Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS700568-0031
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)
Trial Phase	I
Investigational Medicinal Product(s)	Cladribine/Placebo, Microgynon
Clinical Trial Protocol Version	Global 04 July 2019/Version 2.0, Country specific protocol Poland 04 July 2019/Version 2.1
Integrated Analysis Plan Author	**Coordinating Author** On behalf of Biostatistics, Merck PPD **Function** / **Author(s) / Data Analyst(s)** Biostatistics, PPD
Integrated Analysis Plan Date and Version	12 Oct 2020 / Final Version 1.0
Integrated Analysis Plan Reviewers	**Function** / **Name** PPD

Global Version ID:

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PPD	[redacted]
	[redacted]

Signature Page

Integrated Analysis Plan: MS700568-0031

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)

Approval of the IAP by all Merck Data Analysis Responsible is documented within Eldorado/Cara. With the approval within Eldorado/Cara, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

Merck responsible	**Date**	**Signature**
, Biostatistics, Merck	Via ELDORADO/Cara approval process	
, Quantitative Pharmacology – CPK, Merck	Via ELDORADO/Cara approval process	

1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
ANOVA	Analysis of VARIANCE
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
ECG	Electrocardiogram
GeoCV	Geometric Coefficient of Variation
GM	Geometric Mean
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
CCI [redacted]	
PGx	Pharmacogenetics
PK	Pharmacokinetics
SAE	Serious Adverse Event
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
UCI	Upper Confidence Interval
ULOQ	Upper Limit of Quantification

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
Final 1.0	12-Oct-2020	[redacted]	n.a.

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the final analysis of data collected for protocol MS700568-0031. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon section 9 (Statistical Considerations) of the trial protocol and protocol amendments and is prepared in compliance with ICH E9.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	IAP Section
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%).	16.1
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)	15
To examine cladribine exposure	Cladribine C_{max} and t_{max}	16.1
[redacted]		
[redacted]	[redacted]	[redacted]

$_{ss}$=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; [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.

6 Overview of Planned Analyses

All final, planned analyses identified in the Clinical Trial Protocol and in this IAP will be performed only after the last subject has completed the last visit, i.e. end of trial visit/early termination visit with all trial data in-house, all data queries resolved, and the database locked.

A blinded data review meeting will be held prior to database lock. In addition, no database can be locked until this IAP has been approved.

7 Changes to the Planned Analyses in the Clinical Trial Protocol

The statistical methods as described in the protocol were adopted.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations and Analysis Sets

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

The following deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest.

Important protocol deviations include but are not limited to

- Deviations from the inclusion and exclusion criteria
- Concomitant medication violations (see Section 6.5.2 of the protocol)
- Use of prohibited medicines (see Section 6.5.3 of the protocol)
- Subjects that receive incorrect treatment or dose
- Sample processing errors that may lead to inaccurate bioanalytical results
- Deviation from Good Clinical Practice
- Non-compliance to study procedures or deviations from study procedures likely to affect the primary endpoints (e.g. subject develops withdrawal criteria whilst on the study but is not withdrawn)

In addition, for the definition of the PK analysis set (see section 8.2) events likely to affect the comparability between treatments of PK results will be identified. Important events to be considered are:

- Vomiting or diarrhea following oral dosing (these instances will be discussed on a case-by-case basis)
- Deviation from study medication compliance in terms of medical conditions and/or AEs that may have interfered with drug disposition or with respect to factors likely to affect the primary endpoints

All important protocol deviations will be documented in Clinical Data Interchange standard consortium (CDISC) Study Data Tabulation Model (SDTM) dataset whether identified through sites monitoring, medical review or programming.

In addition, pre-dose/trough samples which have been taken after the subsequent dosing will be reported as protocol deviation. The resulting concentrations will be included in concentration listings but excluded from descriptive statistics of trough concentrations.

8.2 Definition of Analysis Sets and Subgroups

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 prior to database lock and unblinding.

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 (ie, examining placebo-controlled cladribine effects on the PK and CC[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.

Table 1 Analysis Populations

Analysis Set	Description
Screening	The Screening Analysis Set will include all participants who provided signed informed consent, regardless of enrollment (start of run-in-period) or randomization or treatment status in the study.
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; • Participants must be 100% compliant to cladribine and placebo; • Absences from 100% compliance taking Microgynon

Analysis Set	Description
	considered as significant by the investigator and/or by the attendees during data review meeting; • 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. Participants will be analyzed according to the actual treatment they receive.
[redacted]	[redacted]

[redacted]; PK=pharmacokinetic; [redacted]

9 General Specifications for Data Analyses

Statistical analyses will be performed using the computer program package SAS® System for Windows™ (Version 9.4 or later; SAS Institute, Cary, North Carolina, USA).

