administration
12-lead ECG	X			X					X			On Day 9 predose and 1.5 h postdose; on Day 14 at 24 h and 25.5 h postdose (Day 13) of cladr bine/placebo administration
Randomization		X										Within 10 days after Run-in-Period Day 21
Participant Diary Delivery	X	X									X	
Microgynon Delivery	X	X									X	During Screening a second appointment needs to be scheduled to deliver Microgynon after lab values for inclusion have been assessed.
Participant Diary Collection		X									X	Run-in-Period on Day 21

Assessments & Procedures (cont'd, Study Period 1)	Screening (up to 21 days before Day 1)[b]	Run-in-Period	Intervention Study Period 1 (Days)									Notes
		D 1 to 28	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 15	D 21	
Empty Microgynon Packing Collection		X										Run-in-Period on Day 21
Administration of Microgynon		Daily D1 to D21	Daily intake D1 to D21									Microgynon should be taken at the same time between 7:00 ante meridiem (a.m.) and 9:00 a.m.
Fasting (≥ 10 h before visit)	X			X	X	X	X	X				≥ 10 h before cladribine / placebo administration and at least 1 h postdose
Standardized Meals / Beverages			X	X	X	X	X	X	X			
Administration of Cladribine / Placebo				X	X	X	X	X		X		Between 8:00 a.m. and 10:00 a.m. after overnight fasting. Participants will receive cladribine/placebo on Days 15-19 of Study Period 1 as well to keep the blinding.
PK Blood Sampling EE and LNG		X						X	X	X		Run-in-Period on Days 7, 14 and 21 in the morning (ambulatory visit). On Day 13 in the morning (predose of Microgynon administration); on Day 14 predose and at 0.5, 1, 2, 4, 6, 8, 12, and 24 h (Day 15) postdose
PK Blood Sampling Cladribine				X	X	X	X	X				On Day 9 predose of cladr bine/placebo administration; on Days 10-13 predose and at 0.25, 0.5, 1, 1.5 and 2.0 h postdose of cladr bine/placebo administration
CCI [redacted]												
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	Recording of Adverse Events starts at signature of Informed Consent

a See information given in the 'notes column' for line 'inclusion and exclusion criteria review.

b In case the Screening period lasts > 21 days and ≤ 60 days due to a delayed menstrual cycle of the participant (Run-in Day 1), the participant can start with a delayed Run-in-Period without having re-performed the Screening assessments. In case of the requirement to re-assess one or more Screening laboratory value(s), the Screening period may be prolonged for up to 8 weeks after the last Screening laboratory assessment and the participant can start with a delayed Run-in-Period without re-assessing the complete set of Screening laboratory assessments.

Schedule of Activities – Study Period 2 and End of Study

Assessments & Procedures	Intervention Study Period 2 (Days)									End of Study	Notes
	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 15	D 21	4-7 days after completion of D21	
Residency	X	X	X	X	X	X	X	X			In individual cases Investigator may allow participants to stay overnight at home from Day 8 to Day 12. In-patient stay is required from the evening of Day 13 until discharge on Day 15 after completion of all planned study assessments.
Ambulatory Visit									X	X	
Physical Examination										X	
Prior and Concomitant Treatment Review	X	X	X	X	X	X	X	X	X	X	
Hematology, Clinical Chemistry & Urine Analysis		X					X			X	
Urine Pregnancy Test	X									X	A negative urine pregnancy test is required prior to cladribine administration on Day 9.
Alcohol Breath Test / Drugs of Abuse	X										See Appendix 5 Urine drug screen is done locally
Weight / BMI	X									X	
Vital Signs		X	X	X	X	X	X			X	On Days 9-13 predose and 1 h postdose; on Day 14 at 24 and 25.5 h postdose (Day 13) of cladribine/placebo administration
12-lead ECG		X					X			X	On Day 9 predose and 1.5 h postdose; on Day 14 at 24 h and 25.5 h postdose (Day 13) of cladribine/placebo administration
Participant Diary Collection										X	

Assessments & Procedures (cont'd, Study Period 2)	Intervention Study Period 2 (Days)									End of Study	Notes
	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 15	D 21	4-7 days after completion of D21	
Empty Microgynon Packing Collection										X	
Administration of Microgynon	Daily intake D1 to D21										Microgynon should be taken at the same time between 7:00 a.m. and 9:00 a.m.
Fasting (≥ 10 h before visit)		X	X	X	X	X					≥ 10 h before cladribine/ placebo administration and at least 1 h postdose
Standardized Meals / Beverages	X	X	X	X	X	X	X				
Administration of Cladribine / Placebo		X	X	X	X	X		X			Between 8:00 a.m. and 10:00 a.m. after overnight fasting. Participants will receive cladr bine/placebo on Days 15-19 of Study Period 2 as well to keep the blinding.
PK Blood sampling EE and LNG						X	X	X			On Day 13 in the morning (predose of Microgynon administration); On Day 14 predose and at 0.5, 1, 2, 4, 6, 8, 12, and 24 h (D15) postdose
PK Blood Sampling Cladribine		X	X	X	X	X					On Day 9 predose of cladribine/placebo administration; on Days 10-13 predose and at 0.25, 0.5, 1, 1.5 and 2.0 h postdose of cladribine/placebo administration
CCI [redacted]											
Adverse Events	X	X	X	X	X	X	X	X	X	X	

2 Introduction

Cladribine is a prodrug, which is activated after intracellular phosphorylation to 2-chlorodeoxy-adenosinetriphosphate (CdATP). Cladribine through its active metabolite exerts reversible selective depletion of lymphocytes, which are thought to underlie the autoimmune processes involved in multiple sclerosis (MS) pathophysiology.

In August 2017, cladribine tablets were granted marketing authorization by the European Commission (EC) for the treatment of highly active relapsing multiple sclerosis (RMS) in the 28 countries of the European Union (EU) and additionally in several further countries. Complete information on the chemistry, pharmacology, efficacy, and safety of cladribine is in the Investigator's Brochure and Package Insert and Summary of Product Characteristics (Merck Serono Europe Ltd., 2017).

2.1 Study Rationale

The primary study rationale is to evaluate the potential effects of cladribine tablets on the pharmacokinetics of an oral contraceptive (Microgynon tablets [EE 30 µg, LNG 150 µg]).

2.2 Background

Cladribine is an innovative treatment approach for patients with highly active relapsing multiple sclerosis (RMS). It is the only disease-modifying drug that can deliver and sustain long-standing disease control with a maximum of 20 days of oral treatment in the first 2 years in patients with highly active RMS (Giovannoni G. 2010, Giovannoni G. 2017a, Giovannoni G. 2017b).

The existing in vitro data in cultured human hepatocytes on the induction potential of cladribine towards cytochrome P450 3A4 (CYP3A4) was considered not entirely conclusive. Based on that, the European Medicines Agency (EMA) requested the conduct of a drug-drug interaction (DDI) study with an oral contraceptive as a post approval commitment of the Marketing Authorization Holder (MAH).

2.3 Benefit/Risk Assessment

Both interventions employed in this study (i.e., cladribine tablets and Microgynon tablets) are approved medications in Europe with established efficacy and safety profiles. The patients enrolled into this study have an established diagnosis of RMS and have been determined by the Investigator to require a disease modifying RMS treatment such as cladribine tablets. The employed cladribine dose in this study is consistent with their labeled use. By application of the inclusion and exclusion criteria of this protocol, it is also ensured that none of the participants enrolled will have any contraindications for the use of cladribine tablets. Essentially similar considerations apply for the use of Microgynon tablets in the present study: The employed Microgynon dose and dose regimen is consistent with the labeled use of the product, and by observation of the inclusion and exclusion criteria of this protocol, it is ensured that none of the participants enrolled will have any contraindications for the use of Microgynon. There are also no known contraindications or warnings established for the concomitant use of both products, and there are no medically important drug-interactions to be expected.

The study is conducted under conditions that ensure a close monitoring and early detection of adverse events (AEs) and adequate medical intervention or study withdrawal (if required).

The total amount of blood taken will be about 400 ml over a period of more than 3 months (with a typical blood donation there will be drawn up to 500 ml of blood at a single occasion).

The use of Microgynon in the present study serves scientific purposes with the aim to provide group ethical benefits by establishing simplified contraception recommendations for women requiring a treatment with cladribine tablets (currently cumbersome non-hormonal, but effective methods of contraception need to be applied for at least 6 months, see Appendix 3).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of cladribine may be found in Section 4.2 (Scientific Rationale for Study Design), the Package Insert and Summary of Product Characteristics (Merck Serono Europe Ltd., 2017).

After careful consideration of the benefits and risks, the performance of the clinical study in women with RMS is considered ethically and medically justified because of the anticipated therapeutic benefit of the product for participants and the group-ethical benefits that are associated with simplified contraception recommendations that are expected to also include hormonal contraceptives based on the results from the present study.

This clinical study will be conducted in compliance with the clinical study protocol, guideline of Good Clinical Practice of the International Conference on Harmonization (ICH Topic E6, GCP) and the applicable regulatory requirements.

Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

3 Objectives and Endpoints

Table 1 Study Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
Primary		
To examine the effect of repeat-dose cladribine 10 mg tablets on the repeat-dose pharmacokinetics of the monophasic oral contraceptive Microgynon by assessment of its constituents, ethinyl estradiol (EE; 30 µg/tablet) and levonorgestrel (LNG; 150 µg/tablet)	• Primary PK parameters calculated for EE and LNG from plasma concentrations: Area under the concentration–time curve from zero to tau at steady state ($AUC_{\tau,ss}$), and the maximum plasma concentration at steady state ($C_{max,ss}$). • Secondary PK parameters calculated for EE and LNG: $C_{min,ss}$; C_{trough}; $t_{max,ss}$; $C_{ave,ss}$; and peak-to-trough fluctuation (PTF%).	Study Periods 1 and 2 on Days 14/15
Secondary		
To examine the safety and tolerability of Microgynon and cladribine co-administration.	Occurrence of treatment-emergent adverse events (TEAEs), changes in safety laboratory tests, 12-lead electrocardiograms (ECGs) (morphology, and time intervals [PR, QRS, RR, QT and corrected QT intervals [QTc]), and vital signs (PR, SBP, DBP, body temperature)	Time from first treatment to last assessment
To examine cladribine exposure	Cladribine C_{max} and t_{max}	Cladribine PK sampling in Study Periods 1 and 2 at predose on Days 9, 10, 11, 12 and 13, and postdose on Days 10, 11, 12 and 13 at 0.25, 0.5, 1.0, 1.5, 2.0 h
[redacted]		
[redacted]	[redacted]	[redacted]

ss=at steady state; AUCτ=Area under the concentration–time curve from zero to tau; C_{av}=average concentration; C_{max}=maximum plasma concentration; C_{min}=minimum observed concentration during a complete dosing interval; C_{trough}=concentration observed immediately before next dosing; DBP=diastolic blood pressure; ECG=electrocardiogram; EE=ethinyl estradiol; [redacted] h=hour; [redacted] LNG=levonorgestrel; CCI [redacted] PK=pharmacokinetic; PTF%=peak-to-trough fluctuation; PR=pulse rate; QTc=corrected QT intervals; SBP=systolic blood pressure; [redacted] t_{max}=time to reach the maximum observed concentration collected during a dosing interval; TEAEs=treatment-emergent adverse events.

4 Study Design

4.1 Overall Design

This is a randomized, double-blind, 2-period, 2-sequence crossover study with a 1 month Run-in-Period in pre-menopausal women with active relapsing multiple sclerosis (RMS) requiring a disease-modifying RMS treatment. The overall study design is shown in Section 1.2, Figure 1.

The study design will comprise a ≤ 21-day Screening period followed by a Microgynon Run-in-Period, followed by 2 sequential treatment periods (Study Periods 1 and 2) of 28 days each.

In case the Screening period lasts > 21 days and ≤ 60 days due to a delayed menstrual cycle of the participant (Run-in Day 1), it is acceptable that the participant starts with a delayed Run-in-Period without having re-performed the Screening assessments (in order to minimize unnecessary investigational burden for the participant). In case of the requirement to re-assess one or more Screening laboratory value(s), the Screening period may be prolonged for up to 8 weeks after the last Screening laboratory assessment and it is acceptable that the participant starts with a delayed Run-in-Period without re-assessing the complete set of Screening laboratory assessments. In both cases, the participant does not need to sign a new Informed Consent Form (ICF).