The results of this trial will be reported using summary tables, figures, and data listings, as appropriate. All data will be summarized by treatment sequence, period, treatment and/or scheduled time point, as appropriate.

For demographic, baseline and safety assessments, continuous measurements will be summarized by means of descriptive statistics (ie, number and percentage of observations, number and percentage of missing observations, mean, standard deviation [SD], median, 25th and 75th percentiles [Q1 and Q3], minimum, and maximum) and categorical data will be summarized by means of frequency tables (ie, count and percentages), if not stated otherwise. Mean, Median, Q1, Q3, Min, Max will have the same precision as the SDTM data (decimal places). SD will be presented with one decimal place more than the mean. For subject disposition and demographic tables, the denominator will be the number of subjects in the analysis set. Counts of missing observations will be included as a separate category.

If not otherwise specified, 'baseline' refers to the last scheduled measurement before administration of cladribine or placebo on Day 9 of each period.

However, if a subject is missing the baseline collection, the previous non-missing evaluation could become the baseline value. If no baseline or previous to baseline evaluations exist, then the baseline value will be treated as missing.

The following calculations and derivations, as applicable, will be used:

- Change from baseline: post-baseline visit value - baseline value
- Duration of AE (in days hh:mm) = end date and time - start date and time of the AE, if missing time for either the beginning or end then = end date – start date + 1; in case of multiple records for the same AE, the duration will be calculated over all these records
- Days hh:mm from last dosing of cladribine/placebo or microgynon = start date and time of the event - date and time of dose administration; (for treatment- emergent AEs), if missing time for either the dosing or event then = event start date – date of dose administration + 1
- Rel. Day in study = start date of the event or measurement – date of first admin of microgynon + 1 (for events or measurements on or after the day of dosing)
- Rel. Day in study = start date of the event or measurement – date of first admin of microgynon (for events or measurements before the day of dosing)

- Rel. Day in period = start date of the event or measurement – date of first admin + 1 of microgynon within run-in period, period 1 or period 2 (for events or measurements on or after the day of dosing)

Repeated laboratory assessments will be flagged as repeats in the subject data listings and not included in summary tables statistics (unless the scheduled measurement was considered unreliable, e.g. due to technical reasons, and needed to be replaced by an unscheduled repeat measurement).

In this phase 1 PK study missing observations will be assumed to be missing completely at random (MCAR). No action will be taken to handle missing data. A subject who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of discontinuation.

10 Trial Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/trial discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Subjects and Discontinuations

This following will be presented in a summary table:

- Total number of subjects screened (ie, subjects who gave informed consent)
- Total number of subjects enrolled
- Total number of subjects randomized
- Number of screened subjects who discontinued from the trial prior to treatment overall and grouped by the main reason for discontinuation:
    - Subject did not meet all eligibility criteria
    - Withdrew consent
    - Other (COVID-19-related and COVID-19-non-related)
- Number of treated subjects overall
- Number and percentage of treated subjects who completed study
- Number and percentage of treated subjects who discontinued the study, with the primary reason of discontinuation:
    - Adverse event

- Lost to follow-up
- Protocol non-compliance
- Death
- Withdrew consent
- Other (COVID-19-related and COVID-19-non-related)

- Number and percentage of treated subjects who completed microgynon treatment
- Number and percentage of subjects who discontinued microgynon treatment with the primary reason of discontinuation
- Number and percentage of treated subjects who completed MS treatment

Number and percentage of subjects who discontinued MS treatment with the primary reason of discontinuation.

A listing of discontinued subjects will be provided.

A listing of participants affected by the COVID-19 related study disruption by unique subject number identifier will also be provided.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

Listings of important protocol deviations will be provided including the date and relative day in relation to dosing in the relevant period.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

All criteria/reasons leading to the exclusion of a subject from an analysis set will be listed based on the safety set.

Reasons for excluding individual PK concentrations will also be listed separately and flagged in the main listing based on the safety analysis set.

Any PK concentrations and/or PK parameters excluded from PK analysis set or summary statistics will be included in subject listings and flagged; a reason for exclusion will be detailed in the CSR (e.g. a footnote or a table of exclusions). Any flags should be included in the study specific ADaM data sets.

11 Demographics and Other Baseline Characteristics

11.1 Demographics

Summaries will be given for the safety, the pharmacokinetic set, and pharmacodynamic set, if different.

Demographic characteristics will be listed by subject and summarized using the following information from the Screening/Baseline Visit CRF pages.

Demographic characteristics:

- Sex: female (only females included in this trial)
- Race: Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, Other
- Ethnic origin - Hispanic or Latino: yes, no
- Ethnic origin - Japanese: yes, no
- Age (years): summary statistics
- Height (cm) at Baseline: summary statistics
- Weight (kg) at Baseline: summary statistics
- BMI (kg/m^2) at Baseline: summary statistics

Age will be taken from the CRF and cannot be derived from the data because only the year of birth is collected in the CRF.

BMI will be re-derived (ie, not taken directly from the database) according to the following formula:

- BMI (kg/m^2) = weight (kg) / (height (m) * height (m))

11.2 Medical History

The medical history will be listed by subject including the preferred term and MedDRA system organ class (SOC) body using MedDRA, current version.

11.3 Other Baseline Characteristics

Other baseline characteristics will be listed by subject and summarized using the following information from the Screening/Baseline Visit CRF pages.

Other baseline characteristics:

- Smoking status
- Alcohol consumption

12 Previous or Concomitant Medications/Procedures

Previous medications are medications, other than trial medications and pre-medications for trial drug, which started and stopped before first administration of trial drug.

Concomitant treatments are medications, other than trial medications, which are taken by subjects any time on-trial (on or after the first day of trial drug treatment for each subject).

In case the date values will not allow to unequivocally allocating a medication to previous or concomitant medication the medication will be considered as concomitant medication

Any previous and concomitant medication will be encoded with WHO-DD, latest version. Prior and concomitant medications will be listed by subject (all subjects).

The following information will be displayed in a listing: generic or trade name (as reported in CRF), WHO drug name (including coding), dose/unit, route, frequency, reason for use, start/end date and time.

Concomitant procedures will be presented in a data listing.

13 Treatment Compliance and Exposure

A listing of date and time of each drug administration and each blood sampling including time deviations will be provided sorted by subject.

14 Efficacy Analyses

Not applicable.

15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as adverse events, laboratory tests and vital signs.

Safety data analysis will be conducted on the Safety Analysis Set.

15.1 Adverse Events

All adverse events will be summarized overall as well as by Run-in period and per treatment sequence by period, Microgynon alone, Microgynon + Cladribine, Microgynon + Placebo and overall.

For subjects assigned to treatment sequence 1, cladribine-placebo (see also Section 1.2 of the study protocol), the following treatment labels will be used in tables and listings:

- Run-in Period: From run-in period until Day 1 of period 1, pre-dose to Microgynon
    - In case of missing AE time on Day 1 of run-in period, the AE will be assigned to Run-in Period.
- Microgynon alone: From Day 1 of period 1, post-dose to Microgynon until Day 9 of period 1, pre-dose of Cladribine
    - In case of missing AE time on Day 1 of period 1, the AE will be assigned to Microgynon alone
- Microgynon + Cladribine: From Day 9 of period 1, post-dose to Cladribine until Day 1 of period 2, pre-dose of Microgynon
    - In case of missing AE time on Day 9 of period 1, the AE will be assigned to Microgynon + Cladribine
    - In case of missing AE time on Day 1 of period 2, the AE will be assigned to Microgynon + Cladribine
- Microgynon alone: From Day 1 of period 2, post-dose to Microgynon until Day 9 of period 2, pre-dose of Placebo
- Microgynon + Placebo: From Day 9 of period 2, post-dose to Placebo until Day 15 of period 2, pre-dose of Cladribine
    - In case of missing AE time on Day 9 of period 2, the AE will be assigned to Microgynon + Placebo
- Microgynon + Cladribine: From Day 15 of period 2, post-dose to Cladribine until end of study.
    - In case of missing AE time on Day 15 of period 2, the AE will be assigned to Microgynon + Cladribine

For subjects assigned to treatment sequence 2, placebo-cladribine, the following treatment labels will be used in tables and listings:

- Run-in Period: From run-in period until Day 1 of period 1, pre-dose to Microgynon
    - In case of missing AE time on Day 1 of run-in period, the AE will be assigned to Run-in Period.
- Microgynon alone: From Day 1 of period 1, post-dose to Microgynon until Day 9 of period 1, pre-dose of Placebo
    - In case of missing AE time on Day 1 of period 1, the AE will be assigned to Microgynon alone
- Microgynon + Placebo: From Day 9 of period 1, post-dose to Placebo until Day 1 of period 2, pre-dose of Microgynon
    - In case of missing AE time on Day 9 of period 1, the AE will be assigned to Microgynon + Placebo
    - In case of missing AE time on Day 1 of period 2, the AE will be assigned to Microgynon + Placebo
- Microgynon alone: From Day 1 of period 2, post-dose to Microgynon until Day 9 of period 2, pre-dose of Cladribine
    - Microgynon + Cladribine: From Day 9 of period 2, post-dose to Cladribine until end of study.In case of missing AE time on Day 9 of period 2, the AE will be assigned to Microgynon+Cladribine

The number and percentage of subjects experiencing at least one TEAE will be summarized by treatment as well as the number of events. A TEAE is an AE with onset after start of treatment. Start of treatment defines the minimum date of first intake of microgynon or cladribine or placebo. Tables by relationship to trial drug and by severity will be generated. AEs will be coded using Medical Dictionary for Regulatory Activities terminology, latest version.