In the Run-in-Period as well as during both treatment periods, Microgynon (1 tablet/day containing 30 µg ethinyl estradiol [EE] and 150 µg levonorgestrel [LNG]) will be administered for 21 days, followed by 7 days off-treatment. In Study Periods 1 and 2 Microgynon will continue to be administered together with randomized treatment sequences of a 5-day once-daily cladribine 10 mg tablet treatment (Day 9 to Day 13 of Study Period 1) followed by a 5-day once-daily matched placebo treatment (Day 9 to Day 13 of Study Period 2) or vice versa; i.e., participants will be randomized to 1 of 2 double-blind treatment sequences, either cladribine-placebo or placebo-cladribine. Additionally, matched placebo treatment (Day 15 to Day 19) will be given in order to protect the blind for the cladribine-placebo sequence, that will receive their second weekly dose of cladribine on Day 15 to Day 19 in Study Period 2. In turn, the placebo-cladribine sequence will receive the second weekly dose of cladribine after the End of Study Visit as part of standard medical care.

An End of Study examination will be performed within 4-7 days after the last visit of Study Period 2. To the extent possible, an Early Termination (ET) visit will be conducted for participants who withdraw prematurely. The same assessments as for the End of Study Visit will be conducted at the ET visit as far as feasible.

During the Run-in-Period participants will take Microgynon on an ambulatory basis and document daily drug intake in a participant diary. Participants will be requested to come to weekly visits in the mornings of Day 7, 14 and 21 for documentation of adverse events, participant diary check, and therapeutic drug monitoring (i.e., pharmacokinetic (PK) sampling for EE and LNG trough levels).

For Study Periods 1 and 2, participants will continue to take Microgynon on an ambulatory basis of Days 1 to 7 and to document drug intake in a participant diary. On Day 8 they will be hospitalized until discharge in the morning of Day 15 after completion of all in-house study-related assessments. At some study sites the hospitalization periods need to be conducted in

another location at so called Clinical Pharmacology study sites (PK-sites). For details regarding the study administrative structure and the complete coverage of Investigator responsibilities in case of a separate Investigational / PK site situation please see Appendix 2 (Study Governance).

In individual cases Investigator may allow participants to stay overnight at home from Day 8 to 12. In this cases Investigator will provide participants with written instructions regarding the necessary compliance with lifestyle requirements.

Serial blood samples will be collected for the safety (hematology, biochemistry, coagulation), and the PK and CCI [redacted] assessments to be performed throughout the residential part of each treatment period.

Participants will have to come for another ambulatory visit on Day 21 for documentation of adverse events, participant diary check, Microgynon medication collection and supply.

Participant's total duration of participation will be 3 cycles of hormonal contraceptive (84 days) plus the Screening period of up to 21 days and the End of Study Visit 4 - 7 days after Day 21 of the second period. Therefore, the total duration of treatment with hormonal contraception (HC) is 63 days (3 cycles of HC of 21 days), treatment duration with cladribine is 5 days for the sequence placebo-cladribine, and 10 days for sequence cladribine-placebo and the total duration of each participant in the study is 82 to 105 days.

A detailed schedule of study procedures/assessments is provided in Section 1.3.

CCI [redacted]

The anticipated clinical duration of the study including a ≤ 1 month Screening phase, a 21 months recruitment phase and the 3 months treatment phase is a total of ≤ 25 months.

4.2 Scientific Rationale for Study Design

This study will investigate the potential effects of cladribine treatment on the pharmacokinetics of the frequently prescribed monophasic oral contraceptive Microgynon. The outcome of the study is expected to be generalizable also to other hormonal oral contraceptives containing EE as estrogen component and LNG or other progestin components metabolized by CYP3A4 (e.g. norethindrone, norelgestromin, etc.), as the available published evidence suggests that LNG is a highly sensitive substrate for the assessment of CYP3A4 induction, and that the effect of CYP3A4 induction (in terms of AUC reduction) on other CYP3A4-metabolized progestins is qualitatively comparable. The study addresses a recent request by the EMA for the conduct of a cladribine DDI study with an oral contraceptive as a post approval commitment.

Cladribine has been shown to have teratogenic effects in preclinical studies, consistent with its pharmacologic mechanisms of action. This study will provide additional important information on the safety of cladribine and the most suitable contraceptive methods to be used with cladribine.

The study design is consistent with DDI studies examining the perpetrator effects of investigational medicinal products (IMPs) on the pharmacokinetics (PK) of hormonal contraceptives. Accordingly, the study aims to compare the effect of repeat-dose cladribine 10 mg tablets and matched placebo on the repeat-dose PK of the monophasic oral contraceptive Microgynon. The study objective is to show that both treatments will have an equivalent effect on the PK of both Microgynon components (EE/LNG). As the dose and posology of cladribine treatment is based on body weight, and participants with a very low body weight (i.e., < 50 kg) would receive only a 4-day treatment per treatment week instead of a 5-day treatment, the study will only enroll participants with a body weight of ≥ 50 kg to allow for a standardized 5-day repeat-dose cladribine treatment of all study participants. This approach will standardize the cladribine treatment duration, thereby reducing the complexity of the study design.

Participants randomized to the treatment sequence placebo-cladribine, will receive their first 5-day cladribine treatment in Study Period 2 (Days 9 to 13), and will receive their second 5-day cladribine treatment between 28 to 35 days thereafter, which conforms to the approved cladribine posology. It is important to note, that this second cladribine treatment week will not be part of the study itself but provided as standard medical care of participants in the following month after end of the study (see Section 6.7).

Participants randomized to the treatment sequence cladribine-placebo, will receive their first 5-day cladribine treatment in Study Period 1 (Days 9 to 13). Since, according to the study design, they will have to receive Placebo treatment 4 weeks thereafter (i.e., Study Period 2, Days 9 to 13), their second 5-day cladribine treatment will have to be deferred by 6 days (i.e., Study Period 2, Days 15 to 19). Accordingly, participants will receive their second 5-day cladribine treatment 34 days after having received their first cladribine 5-day treatment in Study Period 1. This schedule will only marginally deviate from the approved cladribine posology. In view of the long-lasting duration of action of cladribine, this modest deferral of the second cladribine treatment week is unlikely to affect the overall efficacy of cladribine treatment.

The second cladribine treatment on Days 15 to 19 in Study Period 2 will not alter the primary study objectives, as the treatment is only initiated after all PK and [redacted] samples will have been taken on Day 14 with the last sampling in the morning of Day 15 (initiation of second cladribine treatment thereafter).

In order to also enable blinding of the Days 15 to 19 cladribine treatment in Study Period 2, all participants from both treatment sequences will receive placebo on Days 15 to 19 in Study Period 1, and participants randomized to the treatment sequence cladribine-placebo (Days 9 to 13) will receive cladribine on Days 15 to 19 in Study Period 2 as their second dose (see Section 1.2, Figure 1).

It is important to note that only Days 9 to 13 cladribine and placebo treatments are serving the purpose of the primary and secondary study objectives (i.e., examining placebo-controlled cladribine effects on the PK and [redacted] of the active Microgynon components EE and LNG), while Days 15 to 19 cladribine and placebo treatments are only factored into the study design to allow for a timely initiation of the second 5-day cladribine treatment for participants assigned to the treatments sequence cladribine-placebo, in a blinded fashion.

Thus, the purpose of the randomized, double-blind, 2-sequence cladribine-placebo and placebo-cladribine 5-day repeat-dose treatments, is to allow for an unbiased assessment of the PK, [redacted] and safety outcomes of the study, while ensuring that all study participants will receive an effective cladribine treatment, which will be consistent or at least very close to the currently approved cladribine posology.

The study design also took into consideration recent expert and regulatory opinions as presented at the following international scientific meetings:

- Drug Interactions with Hormonal Contraceptives. Public Health and Development Implications. Public FDA Meeting, FDA White Oak Campus, Silver Spring, MD 20993, November 9th, 2015
- 7th International Workshop on Regulatory Requirements and Current Scientific Aspects on the Preclinical and Clinical Investigation of Drug-Drug Interactions. May 29th to 31st, 2016; Session IV: DDIs with Hormonal Contraceptives. Marbach Castle, Oehningen, Germany.

4.3 Justification for Dose

The dose and the posology of both the examined treatments, cladribine tablets (10 mg) and the monophasic oral contraceptive Microgynon will be consistent with the labeled use of both products. Therefore, the results of the study are expected to properly characterize the absence or presence of any cladribine effects on the pharmacokinetics of the active Microgynon components EE and LNG with sufficient confidence, and to adequately quantify the effect size (if any).

4.4 End of Study Definition

A participant has completed the study if she has completed all study parts, including the End of Study Visit, and the following review of all End of Study safety assessments, including the blood sample results have been completed by the Investigator. In case of ongoing adverse events or safety laboratory deviations requiring follow-up activities, the end-of study will be defined for those subjects as the date of the last follow-up visit.

The end of the study is defined as the date when the last End of Study visit of the last study participant globally has been performed and the following review of all safety assessments, including the blood sample results have been completed by the Investigator

Routine standard of care activities (e.g., blood drawing) should only be initiated once the site was unblinded to the patient treatment sequence.

5 Study Population

The criteria in Sections 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria) are designed to enroll only participants, who are appropriate for the study, thereby ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative has provided written informed consent, as indicated in Appendix 2 (Study Governance).

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are 18 to 45 Years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Have a diagnosis of clinically stable and definite RMS by either McDonald MS or Poser criteria.
3. Apart from their underlying primary disease condition (i.e., RMS) are in good health as determined by medical history, physical examination, 12-lead ECG, vital signs, clinical biochemistry, hematology and urinalysis.
4. Have white blood cell counts, absolute lymphocyte counts and absolute neutrophil counts within normal ranges (applies for patients in Year 1) at Screening and on Day 21 of the Run-in-Period (Baseline), respectively. Platelets should not be below 100 x 10^9/L. In case of second year cladribine treatment, lymphocyte counts must be at least 800 cells/mm³ at Screening and on Day 21 of the Run-in-Period (Baseline).

5. Have other safety laboratory values within normal ranges at Screening, or modestly out of range which are assessed by the Investigator as not clinically relevant.
6. Are able and willing to accept dietary restrictions and restrictions regarding the use of concomitant medications (incl. over-the-counter (OTC)) products, herbal medicines and dietary supplements) over the course of the study as further specified in the Exclusion Criteria.
7. Are able and willing to undergo serial venous blood sampling for pharmacokinetic evaluation.
8. Are able to comply with all of the study requirements.

Weight

9. Have a body weight within ≥ 50 kg and ≤ 100 kg and body mass index (BMI) within the range ≥ 18 kg/m^2 and ≤ 30 kg/m^2 (inclusive) at Screening.

Sex

10. Are non-pregnant, non-breast feeding women of any ethnic origin.
11. Are pre-menopausal women with or without child-bearing potential with a negative serum pregnancy test, and women with child-bearing potential receiving adequate birth control. Women with childbearing potential must be willing to avoid pregnancy by using a highly effective method of birth control in addition to the hormonal contraceptive (Microgynon) that is employed in the study. According to World Health Organization (WHO) definition highly effective methods of birth control are those resulting in a less than 1% per Year failure rate when used consistently and correctly, such as intrauterine devices (IUDs). Highly effective contraception should be maintained throughout the study (starting from enrollment), and for at least 4 weeks after the last dose of study intervention. An effective contraceptive method (e.g., by taking a hormonal oral contraceptive or applying another effective birth control method) must be used starting 1 month after last dose of study intervention and continue for at least 5 months (see also Appendix 3). Women without childbearing potential are defined as surgically or medically sterile.

Informed Consent

12. Can give signed informed consent, as indicated in Appendix 2 (Study Governance), which includes compliance with the requirements and restrictions listed in the ICF and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. History of clinically relevant allergy or known hypersensitivity to the active substance or to any of the excipients (e.g., fructose) of cladribine tablets or hypersensitivity to drugs with a similar chemical structure to cladribine.
2. History of clinically relevant allergy or known hypersensitivity to 1 of the active substances levonorgestrel (LNG) or ethinylestradiol (EE) or to any excipients (e.g., lactose and sucrose) of Microgynon tablets.

3. Presence or history of any serious allergy (requiring hospitalization or prolonged systemic treatment).
4. Positive results from serology examination for Hepatitis B surface antigen (HbsAg) not due to vaccination, hepatitis B core antibody (HbcAb), Hepatitis C virus antibody (anti-HCV) or Human Immunodeficiency virus 1 and 2 antibody (anti-HIV1/2).
5. Active chronic infection (tuberculosis or hepatitis).
6. History or current evidence of any significantly immunocompromising comorbidities.
7. Current diagnosis or personal history of cancer.
8. Moderate or severe renal impairment (creatinine clearance < 60 mL/min).
9. Moderate or severe hepatic impairment (Child Pugh B and C).
10. Presence or risk of venous thromboembolism (VTE), e.g., history of deep venous thrombosis (DVT); pulmonary embolism (PE); known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, including Factor V Leiden, antithrombin-III-deficiency, protein C deficiency, protein S deficiency; major surgery with prolonged immobilization; high VTE risk due to the presence of multiple risk factors.
11. Presence or risk of arterial thromboembolism (ATE), e.g., current arterial thrombo-embolism; history of arterial thromboembolism (e.g., myocardial infarction) or prodromal condition (e.g., angina pectoris, diagnosis of coronary artery disease); cerebrovascular disease, e.g., current stroke, history of stroke or prodromal condition such as transient ischemic attack (TIA); history of migraine with focal neurological symptoms; known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinemia and antiphospholipid antibodies (anticardiolipin-antibodies, lupus anticoagulant); a high risk of arterial thromboembolism due to multiple risk factors.
12. Diabetes mellitus (Type 1 or Type 2) with vascular manifestations (e.g., diabetic foot syndrome, retinopathy or arteriosclerosis).
13. Poorly controlled arterial hypertension, i.e., systolic blood pressure ≥ 160 mm, or diastolic blood pressure ≥ 100 mm Hg).
14. Severe hyperlipoproteinemia, i.e., total cholesterol ≥ 240 mg/dL or hypertriglyceridemia ≥ 200 mg/dL in combination with low density lipoprotein (LDL) cholesterol ranging between 160 to 190 mg/dL.
15. Signs and symptoms of Transmissible Spongiform Encephalopathy or Progressive Multifocal Leukencephalopathy (PML) at Screening.
16. Presence of chronic or recurrent infection or any acute infection within the last 2 weeks before first dosing in treatment periods employing cladribine.
17. Signs or symptoms of neurological disease other than MS that could explain the symptoms of the participant.
18. Presence of gastrointestinal (GI) disease or history of gastrointestinal -tract surgery that, in the opinion of the Investigator, may affect the absorption of the study drugs, i.e., the pharmacokinetic outcome of the study.

Prior/Concomitant Therapy

19. Current immune-suppressive or myelosuppressive therapies (e.g., methotrexate, cyclophosphamide, cyclosporine or azathioprine, or chronic use of corticosteroids) or prior treatment with immunomodulatory or immunosuppressive medicinal products within the last year prior to the planned first study intervention, with the exception of the following therapies and application of the specified wash-out criteria below:

    a) Interferon b, Dimethylfumarate, and Glatirameracetate (Copaxone): until remission of treatment-specific effects as indicated by a lymphocyte count not below the lower limit of normal range of central lab (1.000 - 1.200 cells/mm^3) and at least 1 month,

    b) Azathioprine, Cyclosporine A, Mitoxantrone, Methotrexate: until remission of treatment-specific effects as indicated by a lymphocyte count not below the lower limit of normal range of central lab (1.000 - 1.200 cells/mm^3) and at least 3 months,

    c) Alemtuzumab, Rituximab, until remission of treatment-specific effects as indicated by a lymphocyte count not below the lower limit of normal range of central lab (1.000 - 1.200 cells/mm^3) and at least 6 months.

    d) Elimination of teriflunomide and other medications may be accelerated by the administration of cholestyramine or activated charcoal (accelerated elimination procedure [AEP]). In cases where AEP is approved and was carried out according to the summary of product characteristics before Screening, including confirmation by therapeutic drug monitoring, Exclusion Criterion # 19 is therefore not applicable.

    Note: The AEP is an established procedure if pregnancy is desired or if the immune-suppressive or myelosuppressive therapy is to be changed and the previously given medication is to be removed from the body within a short time. Even in the case of a medication with a very long half-life, by means of AEP it is possible to reduce blood levels below the detection limit within a short period of time.

20. Vaccination with live or attenuated live vaccines within 4 weeks prior to cladribine/placebo administration, and participants who are expected to require vaccination with live or attenuated live vaccines throughout the study.

21. Regular use of any medications that can directly influence gastrointestinal motility and absorption of cladribine (e.g., use of histamine receptor antagonists (H_2), proton pump inhibitors, or antacids), and participants who are expected to use such products throughout the study.

22. Participants who have used potent or moderate inducers of CYP3A4 or other cytochrome P450 enzymes or of the drug transporters P-gp and BCRP, such as carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin and pioglitazone within the last 4 weeks prior to the planned first study intervention and participants who are expected to use such products throughout the study.

23. Participants who have used strong or moderate inhibitors of CYP3A4 or other cytochrome P450 enzymes including oral/systemic ketoconazole, itraconazole, miconazole, clotrimazole, fluconazole, posaconazole, voriconazole, clarithromycin, erythromycin, ciprofloxacin, verapamil, diltiazem, indinavir, nelfinavir, saquinavir, ritonavir, amprenavir, lopinavir, atazanavir, darunavir and cyclosporine within the last 4 weeks prior to the planned first study intervention, and participants who are expected to use such products throughout the study.

24. Participants who have used equilibrative nucleoside (ENT1) and concentrative nucleoside (CNT3) transport proteins inhibitors such as dilazep, nifedipine, nimodipine, cilostazol, sulindac or reserpine within 2 weeks prior to the first scheduled study intervention, and participants who are expected to use such products throughout the study.
25. Use of any herbal medications such as St John's Wort, milk thistle/silymarin, goldenseal/ berberine and Echinacea, or any dietary supplements (including vitamins and minerals) within 2 weeks prior to the first scheduled study intervention, and participants who are expected to use such products throughout the study.
26. Participants reporting consumption of any drug metabolizing enzyme (e.g., CYP3A4 or other cytochrome P450 enzymes) inducing or inhibiting aliments, beverages or food supplements, e.g., broccoli, Brussels sprouts, grapefruit, grapefruit juice, Seville orange, star fruit, and products containing such fruit components (e.g., juices, marmalade, jam, etc.) within 2 weeks prior to the first scheduled study intervention, and participants who are expected to use such products throughout the study.

Prior/Concurrent Clinical Study Experience

27. Exposure to another investigational drug within the last 2 months or within last 6 month if agent is known to be immunosuppressive.
28. Participant has previously received at least 1 dose of study intervention in the current study.

Diagnostic Assessments

29. Clinically significant abnormal finding in the 12-lead ECG recording at the Screening examination, including QTc > 450 ms (Fridericia's formula) or participants with congenital long QT syndrome, or other clinically significant abnormal ECG findings that in the opinion of the Investigator may increase the safety risk to the participant.

Other Exclusions

30. Current history or presence of drug or alcohol abuse, confirmed by positive test results for drugs of abuse and/or alcohol or have a history of drug or alcohol abuse. Alcohol abuse is defined as: an average daily intake of more than 3 units or a weekly intake of more than 14 units for females where 1 unit equals 8-10 g alcohol (1 unit equals 340 mL of beer, 115 mL of wine or 43 mL of spirits).
31. Smoking of > 10 cigarettes per day or equivalent.
32. Loss or donation of more than 400 mL of blood in the 12 weeks prior to first dose.
33. Participant plans to donate oocytes for medically assisted reproduction techniques (ART) within 6 months after the last cladribine dose.
34. Participant is a "vulnerable" individual (e.g., person is kept in detention).
35. Participant is Investigator in the current study, or a first-degree relative of a study Investigator, or is an employee of the sponsor or study centers.
36. Participant is considered unable or unwilling to co-operate adequately, i.e., to follow study procedures and Investigator instructions adequately (e.g., language difficulties, etc.).
37. Participant is anticipated to be unavailable for scheduled study visits/procedures.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

The following restrictions apply:

Participants will be on a controlled diet during the hospitalized periods and accordingly before the start of study intervention cladribine/placebo until after the final dose

- Participants will refrain from consumption of Seville oranges, grapefruit or grapefruit juice and of any other drug metabolizing enzyme (e.g., CYP3A4 or other cytochrome P450 enzymes) inducing or inhibiting aliments, beverages or food supplements, e.g., broccoli, Brussels sprouts, star fruit, and products containing such fruit components (e.g., juices, marmalade, jam, etc.) from 2 weeks before the start of study intervention until after final dose.

5.3.2 Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 12 hours before the start of dosing until after collection of the final pharmacokinetic (PK) and/or CCI [redacted] sample
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or CCI [redacted] sample
- Use of tobacco products will not be allowed from Screening until after the End of Study Visit beyond the limits specified in Exclusion Criterion #31. Exemption: In each period requiring PK blood sampling EE and LNG, participants are not allowed to consume tobacco products for 10 hours before the start of dosing on D14 until 4 hours postdose.

5.3.3 Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

5.3.4 COVID-19 Vaccination Considerations

mRNA Vaccines:

No study drug interactions or specific consideration for the study population are so far known for mRNA vaccines. Therefore, there is no need to generally restrict the use of these vaccines prior, during, or after participating to the study.

In case that vaccination during the study may be considered, it should be scheduled either for the Run-in-Period or between Day 21 and Day 28 of study Periods 1 or 2, respectively, because vaccination during the treatment periods (between Days 1 to 20) shortly before cladribine/placebo administration may complicate causality assessment of AEs, and because there may be the possibility that cytokine release upon vaccination may increase the variability of the PK assessments after cladribine/placebo administration.

It is to be noted, that any vaccination during the study must be properly documented in the concomitant medication section of the eCRF.

Viral Vector Vaccines:

No study drug interactions are so far known for viral vector vaccines.

In contrast to the mRNA vaccines, since 01 April 2021, the use of viral vector vaccines for persons under 60 years of age is no longer recommended per CCI [redacted] as the risk of thrombosis is increased.

This guidance therefore also applies to the study population women aged 18 to 45 and should be adhered to, therefore no vaccination with a viral vector vaccine should be carried out during the study.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants will be assigned a new participant number.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention(s) Administration

Study intervention administration details are provided in the table below.

Study Intervention Name:	**Cladribine Tablets**	**Cladribine Placebo Tablets**	**Microgynon**
Dose Formulation:	White, round, biconvex tablets of 8.5 mm diameter, engraved with 'C' on 1 side and '10' on the other side.	White, round, biconvex tablets of 8.5 mm diameter, engraved with 'C' on 1 side and '10' on the other side	Beige, sugar-coated tablets
Unit Dose Strength(s)/ Dosage Level(s):	10 mg / tablet	N/A (placebo)	Levonorgestrel (LNG) 150 µg and ethinyl estradiol (EE) 30 µg
Route of Administration:	Oral	Oral	Oral
Dosing Instructions:	Each treatment week consists of 5 consecutive days on which a participant receives 10 mg or 20 mg (one or 2 tablets) taken with water in the morning as a single daily dose, depending on body weight. For details, see Section 6.6	As for cladribine. For details, see Section 6.6	1 tablet daily for 21 days, starting on the first day of the menstrual cycle followed by 7 treatment-free days. Subsequent cycles (Study Periods 1 and 2): Tablet-taking from the next pack of Microgynon is continued after a 7-day treatment-free interval, beginning on the same day of the week as the Run-in-Period. For details, see Section 6.6
Supplier:	Merck KGaA	Merck KGaA	From commercially available sources; provided by Merck KGaA
Packaging and Labeling	Cladribine will be supplied in blister packages, containing 1, 4 and 6 tablets. Packages with 1 tablet for the study and the medical care treatment of the first year will be used. All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.	Placebo will be supplied in blister packages, containing 1, 4 and 6 tablets. All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.	Microgynon 21 will be supplied and packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

EE=ethinyl estradiol; IMP=investigational medicinal product; LNG=levonorgestrel; N/A=not applicable; µg=microgram; mg= milligram; mm= millimeter

6.1.1 Medical Device(s) Use

Not applicable.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate document and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply or administer it (where enrolled is defined as a participant who has started the Run-in-Period, see Table 7). All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
    - Confirmation of receipt, in good condition and in the defined temperature range
    - The inventory provided for the clinical study and prepared at the site
    - The dose(s) each participant used during the study
    - The disposition (including return, if applicable) of any unused study intervention(s)
    - Dates, quantities, batch numbers, container numbers, expiry dates, formulations for study interventions prepared at the site, and the participant numbers
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant
- A Study Monitor will periodically collect the study intervention(s) accountability forms and check all returns (both unused and used containers) before authorizing their destruction by the study site or arranging for their return to the Sponsor or designee. In the event the site is unable to destroy unused and used containers, it is recommended local or regional destruction is organized by the CRO. Unused and used containers must only be returned to the Sponsor CMO depot, if required by the local law
- Further guidance and information for the final disposition of unused study interventions are provided in the Operations Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Participants will be randomized in a 1:1 ratio to 1 of the 2 sequences of the crossover design.

On Day 21 of the Run-in-Period, participants will be assigned a unique number (randomization number) in ascending numerical order at each study site. The randomization number encodes the participant's assignment to 1 of the 2 sequences of the study, per the randomization schedule generated prior to the study by the Clinical Trial Supply Department (CTS) Department at PPD .

6.3.2 Blinding

Blinding Method

To blind cladribine treatment, matched placebo tablets will be used. Microgynon tablets will be administered open-label.

Assignment Method Retention

Unblinding may be done utilizing blind-break envelopes provided to each site. All breaks of the study blind must be adequately documented.

Unblinding Clinical Studies for Sample Analysis of Special Data

Not applicable.

Unblinding Process After End of Study for Each Participant

Each participant assigned to the placebo-cladribine sequence will receive the second weekly dose of cladribine after the End of Study Visit as part of standard medical care (see also Section 4.1). Therefore, after the End of Study Visit of each participant, the Investigator will be unblinded for that participant, according to the timelines and procedures specified in the following:

After data entry of Day 21 of Study Period 2 in the electronic Case Report Form (eCRF), a trigger email is initiated to the PPD Project Manager (PM) and the Clinical Research Associate announcing the date of the End of Study Visit for the participant. At the End of Study Visit, in the eCRF a confirmation form is completed by the Investigator that all data have been entered. Subsequently, a second trigger email is initiated confirming the End of Study Visit for the participant has been completed. Thereafter, the PPD PM is requesting unblinding for the participant's study intervention at the PPD CTS Department. Information on unblinded treatment assignment is transferred from PPD CTS to the site via PM and Clinical Research Associate. This information is forwarded to the designated IMP distribution site responsible for delivering cladribine tablets for the second cladribine 5-day treatment.

For further information on study intervention after the end of the study, see Section 6.7.

6.3.3 Emergency Unblinding

In an emergency, the Investigator is solely responsible for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in this decision. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to the unblinding, unless this could delay emergency treatment. The Sponsor must be notified within 24 hours after unblinding. The Investigator must provide the Sponsor the reason for unblinding without revealing the study intervention, except to the designated drug safety representative via the Emergency Unblinding Notification Form. The date of and reason for unblinding must be recorded in the source documents. Contact information for unblinding in an emergency is given on the participant emergency card provided to each participant, as noted in Appendix 2 (Study Governance Considerations).

The Sponsor's Global Patient Safety department will submit any Suspected Unexpected Serious Adverse Reactions (SUSAR) reports to regulatory authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

Under certain circumstances, Global Patient Safety may be required to unblind the treatment assignment for an individual participant following a serious adverse event (SAE) or other serious event; for example, if an expedited regulatory report is required. See Section 8.3.4 for further details on expedited reporting and SAEs.

Unblinding of the period assignment of an individual participant due to emergency will not per se render this participant unevaluable for PK and [redacted] assessments, provided the unblinding or related emergency procedure will not alter the planned per-protocol study interventions (see Section 9.3).

6.4 Study Intervention Compliance

During the 2 cladribine treatment periods, while participants are hospitalized, administrations of cladribine tablets will be performed by dedicated site staff in accordance with the protocol requirements and specifications of the Investigator. This includes checking the oral and buccal cavity with the aid of a flashlight and tongue depressor. The proper administration of the study medication will be documented on the individual eCRF.

Participants will be provided with a pack of Microgynon for 1 cycle during the Screening Visit and a diary for recording daily Microgynon intake. The diary entries are checked for compliance of Microgynon intake during ambulatory visits on Day 7, 14 and 21 of the first cycle (Run-in-Period). On Day 21 of the first cycle (Run-in-Period) and Day 21 of Study Period 1, participant diary and empty Microgynon packing is collected, and a new diary and Microgynon pack is delivered. Additionally, therapeutic drug monitoring (PK sampling for EE and LNG) is performed on Days 7, 14 and 21 of the first cycle (Run-in-Period), and on Days 13, 14 and 15 of each period.

Participants must be 100% compliant to cladribine and placebo intake to be eligible for Pharmacokinetic and [redacted] evaluation (see Populations for Analysis, Section 9.3).

Assessment of compliance with respect to Microgynon intake will be based on participant reports (diary) and pill counts during the study, and at the end of the study on retrospective analysis of EE/LNG blood levels of all samples collected. Deviations from compliance to Microgynon for each of the 21 days of intake per cycle, if any, will be judged by the Investigator whether such protocol non-compliance is considered significant. In case of significant non-compliance, the participant would be withdrawn from further therapy or the study (see Section 7.1 and 7.2).

6.5 Concomitant Therapy

Record in the eCRF all concomitant interventions (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.5.1 Rescue Medicine

Not applicable.

6.5.2 Permitted Medicines

The only permitted medications are the following:

- Acetaminophen (Paracetamol) up to 1 g per day, at the discretion of the Investigator
- Established treatments for chronic stable concomitant diseases (e.g., for hypertension, hyperlipidemia, etc.) are allowed, when kept stable throughout the study.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

Cladribine pretreatment is permitted, provided

- the participant has completed a full first year course of treatment, and
- the second year treatment initiated during this study (Day 8 of Study Period 1) is initiated within 12-18 months after the first dose of cladribine in Year one, and
- lymphocyte count is at least 800 cells/mm^3 at Screening and on Day 21 of the Run-in-Period (Baseline) before initiating treatment in year 2.

6.5.3 Prohibited Medicines

During intake of Microgynon and Cladribine (Day 9 – Day 13 and Day 15 – Day 19), intake of concomitant oral medication, including medicines as permitted in Section 6.5.2, is not allowed from 3 hours before to 3 hours after cladribine intake except of Microgynon.

On Day 14 until the last PK sample is drawn on Day 15 concomitant medications, including medicines as permitted in Section 6.5.2, have to be paused, unless interruption of a specific chronic concomitant medication for one day would be considered to pose a medical risk to a subject.

Prohibited medicines include:

Previous immune-suppressive or myelosuppressive therapies or prior treatment with immunomodulatory or immunosuppressive medicinal products within the last year prior to the planned first study intervention or expected use of such products throughout the study with the exception of the therapies and application of the specified wash-out criteria described in Exclusion Criterion #19.

Previous use of potent or moderate inducers of CYP3A4 or other cytochrome P450 enzymes or of the drug transporters P-gp and BCRP, such as carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin, pioglitazone, oral/systemic ketoconazole, itraconazole, miconazole, clotrimazole, fluconazole, posaconazole, voriconazole, clarithromycin, erythromycin, ciprofloxacin, verapamil, diltiazem, indinavir, nelfinavir, saquinavir, ritonavir, amprenavir, lopinavir, atazanavir, darunavir and cyclosporine within the last 4 weeks prior to the planned first study intervention, or use of such products throughout the study (see Exclusion Criteria #22 and #23)

Regular previous and expected concomitant use of any medications that can directly influence GI motility and absorption of cladribine (e.g., use of histamine receptor antagonists (H_2), proton pump inhibitors, or antacids), and expected use of such products throughout the study (see Exclusion Criterion #21)

Previous use of equilibrative nucleoside (ENT1) and concentrative nucleoside (CNT3) transport proteins inhibitors such as dilazep, nifedipine, nimodipine, cilostazol, sulindac or reserpine within 2 weeks prior to the first scheduled study intervention, and expected use of such products throughout the study (see Exclusion Criterion #24).

Use of any herbal medications such as St John's Wort, milk thistle/silymarin, goldenseal/ berberine and Echinacea, or any dietary supplements (including vitamins and minerals) within 2 weeks prior to the first scheduled study intervention, and expected use such products throughout the study (see Exclusion Criterion #25).

Participants that had undergone a previous 1 year cycle of cladribine may be considered for inclusion into this study as their second year treatment course. Therefore, previous cladribine treatment is permitted, provided the participant has completed a full first year course of treatment and that the second year treatment initiated during this study (Day 9 of Study Period 1 or 2, respectively depending on treatment group) is initiated within 12 to 18 months after the first dose of cladribine in year one. Note that lymphocyte counts for these participants needs to be at least 800 cells/mm³ before initiating cladribine treatment in year 2 (see Section 6.7) rather than within normal ranges (see Inclusion Criterion #4)

The participants are prohibited from using prescription or over-the-counter medications, herbal medicines and dietary supplements (e.g., vitamins and minerals) as detailed in the Exclusion Criteria (see Section 5.2), apart from acetaminophen up to 1 g per day, as judged appropriate by the Investigator, within the specified time-periods prior to the first study intervention during the study, and until after the End of Study Visit.

6.5.4 Other Interventions

Study participants should adhere to the following restrictions from Day -1 (screening phase) until the End of Study Visit, if periods of prohibition are not specified otherwise:

- Women of childbearing potential must agree to comply with the requirements of reliable contraception as specified in Inclusion Criterion #11.
- Vaccination with live or life attenuated vaccines as specified in Exclusion Criterion #20
- Alcohol intake beyond the limits as specified in Exclusion Criterion #30
- Smoking beyond the limits as specified in Exclusion Criterion #31
- Dietary restrictions as specified regarding CYP enzyme inducing or inhibiting foods and beverages as specified in the Exclusion Criterion #26
- Oocyte donation as specified in as specified in Exclusion Criterion #33
- Planned (i.e., elective) hospital visits or surgical procedures during the course of the study are not permitted. In case of emergency or other strong medical need arising for such procedures, the participant would be withdrawn from the study
- Participation in a clinical study with intake of an investigational drug up to 2 months prior to inclusion is not permitted (see Exclusion Criterion #27). However, participation in non-interventional studies or registries in the indication RMS are permitted prior to and during the study.

6.6 Dose Selection and Modification

6.6.1 Cladribine

The recommended cumulative dose of cladribine 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, 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 5 days on which a participant receives 10 mg or 20 mg (one or 2 tablets) as a single daily dose, depending on body weight. The distribution of the total dose over the 2 years of treatment is provided in Table 3. For some weight ranges the number of tablets may vary from 1 treatment week to the next. Only if weight changes drastically (± 10 kg), cladribine dose for the second treatment needs to be adapted. Details are described in the IMP Handling Manual.

Note that for participants randomized to the treatment sequence placebo-cladribine only the first cladribine 5-day treatment will be part of the study, while the second cladribine 5-day treatment will be offered to the study participants as medical care of participants in the month after End of Study (see Section 6.7). The same applies for the completion for cladribine treatment in year 2 for those participants that receive their first year treatment course under the current protocol, in which case the second year treatment will be offered to the study participants as continued medical care after end of study (see Section 6.7).

Cladribine or matched placebo tablets must be taken orally with 200 mL non-carbonated tap water, and swallowed without chewing in fasted state in the mornings (between 8:00 and 10:00) of Days 9, 10, 11, 12, 13, and Days 15, 16, 17, 18, and 19. As the tablets are uncoated, they

must be swallowed immediately once removed from the blister and not be left exposed on surfaces or handled for any period of time greater than that required for dosing.

The hands of the participant or study nurses (whoever will handle the tablet for administration) must be dry when handling the tablets and washed thoroughly afterwards.

Table 2 **Dose of cladribine per treatment week by participant weight in each treatment Year**

Weight range	Dose in mg (number of 10 mg tablets) per treatment week	
Kg	***Treatment Week 1***	***Treatment Week 2***
50 to < 60	50 mg (5 tablets)	50 mg (5 tablets)
60 to < 70	60 mg (6 tablets)	60 mg (6 tablets)
70 to < 80	70 mg (7 tablets)	70 mg (7 tablets)
80 to < 90	80 mg (8 tablets)	70 mg (7 tablets)
90 to < 100	90 mg (9 tablets)	80 mg (8 tablets)
100 to < 110	100 mg (10 tablets)	90 mg (9 tablets)
110 and above	100 mg (10 tablets)	100 mg (10 tablets)

kg=kilogram; mg=milligram

Table 2 above shows how the total number of tablets per treatment week is distributed over the individual days. The daily cladribine doses in each treatment week are to be taken at intervals of 24 hours at approximately the same time each day, i.e., in the morning after an overnight fast. If a daily dose consists of 2 tablets, both tablets are taken together as a single dose. Table 3 below shows the number of tablets to be given for each day as a function of the total numbers of tablets per week.

Table 3 **Cladribine 10 mg tablets per week day for study days**

Total number of tablets per week	Day 9	Day 10	Day 11	Day 12	Day 13
5	1	1	1	1	1
6	2	1	1	1	1
7	2	2	1	1	1
8	2	2	2	1	1
9	2	2	2	2	1
10	2	2	2	2	2

Days are shown as Study Days as per Schedule of Assessments, where Day 9 of each period is the first day of study intervention administration.

6.6.2 Matching Placebo Tablets

Matching placebo tablets will be handled and administered according to the same methodology and posology as described in Section 6.6.1 for the cladribine treatment. Participants will be randomized to receive cladribine placebo tablets either in Study Period 1 or 2 on Days 9, 10, 11, 12, 13 or/and on Days 15, 16, 17, 18, and 19 on top of the ongoing repeat-dose Microgynon treatment.

6.6.3 Microgynon

Microgynon tablets must be taken orally with 200 mL non-carbonated tap water, and swallowed without chewing. Tablets must be taken in the order directed on the blister package at about the same time every day between 7:00 and 9:00 in the morning after an overnight fast.

On days with concomitant cladribine/placebo intake, Microgynon tablets need to be taken 1 hour before cladribine administration with 200 mL non-carbonated tap water.

- First treatment cycle (Run-in-Period): 1 tablet daily for 21 days, starting on the first day of the menstrual cycle followed by 7 treatment-free days. Contraceptive protection begins immediately.
- Subsequent cycles (Study Periods 1 and 2): Tablet-taking from the next pack of Microgynon is continued after a 7-day treatment-free interval, beginning on the same day of the week as the Run-in-Period.

6.7 Study Intervention after the End of the Study

The dose and the posology of both the examined treatments, cladribine tablets and the monophasic oral contraceptive Microgynon as per this study protocol will be consistent with the labeled use of both products. The study design ensures that participants would be able to receive the full dose and dosage regimen as per label with only minimum deviations, as further described in Section 4.1 and below.

Study participants will be offered the approved 2-year use of cladribine. Following completion of the 2 annual treatment courses, no further cladribine treatment is required in years 3 and 4.

Participants randomized to the treatment sequence cladribine-placebo will receive their first and second 5-day repeat-dose treatments as part of their study participation.

For participants randomized to the treatment sequence placebo-cladribine, only the first cladribine 5-day treatment will be part of the study, while the second cladribine 5-day treatment will be offered to the study participants as medical care in the month after end of study provided by the Sponsor.

Further on, 1 year after having received the first dose of cladribine of the first 5-day repeat-dose treatments (as part of the study), participants will embark into treatment course 2 which also consists of 2 5-day repeat-dose treatments, 1 at the beginning of the first month and 1 at the beginning of the second month of the second treatment year. Cladribine treatment will be provided by the Sponsor outside of the study.

Study participants that enter the study as their second year treatment course (see Section 6.5.3) will complete their full 2-year treatment course during or shortly after the End of Study Visit, and no further treatment will be provided by the Sponsor.

Principal Investigators will be informed of the treatment sequence of each participant once a participant has completed the End of Study Visit, as they need to know whether another dose of cladribine needs to be given. Details on this procedure are described in the IMP Handling Manual.

Criteria for initiating and continuing cladribine therapy are as follows:

Lymphocyte counts must be

- normal before initiating cladribine treatment in Study Period 1 of the study;
- at least 800 cells/mm³ before initiating cladribine treatment in year 2.

If necessary, the treatment course in year 2 can be delayed for up to 6 months to allow for recovery of lymphocytes. If this recovery takes more than 6 months, the participant should not receive cladribine anymore.

With respect to treatment with Microgynon, contraceptive measures may or may not be altered after end of the study as per preference of treating physician and participant. In any case, after conclusion of the study effective contraception (e.g., by taking a hormonal oral contraceptive or applying another highly effective birth control method) starting 1 month after last dose of study intervention must be used and continue for at least 5 months (see Inclusion Criterion #11, and Appendix 3).

6.8 Special Precautions

Not applicable. For details, refer to the Product Information for cladribine tablets and Microgynon.

6.9 Management of Adverse Events of Interest

Hematological Monitoring:

- Cladribine's mode of action is associated with a reduction in lymphocyte count. The effect on lymphocyte count is dose-dependent. Decreases in neutrophil count, red blood cell (RBC) count, hematocrit, hemoglobin or platelet count compared to baseline values have also been observed in clinical studies, although these parameters usually remain within normal limits
- Lymphocyte counts should be measured at Screening, on Day 21 of the Run-in-Period (Baseline), at the end of each treatment period, and 2 and 6 months after start of cladribine treatment. If the lymphocyte count is below 500 cells/mm³, it should be actively monitored until values increase again.

  With exception of the Screening and Run-In-Period Day 21 blood samples, the white blood count (WBC), which includes lymphocyte count will not be distributed to the Investigator during study conduct but will be forwarded to the Medical Monitor for review and clinical judgement. This is to exclude the possibility of unblinding of the Investigator for the treatment sequence (i.e., placebo/cladribine or cladribine/placebo). In case of medically

significant decreases in lymphocyte counts (Grade 3 to 4 lymphopenia) the Medical Monitor informs the Investigator directly by e-mail and/or phone (if feasible).

Infections:

- Cladribine can reduce the body's immune defense and may increase the likelihood of infections. HIV infection, active tuberculosis and active hepatitis must be excluded before initiation of cladribine therapy
- Latent infections may be activated, including tuberculosis or hepatitis. Therefore, screening for latent infections, in particular tuberculosis and hepatitis B and C, must be performed prior to initiation of therapy as specified in Exclusion Criterion #5
- A delay in initiation of cladribine treatment should also be considered in participants with an acute infection until the infection is fully controlled (see Exclusion Criterion #20)
- Particular attention is recommended for participants who have no history of exposure to varicella zoster virus. Vaccination of antibody-negative participants is recommended prior to initiation of cladribine therapy. Initiation of treatment with cladribine must be postponed for 4 to 6 weeks to allow for the full effect of vaccination to occur

Blood transfusions:

- In participants who require blood transfusion, irradiation of cellular blood components is recommended prior to administration to prevent transfusion-related graft-versus-host disease. Consultation with a hematologist is advised.

Further details on the monitoring of participants with adverse events, serious adverse events and adverse events of special interest are provided in Appendix 4.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

The Schedule of Activities (SoA, see Section 1.3) specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed.

ECG recordings / potential cardiac changes: If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Bazett's formula [QTcB] or Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.1 Temporary Discontinuation

Not applicable.

7.1.2 Rechallenge

Not applicable.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time, at her own request (i.e., withdrawal of consent), and without giving a reason
- The participant may be withdrawn by the Investigator due to participation in another clinical study
- The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons
- The SoA (see Section 1.3) specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.

A participant must also be withdrawn if any of the following occur:

- Occurrence of pregnancy (for further details in case of pregnancy see Section 8.3.5),
- Use of non-permitted concomitant therapy, as defined in Section 6.5). However, any medications that are considered necessary for the participant's wellbeing (e.g., Acetaminophen up to 1 g per day) may be given at the discretion of the Investigator,
- Protocol non-compliance judged as significant by the Investigator, including non-compliance to the required study considerations (e.g., food/diet requirements), as defined in Section 6.4,
- Participant lost to follow-up (see Section 7.3)
- Any events that endanger the safety of the participant.

If a participant has failed to attend scheduled study assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case a participant has to be withdrawn from the study, the medical monitor and clinical study leader of the Sponsor will be informed immediately.

If there is a medical reason for the withdrawal, the participant will remain under the supervision of the Investigator until satisfactory health has returned or care has been transferred to the participant's general practitioner or to a hospital consultant.

In case of premature withdrawal from the study, the assessments scheduled for the End of Study Visit should be performed with focus on the most relevant assessments (see Section 1.3). In any case, the appropriate electronic case report form (eCRF) section must be completed.

Participants who withdraw from the study for any reason or do not have a full PK dataset will not routinely be replaced. If the assumed drop-out rate of 18 % to 30% will be unexpectedly higher, a discussion should occur between the Investigator and the Sponsor regarding whether a replacement may be considered. The number of participants evaluable for BE (16 participants) need to be maintained. Each replacer will be assigned to the treatment sequence of the replaced participant. Details on this procedure are described in the Operations Manual.

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wants to or should continue in the study
- Before a participant is deemed "lost to follow up", the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts should be documented in the participant's medical record
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study.

In any case, the appropriate electronic case report form (eCRF) section must be completed.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA, see Section 1.3
- No protocol waivers or exemptions are allowed
- Immediate safety concerns should be discussed with the Sponsor's Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention
- Adherence to the study design requirements, including those specified in the SoA (see Section 1.3), is essential and required for study conduct
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2 (Study Governance)
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA, see Section 1.3.

Participant's total duration of participation will be 3 cycles of hormonal contraceptive (84 days) plus the Screening period of up to 21 days and the End of Study Visit 4 - 7 days after Day 21 of the second period. Therefore, the total duration of treatment with HC is 63 days (3 cycles of

HC of 21 days), treatment duration with cladribine is 5 days for the sequence placebo-cladribine, and 10 days for sequence cladribine-placebo and the total duration of each participant in the study is 82 - 105 days.

Sites will be visited by the Study Monitor in regular intervals of usually every 4-8 weeks, depending on recruitment, for monitoring and source data verification (see also Appendix 2).

8.1 Efficacy Assessments and Procedures

Not applicable, see under Section 8.5 and 8.6.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, adverse events (AEs), physical examination findings, vital signs, electrocardiograms, and laboratory tests.

Comprehensive assessment of any potential AE experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information).

For cladribine tablets an established safety and adverse event (AE) profile is available, which is based on a complete clinical development program in RMS participants. Adverse reactions described in the list below are derived from pooled data from clinical studies in RMS in which oral cladribine was used as monotherapy at a cumulative dose of 3.5 mg/kg. The safety database from these studies comprises 923 participants.

The following definitions apply to the frequency terminology used hereafter:

- very common (≥ 1/10);
- common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100);
- rare (≥ 1/10,000 to < 1/1,000);
- very rare (< 1/10,000);
- frequency not known (cannot be estimated from the available data).

Infections and infestations

- Common: Oral herpes, dermatomal herpes zoster
- Very rare: Tuberculosis

Blood and lymphatic system disorders

- Very common: Lymphopenia
- Common: Decrease in neutrophil count

Skin and subcutaneous tissue disorders

- Common: Rash, alopecia

Safety & Tolerability of Microgynon

The decision to use Microgynon should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE). This risk is adequately managed by application of respective Inclusion and Exclusion Criteria as detailed in Section 5.

However, there are medical reasons for which the Investigator must stop the treatment with Microgynon immediately:

- Occurrence for the first time, or exacerbation, of migrainous headaches or unusually frequent or unusually severe headaches
- Sudden disturbances of vision, of hearing or other perceptual disorders
- First signs of thrombosis or blood clots (e.g., unusual pains in or swelling of the leg(s), stabbing pains on breathing or coughing for no apparent reason). Feeling of pain and tightness in the chest
- 6 weeks before an elective major operation (e.g., abdominal, orthopedic), any surgery to the legs, medical treatment for varicose veins or prolonged immobilization, e.g., after accidents or surgery. Do not restart until 2 weeks after full ambulation. In case of emergency surgery, thrombotic prophylaxis is usually indicated e.g., subcutaneous heparin
- Onset of jaundice, hepatitis, itching of the whole body
- Significant rise in blood pressure
- Severe upper abdominal pain or liver enlargement
- Clear exacerbation of conditions known to be capable of deteriorating during oral contraception or pregnancy.

When stopping the oral contraception with Microgynon during the study highly effective non-hormonal contraception should be used to ensure contraceptive protection is maintained.

8.2.1 Physical Examinations

Physical examination will be performed on the Screening Visit and on the End of Study Visit as scheduled in the Schedule of Assessments (see Section 1.3).

- A complete physical examination will include, at a minimum assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (at Screen) and weight will also be measured and recorded. In addition, weight will be measured on Day 21 of Run-in-Period and Day 21 of Study Period 1 (to be able to calculate/adapt dosage of study intervention accordingly to actual weight) and Day 8 of Study Period 2.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen)
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any relevant findings are to be recorded on the Medical History form in the eCRF (for findings from the past that occurred prior to ICF signature) or on the AE form in the eCRF (for findings presently occurring; events existing but unresolved prior to study intervention).

8.2.2 Vital Signs

Vital signs will be measured on the Screening Visit, on Days 7, 14, 21 of the Run-in-Period, in Study Periods 1 and 2 on Days 9- 13 predose and 1 hour (h) postdose after cladribine / placebo administration, on Day 14 at 24 hours and 25.5 hours after cladribine / placebo administration (Day 13), and on the End of Study Visit (as scheduled in the Schedule of Assessments, see Section 1.3).

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse and respiratory rate:
- Tympanic temperature will be measured,
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

For safety evaluation, 12-lead ECGs will be recorded on the Screening Visit, in Study Periods 1 and 2 on Day 9 at predose and at 1.5 hours postdose after cladribine / placebo administration, on Day 14 at 24 hours and 25.5 hours after cladribine / placebo administration (Day 13) and at the End of Study Visit as scheduled in the Schedule of Assessments (see Section 1.3).

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. See Section 7 (Discontinuation of Study Intervention and Participant/Withdrawal) for QTc withdrawal criteria and any additional QTc readings that may be necessary
- The ECGs will be recorded in supine position after at least 5 minutes rest
- The ECG should be interpreted by the Investigator (normal/abnormal). For abnormal ECGs the clinical significance (yes/no) should be judged by the Investigator and the abnormality is to be specified
- Local safety ECGs for real-time monitoring will be used.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5, at the time points listed in the SoA (see Section 1.3). All samples should be clearly identified
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations
- The tests will be performed by the central laboratory with exception of the following tests done locally: Urine test for pregnancy and drug screening, QuantiFERON®-TB test
- The Sponsor must receive a list of the central laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the Sponsor or designated organization

- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents
- Laboratory/analyte results that could potentially unblind the study will not be reported to investigative sites or other blinded personnel. Instead the medical monitor will review lymphocyte counts. Details are described in Section 6.9.
- Any abnormalities in any of the laboratory parameters will be judged by a physician individually in relation to the reference ranges from the laboratory. For all findings of clinical relevance, follow-up examinations will be carried out until the deviation returns to normal or the absence of pathological relevance can be confirmed
- For specific laboratory parameters such as lymphocyte count, however, that are reflecting a direct and long-lasting cladribine treatment effect, monitoring will follow the recommendations in the SmPC (Merck Serono Europe Ltd., 2017)
- In case of the requirement to re-assess one or more Screening laboratory value(s), the Screening period may be prolonged for up to 8 weeks after the last Screening laboratory assessment. From a participant safety perspective and in order to minimize unnecessary investigational burden for the participant it is acceptable that the participant starts with a delayed Run-in-Period of the study without re-assessing the complete set of Screening laboratory assessments. The participant does not need to sign a new ICF.

The laboratory parameters to be determined are provided in detail in Appendix 5.

8.2.5 Suicidal Risk Monitoring

Not applicable.

8.3 Adverse Events and Serious Adverse Events

The definitions of an adverse event (AE), a serious adverse event (SAE), and adverse event of special interest (AESI) are in Appendix 4.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of first informed consent) and continues until the End of Study Visit.

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 4, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are presented in Appendix 4.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless if reported by the participant, observed by the Investigator or evidenced by diagnostic procedures (e.g., safety laboratory, ECG, etc.).

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs and all nonserious AEs of special interest must be additionally documented and reported using the appropriate Report Form as specified in Appendix 4.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) and are assessed for their outcome at the End of Study Visit. All SAEs ongoing at the End of Study Visit as well as any nonserious AEs of special interest must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable best efforts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 4 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reports).

Monitoring of Specific Adverse Events is further detailed in Section 9.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the study.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific

regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

8.3.5 Pregnancy

In the event of a pregnancy in a participant occurring during the study, the participant must be discontinued from study intervention. The Sponsor/designee must be notified without delay and the participant must be followed as indicated above.

Only pregnancies the Investigator considers to be related to the study intervention (e.g., resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) must be recorded in the AE page/section of the eCRF for pregnancies in female participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 4, section on Reporting Serious Adverse Events and Adverse Events of Special Interest.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the participants are withdrawn from the study.

The participant's primary care physician or gynecologist should be informed regarding the extent of the participant's participation in the current study with the study intervention. The Sponsor will provide to the participant's primary care physician or gynecologist all information pertinent to the risk assessment for the pregnancy outcome and potential fetal harm. Accordingly, the primary care physician or gynecologist will counsel the participant regarding medical considerations in decision making on continuation or discontinuation of the pregnancy.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

8.4 Treatment of Overdose

For this study, any dose of cladribine greater than the dose specified in the protocol according to participants' body weight (see Table 2) within a 24-hour time period (for definition of daily doses by body weight see Table 3) will be considered an overdose.

Even if it not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 4, section on Reporting Serious Adverse Events and Adverse Events of Special Interest.

For details on treatment of overdose, refer to the Product Information for cladribine tablets and Microgynon.

8.5 Pharmacokinetics

Whole blood samples of approximately 5 mL will be collected for measurement of plasma concentrations of EE and LNG, as specified in the SoA (see Section 1.3). A maximum of 4 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Whole blood samples of approximately 3 mL will be collected for measurement of plasma cladribine, as specified in the SoA (see Section 1.3). A maximum of 4 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The quantification of EE, LNG and cladribine in plasma will be performed using a validated bioanalytical method. Concentrations will be used to evaluate the PK of EE, LNG and cladribine.

Remaining samples collected for analyses of EE, LNG and cladribine concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Details on process for collection and shipment of these samples are in a separate Lab Manual provided by PPD Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel.

Full details of the bioanalytical methods used will be described in a separate bioanalytical protocol. Venous blood samples will be collected as listed in the Schedule of Assessments (see Section 1.3).

- In the Run-in-Period, plasma samples for PK analysis of EE and LNG will be collected on Days 7, 14, and 21. In Study Periods 1 and 2 plasma samples for PK analysis of EE and LNG will be collected on Day 13 in the morning predose of Microgynon administration, and on Day 14 predose (with respect to Microgynon) and at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours (Day 15) postdose.

- Plasma samples for PK analysis of cladribine will be collected as follows: A predose sample in the morning of Day 9 before first cladribine/placebo administration; predose samples (= through samples) and postdose samples on Days 10, 11, 12, and 13 at the following times: predose, 0.25, 0.5, 1.0, 1.5, 2.0 hours postdose. These determinations serve the purpose to ensure appropriate exposure to study drug, and not to determine PK endpoints.

The exact date/time of sample collection should be recorded in the eCRF. The accepted time deviations from planned PK sampling times are listed in the table below:

Table 4 Accepted Time Deviations From Planned PK Sampling Times

Time Point (Relative Time)	Window Allowance
Predose	- 60 min to - 1 min
0.25 – 1 h postdose	± 2 min
> 1 h – 12 h postdose	± 5 min
> 12 h – 48 h postdose	± 10 min

h=hour; min=minutes.

Pharmacokinetic calculations will be performed using commercial software such as PPD

Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the statistical analysis plan.

Pharmacokinetic analysis will use actual dates and times as recorded on the eCRF. Other data handling procedures will be detailed in the statistical analysis plan.

The following PK parameters will be calculated, when appropriate:

Table 5 PK Parameters of EE and LNG

Symbol	Definition
$C_{max,ss}$	Maximum observed concentration in steady state
$C_{min,ss}$	Minimum observed concentration in steady state during a complete dosing interval (τ)
C_{trough}	Measured concentration at the end of a dosing interval at steady state (taken directly before next administration)
$t_{max,ss}$	Time to reach the observed maximum (peak) concentration at steady state
$AUC_{\tau,ss}$	Area under the plasma concentration-time curve in steady state during a complete dosing interval (τ)
$AUC_{\tau,ss} / \tau$	Average plasma concentration at steady state during a complete dosing interval (τ)
PTF %	Peak-to-trough fluctuation over 1 complete dosing interval at steady state

Table 6 **PK Parameters of Cladribine[a]**

Parameter	Full description
C_{max}	Maximum observed concentration
t_{max}	Time to reach the observed maximum (peak) concentration
C_{pre}	Measured concentration at the end of a dosing interval during repeat-dosing (taken directly before next administration)

a A steady-state will not be achieved with once daily dosing of cladribine, therefore single-dose PK parameters are given. The PK sampling of cladribine only serves the purpose to proof regular exposure to cladr bine.

[redacted]

8.7 Genetics

Not applicable.

8.8 Biomarkers

Not applicable.

8.9 Health Economics

Not applicable.

8.10 Immunogenicity Assessments

Not applicable.

[redacted]

9.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a blinded data review meeting with blinded team members prior to database lock. As described in Section 6.3.2, after a participant's End of Study Visit, the PPD PM, Investigator and site staff are informed of this individual participant's treatment assignment. [redacted] PM, Investigator, and site staff will therefore not be part of the blinded data review meeting.

Table 7 Analysis Populations

Analysis Set	Description
Enrolled	All participants who start the Run-in-Period
Safety	The Safety Analysis Set will include all participants who receive at least 1 dose of study intervention. Participants will be analyzed according to the actual treatment they receive.
Pharmacokinetic	The evaluation of PK data will be based on the PK Analysis Set, a subset of the Safety Analysis Set, which is characterized by the following criteria: • The completion of both periods; • The availability of all 4 primary endpoints; The absence of any important protocol deviation or events, which would render the data incomparable between treatments. Reasons to exclude a participant are events such as nonconformance during study intervention, vomiting and diarrhea or any other reason which could render the plasma concentration-time profile unreliable. In exceptional cases, the use of concomitant medication could be a reason for excluding a participant.
[redacted]	[redacted]

CCI [redacted]

9.4 Statistical Analyses

The results of this study will be reported using summary tables, figures, and data listings, as appropriate. Continuous variables will be summarized using mean, SD, CV% (as appropriate), median, minimum, maximum, and, as appropriate, geometric mean and CIs for calculated PK and [redacted] parameters. Categorical variables will be summarized by presenting the number (frequency) and percentage in each category. Demographic (e.g., age [derived], race, etc.) and baseline information will be presented and summarized by dose category for all participants.

9.4.1 Efficacy Analyses

Not applicable.

9.4.2 Safety Analyses

Safety data analysis will be conducted on the Safety Analysis Set. The number and percentage of participants experiencing at least 1 TEAE will be summarized by treatment as well as the number of events. Tables by relationship to study drug and by severity will be generated. AEs will be coded using Medical Dictionary for Regulatory Activities terminology.

All laboratory data will be reported with SI units. Laboratory parameters will be summarized using descriptive statistics for absolute values and change from baseline over time, by postdose shifts relative to baseline, Box and Whisker plots plus and data listings of clinically significant abnormalities/outliers as per the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials/out of the normal range.

Vital signs and ECG data will be summarized by changes-from-baseline values by treatment and for each sequence group using descriptive statistics. Clinical noteworthy ECG findings for individual participants will be listed and summarized as appropriate.

The following are defined as clinical noteworthy (not limited to but including) QTcF categories:

- QTcF duration ≥ 450, 470, and 500 ms;
- QTcF change from baseline ≥ 30 and 60 ms

Endpoint	Statistical Analysis Methods
Primary	N/A
Secondary	For safety assessments and continuous measurements will be summarized by means of descriptive statistics (i.e., number and percentage of observations, number and percentage of missing observations, mean, standard deviation, median, 25th and 75th percentiles [Q1 and Q3], minimum, and maximum) and categorical data will be summarized by means of frequency tables (i.e., count and percentages), if not stated otherwise.
Tertiary/Exploratory	N/A

N/A=not applicable.

9.4.3 Other Analyses

Estimation of Individual PK Parameters:

- Pharmacokinetic parameters (see Appendix 6) will be calculated by the PK/[redacted] Data Processing Group of [redacted] Merck, Darmstadt, Germany, or by a Contract Research Organization (CRO) selected by the Sponsor, using standard non-compartmental methods and the actual administered dose. PK parameters will be calculated using the actual elapsed time since dosing, given with a precision of 14 significant digits or the SAS format Best12. When the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data
- Non-compartmental computation of pharmacokinetic parameters (see Appendix 6) will be performed using the computer program Phoenix® WinNonlin® CCI [redacted] or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA)
- The statistical software SAS (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows CCI [redacted] or higher) may be used to produce tables, listings and figures and in the calculation of PK Parameters if appropriate.

9.4.4 Analysis of Primary Endpoints

The PK evaluation will be based upon the PK Analysis Set. The statistical analysis of primary PK parameters $AUC_{\tau,ss}$ and $C_{max,ss}$ of EE and LNG (the active ingredients of the Microgynon treatment) will be performed using an analysis of variance (ANOVA) model including TREATMENT, PERIOD, SEQUENCE and SUBJECT (SEQUENCE) as fixed effects. Parameters will be log-transformed before they are processed. LSMEANS for Test – Reference differences will be estimated for all 4 primary endpoints together with 90% confidence intervals, resulting in Test/Reference ratios and corresponding 90% confidence intervals following back-transformation.

Bioequivalence (which means absence of drug-drug interaction) will be concluded, if all 4 90% CIs for the TEST/REFERENCE ratios are fully contained within the [0.8000 to 1.2500] acceptance range.

[redacted]

9.4.6 Sequence of Analyses

Not applicable.

10 References

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Martin P, et al. Effects of Fostamatinib on the Pharmacokinetics of Oral Contraceptive, Warfarin, and the Statins Rosuvastatin and Simvastatin: Results From Phase I Clinical Studies. Drugs RD 2016;16:93-107.

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11 Appendices

Appendix 1 Abbreviations

ABS	Antibody serum
AE	Adverse Event
AEP	Accelerated elimination procedure
AESI	Adverse Event of special interest
ALT	Alanine aminotransferase
a.m.	ante meridiem
ANOVA	Analysis of variance
Anti-HCV	Hepatitis C virus antibody
Anti-HIV1/2	Human Immunodeficiency virus 1 and 2 antibody
ART	Assisted reproduction techniques
AST	Aspartate aminotransferase
ATE	Arterial thromboembolism
AUC	Area under the curve
BE	Bioequivalence
BMI	Body mass index
BUN	Blood urea nitrogen
CdATP	2-chlorodeoxy-adenosinetriphosphate
CI	Confidence interval
CRO	Contract Research Organization
CTFG	Clinical Trial Facilitation Group
CV	Coefficient of variation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DVT	Deep venous thrombosis
ECG	Electrocardiogram
(e)CRF	Electronic Case Report Form
EE	Ethinyl estradiol
EMA	European Medicines Agency
ET	Early termination (visit)
[redacted]	[redacted]
GCP	Good Clinical Practice
GI	Gastro-intestinal

h	Hour(s)
HbcAb	Hepatitis B core antibody
HbsAg	Hepatitis B surface antigen
HC	Hormonal contraceptives/contraception
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUD	Intrauterine device
LDL	Low density lipoprotein
[redacted]	[redacted]
LNG	Levonorgestrel
MAH	Marketing Authorization Holder
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
MS	Multiple sclerosis
OTC	Over-the-counter
[redacted]	[redacted]
PE	Pulmonary embolism
PK	Pharmacokinetics
PML	Progressive multifocal leukencephalopathy
RBC	Red Blood Cell
RMS	Relapsing Multiple Sclerosis
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SD	Standard deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
[redacted]	[redacted]

SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis
TIA	Transient ischemic attack
VTE	Venous thromboembolism
WBC	White Blood Cell
WHO	World Health Organization

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions on the study
- Participants must be informed that their participation is voluntary
- Participants or their legally-authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF
- If the ICF is [redacted] during their participation in the study, participants must be re-consented to the most current, approved version
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes
- Participants who are rescreened are required to sign a new ICF

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred
- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the participant
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative Structure

This clinical study will be sponsored by Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany.

Cladribine will be administered in the present study as per its approved posology, therefore no Safety Monitoring Committee is foreseen.

The study will be conducted in European countries in University hospitals and Centers / Clinics of Neurology. The PK-part of the study requires hospitalization from Days 8 to 15 of Study Periods 1 and 2. In case specialized Centers/Clinics of Neurology do not have the structure and capability to allow hospitalizations and extensive PK sampling / sample handling, the Days 8 to 15 of Study Period 1 and 2 will be conducted in another study site (herein referred to as "PK site"; e.g., in Germany the [redacted] in [redacted] a dedicated Phase 1 unit). The specialized Centers/Clinics of Neurology which are only responsible for participant recruitment, ambulatory visits, and referral to the PK sites are herein referred to as "Investigational sites". There may be up to 6 Investigational sites collaborating with one PK site.

In this case the PI responsibilities of "Investigational site" and "PK site" within the study are as follows:

Investigational site (see also Section 1.3 "Schedule of Activities"):

- Main study contact for Screening and Run-in-Period, until Day 7 and after hospitalization discharge at Day 15 of each study period and End of Study
- Informing and Obtaining of Informed Consent for the entire study
- Screening Activities
- Assessment of Inclusion/Exclusion criteria
- Microgynon: delivery, return, compliance and drug accountability activities
- Cladribine/Placebo: delivery and compliance activities on Days 16-19, collection of empty blisters for transfer to PK site
- Run-in-Period-activities on Days 7, 14 and 21
- Request randomization on Day 21 of Run-in-Period at CTS Department at [redacted] GmbH
- Ambulatory visit activities on Day 21 of each study period and End of Study
- Recording of adverse events and prior/concomitant medication.

PK site (see also Section 1.3 "Schedule of Activities"):

- Main study contact on Days 8-15 of Study Periods 1 and 2
- Intervention period Days 8 – 15 activities incl. PK/[redacted] sampling
- Recheck of relevant inclusion/exclusion criteria on Day 8 in Study Period 1
- Recording of adverse events and concomitant medication on Days 8-15 of Study Periods 1 and 2

- Cladribine: delivery, return, compliance and drug accountability activities of Study Periods 1 and 2

  (Cladribine packages for Days 16-19 will be forwarded from Investigational site to PK site after Day 21)

Communication between Investigational site and PK site:

After completed screening and enrolment of a new subject the Investigational site will forward a copy of the signed ICF per e-Mail / Fax to the corresponding PK site (if applicable).

The [redacted] will inform the corresponding PK site by email when a Cladribine/Placebo shipment and randomization request has been received from an Investigational site.

On Day 21 of the Run-in-Period the PK site will inform the corresponding investigational site of the successful randomization of the patient per e-Mail / Fax. On Day 15 of the Study Periods 1 and 2 the PK site will inform the corresponding investigational site of the successful discharge of the patient per e-Mail / Fax.

A contact list of the PK site study team will be filled in the Investigator Site File of the Investigational sites. The contact lists of the Investigational sites will be filed in the Investigator site file of the PK study site.

In case of clarification or emergency with regards to a participant of the study the Investigators / study team of the corresponding sites will get in touch as needed.

Capture of Source Data and CRF data:

Safety blood sampling, Adverse Event/SAE, concomitant medication and any other safety reporting are the responsibility of the Investigational site with exception of Days 8-15 of Study Periods 1 and 2 where these responsibilities pass over to the PK site.

Investigational and PK sites are entering subject data in the same eCRF therefore both sites are aware of the current participant situation. Safety-relevant data must have been completely entered into the eCRF at the days when a patient is referred from an Investigational site to a PK site and vice versa.

Safety lab reports from the Central lab will be sent to the PK site and the corresponding Investigational site in parallel.

All sites may engage so called "referral sites" (e.g. Neurology Outpatient Practices). Referral sites refer patients to Investigational sites for potential inclusion into the study.

The Coordinating Investigator [redacted] on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

Signature pages for the Sponsor Medical Responsible and the Coordinating Investigator are provided in are provided in Appendix 8 and Appendix 9.

The study will appear in the following clinical studies registries: EUDRA-CT with the number 2018-001015-70 and ClinicalTrials.gov.

An operational manual will be compiled for this study. Operations manual herein refers to a collection of plans and/or manuals, including but not limited to Project Management Plan, Data Management Plan, Analytical Plan, IMP Handling manual, Medical Monitoring Plan, Monitoring Plan, and Safety Management Plan.

a contract research organization, will, further to be a PK site (as described above), conduct the study including study set-up, coordination, analytical lab, monitoring, data capture, data management, statistical analysis, and clinical study reporting. Clinical Monitoring in Germany will be done by , monitoring and regulatory services in the additional countries may be subcontracted to a Contract Research Organization (CRO) Partner of Medical Monitoring will be done by The Sponsor will apply oversight to all outsourced activities.

Laboratory sample processing, handling, and storage instructions will be presented in a separate Lab Manual which will be prepared by in cooperation with the Sponsor. Monitoring and data management procedures will be defined in separate Monitoring and Data Management Plans prepared by Medical Monitoring activities and procedures will be defined in a separate Medical Monitoring Plan prepared by Clinical Research Appliance.

The Sponsor will provide the IMP cladribine tablets and oral contraceptive Microgynon. Manufacture, packaging and labeling of all IMPs will be conducted by a designated contract manufacturing organization. Release, distribution to the study sites and return of IMPs will be done by . Details of structures and associated procedures will be defined in separate Operations Manuals (e.g., laboratory manual, IMP handling manual etc.), which will be prepared under the oversight of the .

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated

- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures
  - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
  - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable)
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician (i.e., Medical Monitor or deputy). This includes provision of a 24-hour contact number, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

Participants will be compensated for travel cost and loss of workdays with respect to the hospitalization periods.

Clinical Study Report

After completion of the study, a clinical study report will be written by [redacted] on behalf of the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- The first publication will include the results of the analysis of the primary endpoints and 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 review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights
- Posting of data on the EU Clinical Trial Register and on ClinicalTrials.gov is planned and will occur within 12 months after the last clinic visit of the final study participant or another appropriate date to meet applicable requirements

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Operations Manual
- The Investigator must maintain accurate documentation (source data) that supports the information in the CRF
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. [redacted] files of the CRFs will be provided to the Investigators at study completion
- Study monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
  - Participant's full name, date of birth, sex, height, and weight
  - Medical history and concomitant diseases
  - Prior and concomitant therapies (including changes during the study)
  - Study identifier (i.e., the Sponsor's study number) and participant's study number
  - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
  - Any medical examinations and clinical findings predefined in the protocol
  - All AEs
  - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- All source data must be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator
- Data recorded on printed or electronic CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available
- The study monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator, and kept in the study file
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval
- For data that may be recorded directly in the CRF such as a diary, there will be no record in the original participant file and therefore the data entered in the CRF will be considered source data

Study and Site Closure

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor’s compound.

Appendix 3 Contraception

Woman of Childbearing Potential (WOCBP)

A woman is of childbearing potential (i.e., fertile), following menarche and until either:

1) Becoming postmenopausal; or,

2) is permanently sterile by means of a hysterectomy, bilateral salpingectomy or bilateral oophorectomy.

Postmenopausal is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly Effective Contraceptive Methods

A highly effective contraceptive method must be applied from enrollment to 1 month after last dose of study intervention.

Highly effective methods are those with a failure rate of less than 1% per year when used consistently and correctly.

These methods are further classified into user-independent and user-dependent methods. Because user-independent methods do not depend on the participant's ability to use them consistently and correctly, they are preferred when contraception is introduced as a condition for study participation.

Caution should be taken for hormonal contraception, as it may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraception method. Hence, a second highly effective method of contraception should be used from enrollment to 1 month after last dose of study intervention.

Highly effective contraceptive methods, to be used in addition to the hormonal contraceptive (Microgynon) as per this study protocol are listed below:

Permitted:

User-Independent

- Intrauterine device (IUD)
- Bilateral tubal occlusion
- Vasectomized partner: This is a highly effective contraception method only if the partner is the sole sexual partner of the WOCBP and he has received medical assessment of the surgical success

- Sexual abstinence: This is a highly effective method only if the WOCBP refrains from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Not permitted, since they would interfere with the study objective:

User-Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable

User-Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine hormone-releasing system (IUS)

Effective Contraceptive Method

An effective contraceptive method must be used starting 1 month after last dose of study intervention and continue for at least 5 months.

Allowed only under certain situations as specified in the Clinical Trial Facilitation Group (CTFG) recommendations, because they have a failure rate of **more than** 1% per year and therefore are not considered to be highly effective methods.

- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Combination of a male condom with cap, diaphragm or sponge with spermicide (i.e., double barrier method)

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity of each AE.

Investigators must assess the severity of AEs per the Qualitative Toxicity Scale, as follows:

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

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

Severe: Significant impairment of functioning: the participant is unable to carry out his or her usual activities.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other non-study interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study intervention include, but may not be limited to, temporal relationship between the AE and the study intervention, known side effects of study intervention, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased alanine aminotransferase (ALT)) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

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

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs, AESIs (Adverse Event of special interest) and DLTs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions, and are not to be considered AEs.

Adverse Events of Special Interest

Description of selected adverse reactions

Lymphopenia

Only lymphopenia Grade 3 or Grade 4 represents AESIs. In clinical studies, 20% to 25% of the participants treated with a cumulative dose of cladribine 3.5 mg/kg over 2 years as monotherapy developed transient Grade 3 or 4 lymphopenia. Grade 4 lymphopenia was seen in less than 1% of the participants. The largest proportion of participants with grade 3 or 4 lymphopenia was seen 2 months after the first cladribine dose in each year (4.0% and 11.3% of participants with grade 3 lymphopenia in year 1 and year 2, 0% and 0.4% of participants with grade 4 lymphopenia in year 1 and year 2). It is expected that most participants recover to either normal lymphocyte counts or grade 1 lymphopenia within 9 months.

To decrease the risk for severe lymphopenia, lymphocyte counts must be determined before, during and after cladribine treatment (see Section 1.3) and strict criteria for initiating and continuing cladribine treatment must be followed (see Section 6.5).

Malignancies

In clinical studies and long-term follow-up of participants treated with a cumulative dose of 3.5 mg/kg oral cladribine, events of malignancies were observed more frequently in cladribine-treated participants (10 events in 3,414 participant-years [0.29 events per 100 participant-Years]) compared to participants who received placebo (3 events in 2,022 participant-years [0.15 events per 100 participant-years]).

Other Adverse Events to be Reported Following a Specialized Procedure

Not applicable.

Recording and Follow-Up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance is in the CRF Completion and Monitoring Conventions provided by the Sponsor or its designee.

Reporting Serious Adverse Events and Adverse Events of Special Interest

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter by fax or e-mail. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the study specific SAE Report Form.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the CRF.

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

In the event of a nonserious Grade 3 or 4 AESI (lymphopenia), the Investigator will complete the AESI Report Form and send it to the Sponsor/designee within 24 hours. Names, addresses, and telephone and fax numbers for AESI reporting will be included on the Report Form. Serious AESIs must be reported in an expedited manner as SAEs as outlined above.

Dose-Limiting Toxicities

Not applicable.

Appendix 5 Clinical Laboratory Tests

Clinical laboratory tests utilized for the study are shown in the table below.

Table 8 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit		RBC Indices: • MCV • MCH • %Reticulocytes	WBC Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Clinical Chemistry	BUN	Potassium	Aspartate aminotransferase (AST) / serum glutamic-oxaloacetic transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT) /serum glutamic-pyruvic transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Uric acid
	Amylase	Lipase	γ-Glutamyl-transferase	Triglycerides
	Lactate dehydrogenase	Creatine phosphokinase	Urea	LDL-/HDL-cholesterol and cholesterol
Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal). Only if blood, protein, nitrite, or leukocyte esterase are positive on the dipstick • Urine pregnancy test (as needed for women of childbearing potential)			

Other Tests	• Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).
	• Serology (HIV 1 and 2 antibody (anti-HIV1/2), hepatitis B surface antigen (HbsAG), hepatitis B core antibody (HbcAb), hepatitis C virus (anti-HCV) and Herpes Zoster
	• QuantifFERON®-TB Gold or Gold Plus test
	• Alcohol breath test,
	• TSH
	• Urine drug screen:
	  • Cocaine
	  • Amphetamines
	  • Methamphetamines
	  • Opiates
	  • Barbiturates
	  • Ecstasy
	  • Benzodiazepine
	  • Methadone
	  • Cannabinoids
	  • Phencyclidine
	  • Tricyclic antidepressants			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; HbcAB=hepatitis B core antibody; HbsAG=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HDL=high density lipoprotein; HIV=human immunodeficiency virus; LDL=low density lipoprotein; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; TSH = thyroid stimulating hormone, WBC=white blood cell

Appendix 6 Pharmacokinetic Parameters

Symbol	Definition
AUC_τ	The area under the concentration-time curve (AUC) over the dosing interval from T_1=0 hours to T_2=τ h. Calculated using the mixed log linear trapezoidal rule (linear up, log down). For single dose, AUCτ is calculated as a partial area with the defined time range. In multiple dose profiles AUC_τ is calculated at steady state from 1 predose time point to the dosing interval time. In cases where the actual observation time is not equal to the scheduled observation time AUC_τ will be calculated based on the estimated concentration at τ hours, and not the concentration at the actual observation time.
C_{av}	The average concentration at steady state. $C_{av} = AUC_\tau / \tau$.
C_{pre}	Measured concentration at the end of a dosing interval during repeat-dosing (taken directly before next administration)
C_{max}	Maximum observed concentration
C_{min}	The minimum observed concentration during a complete dosing interval
C_{trough}	The concentration observed immediately before next dosing (corresponding to predose or trough concentration for multiple dosing)
PTF%	The peak trough fluctuation within a complete dosing interval at steady state. $PTF = 100*(C_{max}-C_{min})/C_{av}$.
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the first occurrence in case of multiple/identical C_{max} values)
t_{min}	The time to reach the minimum observed concentration collected during a dosing interval
τ	Dosing interval

Appendix 7 Protocol Amendment History

The information for the current amendment is on the title page.

Non-substantial amendment 3 to the original protocol (CSP v4.0, version date: 20 November 2020)

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Specified exclusion criterion #19	Wash-out requirements/procedures for additional medications added

Non-substantial amendment 2 to the original protocol (CSP v3.0, version date: 06 April 2020):

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Overall Design 1.3 Schedule of Activities	Clarified wording for extended Screening period due to a delayed menstrual cycle and laboratory value(s) re-testing	Clarification of process
1.2 Schema, Figure 1 Study Design Diagram	[redacted] of study design diagram to clarify wording	Clarification of process
1.3 Schedule of Activities	Weight control added on Day 21 of Run-in-Period and Day 21 of Study Period 1 Minor formatting revision	Ability to calculate/adapt dosage of study intervention accordingly to actual weight Minor corrections
4.1 Overall Design	Clarified wording for extended Screening period due to a delayed menstrual cycle and laboratory value(s) re-testing Correction of recruitment phase from "12 months" to "**21** months" and total clinical duration of the study from "16 months" to "**25** months"	Clarification of process
4.2 Scientific Rationale for Study Design	Extension of time window to "between 28 to 35 days" for the second 5-day cladribine treatment (medical care) for Sequence 2 (placebo-cladribine) For Sequence 1 (cladribine-placebo) change of wording from "Accordingly, participants will receive their second 5-day cladribine treatment 4 weeks and 6 days after …" to "Accordingly, participants will receive their second 5-day cladribine treatment **34 days** after …".	Clarification of study rationale To be in alignment with the wording in the section
6.3.2 Blinding	To further detail wording for the unblinding process after the End of Study	Clarification of process
6.3.3 Emergency Unblinding	Clarified wording for recording the date and reason for unblinding	Clarification of process

Section # and Name	Description of Change	Brief Rationale
6.4 Study Intervention Compliance	Clarified wording for assessment of compliance	Clarification of process
6.7 Study Intervention after the End of the Study	Clarified wording for informing Principal Investigators of the treatment sequences once participants have completed the End of Study Visit	Clarification of process
8.2.1 Physical Examination	Weight control added on Day 21 of Run-in-Period, Day 21 of Study Period 1 and Day 8 of Study Period 2	Alignment with Section 1.3 Schedule of Activities
8.2.4 Clinical Safety Laboratory Assessments	Clarified wording for extended Screening period due to laboratory value(s) retesting	Clarification of process
9.3 Populations for Analyses	First paragraph rephrased to clarify participants of the data review meeting	Clarification of process
Appendix 2 Study Governance	Sentence deleted "• Definition of what constitutes source data is found in the Data Management Plan"	Clarification of which definition is given in the Data Management Plan
Whole document	Minor editorial and document formatting revisions	Minor corrections; therefore, have not been summarized

Non-substantial amendment 1 to the original protocol (CSP v2.0, version date: 04 July 2019):

Section# and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	The safety blood sample, including hematology assessments, was moved from Day 9 of Study Period 1 to Day 21 of Run-in-Period. This assures that results of the safety laboratory including hematology are in place before start of IMP treatment for fulfillment of inclusion criterion #4. Lymphocyte requirements (inclusion criterion #4) were differentiated for treatment in year 1 and year 2. Range definition for white blood cell counts, absolute lymphocyte counts and absolute neutrophil counts was changed from strictly normal range to normal range (applies for patients in year 1).	In order to clarify inclusion criterion #4 in Section 5.1.
6.3.1 Study Intervention Assignment	The randomization of participants was moved from Day 8 of Study Period 1 to Day 21 of Run-in-Period. This assures that participant's assigned study intervention is available at site in time.	In order to correct time point of randomization in Section 6.3.1.
Whole document	Minor editorial and document formatting revisions	Minor corrections

Appendix 8 Sponsor Signature Page

Study Title:	A randomized, double-blind, 2-period, 2-sequence crossover Phase I study with a 1 month run-in-period to examine the effect of cladribine tablets on the pharmacokinetics of a monophasic oral contraceptive containing ethinyl estradiol and levonorgestrel (Microgynon) in pre-menopausal women with relapsing multiple sclerosis (RMS)
Regulatory Agency Identifying Numbers:	EudraCT Number: 2018-001015-70
Clinical Study Protocol Version:	29 July 2021 / Version 5.0

I approve the design of the clinical study:

[redacted]

Signature [redacted]

Name, academic degree:	[redacted]
Function/Title:	Medical Responsible
Institution:	Merck KGaA
Address:	Frankfurter Strasse 250, 64293 Darmstadt, Germany
Telephone number:	[redacted]
Fax number:	[redacted]
E-mail address:	[redacted]

Appendix 9 Coordinating Investigator Signature Page

Study Title:	A randomized, double-blind, 2-period, 2-sequence crossover Phase I study with a 1 month run-in-period to examine the effect of cladribine tablets on the pharmacokinetics of a monophasic oral contraceptive containing ethinyl estradiol and levonorgestrel (Microgynon) in pre-menopausal women with relapsing multiple sclerosis (RMS)
Regulatory Agency Identifying Numbers:	EudraCT Number: 2018-001015-70
Clinical Study Protocol Version:	29 July 2021 / Version 5.0
Site Number:	[redacted]

I approve the design of the clinical study, am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Conference on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

[redacted] _____ [redacted] _____

Date of Signature

Name, academic degree:	[redacted]
Function/Title:	Coordinating Investigator
Institution:	[redacted]
Address:	[redacted]
Telephone number:	[redacted]
Fax number:	[redacted]
E-mail address:	[redacted]

Appendix 10 Principal Investigator Signature Page

Study Title:	A randomized, double-blind, 2-period, 2-sequence crossover Phase I study with a 1 month run-in-period to examine the effect of cladribine tablets on the pharmacokinetics of a monophasic oral contraceptive containing ethinyl estradiol and levonorgestrel (Microgynon) in pre-menopausal women with relapsing multiple sclerosis (RMS)
Regulatory Agency Identifying Numbers:	EudraCT Number: 2018-001015-70
Clinical Study Protocol Version:	29 July 2021 / Version 5.0
Site Number:	

I am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Conference on Harmonisation Good Clinical Practice (Topic E6) 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:	