If an event was reported more than once, the worst severity will be tabulated.

Incomplete TEAE-related dates will be handled as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of trial treatment then the onset date will be replaced by the minimum of start of trial treatment and TEAE resolution date.
- In all other cases the missing onset day or missing onset month will be replaced by 1.

- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case, the date of death will be used to impute the incomplete stop date.

- In all other cases the incomplete stop date will not be imputed.

15.1.1 All Adverse Events

All AEs recorded during the course of the trial (ie, assessed from signature of informed consent until the end of the Follow-up/End of Trial visit) will be coded according to MedDRA latest version and assigned to a SOC and PT.

TEAEs will be summarized by severity, using MedDRA latest version preferred term as event category and MedDRA primary system organ class (SOC) body term as Body System category.

The severity of AEs is assessed by the investigator 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.

TEAEs related to trial treatment are those events with relationship missing, unknown or related.

The following will be summarized in an overview table with the number and percentage of subjects (and the number of events).

- Any TEAE

- TEAEs of special interest

- Trial treatment (either MS treatment or microgynon) related TEAEs

- MS treatment related TEAEs

- Microgynon related TEAEs

- Any serious TEAEs

- Trial treatment (either MS treatment or microgynon) related serious TEAEs

- MS treatment related serious TEAEs

- Microgynon related serious TEAEs
- Any severe TEAE
- Trial treatment (either MS treatment or microgynon) related severe TEAE
- MS treatment related severe TEAE
- Microgynon related severe TEAE
- TEAEs leading to death
- Trial treatment (either MS treatment or microgynon) related TEAEs leading to death
- MS treatment related TEAEs leading to death
- Microgynon related TEAEs leading to death

TEAEs will be summarized in tables with:

- The number and percentage of subjects by treatment with at least one TEAE and the number of events overall and by SOC and PT. Group/SOC terms will be sorted alphabetically and PTs within each group/SOC term will be sorted by descending frequency.
- The number and percentage of subjects by treatment with at least one non-serious TEAE and the number of non-serious TEAE applying frequency threshold of 5%. Group/SOC terms will be sorted alphabetically and PTs within each group/SOC term will be sorted by descending frequency.

In addition, the following tables will be provided. Group/SOC terms will be sorted alphabetically and PTs within each group/SOC term will be sorted by descending frequency (based on all treatment groups combined):

- A table by severity of TEAEs with the number and percentage of subjects by treatment with at least one TEAE and the number of events by SOC and PT.
- A table by relationship to trial treatment (either MS treatment or microgynon) with the number and percentage of subjects by treatment with at least one TEAE and the number of events by SOC and PT.
- A table by relationship to MS treatment with the number and percentage of subjects by treatment with at least one TEAE and the number of events by SOC and PT.
- A table by relationship to microgynon with the number and percentage of subjects by treatment with at least one TEAE and the number of events by SOC and PT.

Pre-treatment AEs (AEs with onset after informed consent but before start of treatment) and TEAEs will be listed separately.

15.1.2 Adverse Events Leading to Treatment Discontinuation

TEAEs leading to permanent discontinuation of trial treatment will be summarized including number of subjects, percentage and number of events.

A listing of TEAEs leading to permanent discontinuation of a trial treatment will additionally be provided.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

All deaths as well as reason for death will be based on information from the "Report of Subject Death" CRFs.

Listing of deaths, if any, will be provided displaying date and cause of death (including TEAE leading to death and relatedness to trial treatment, when applicable), and date and time of treatment administration.

15.2.2 Serious Adverse Events

A summary table of SAEs, if any, by treatment and overall will be provided displaying the number and percentage of subjects by treatment with at least one SAE and the number of SAE overall and by system organ class and preferred term. Group/SOC terms and PTs within each group/SOC term will be sorted alphabetically.

Listing of SAEs, if any, will be provided in addition.

15.2.3 Other Significant Adverse Event

15.2.3.1 Adverse Events of Special Interest

AEs that were identified as AEs of special interest (see Appendix 4 of the clinical study protocol) will be presented in a separate data listing.

15.3 Clinical Laboratory Evaluation

The following treatment labels will be used in tables and listings:

- Screening: During the screening period
- Run-in Period: During run-in period

- Microgynon + Placebo or Microgynon + Cladribine: For the measurement on Day 8, Day 9 and Day 14

- Follow-up: During follow-up/end of study period

All laboratory data will be reported with SI units. Laboratory parameters will be listed by subject and time-point and summarized indicating the treatment at the respective time-point using descriptive statistics and Box and Whisker plot for absolute values and change from baseline over time by treatment sequence, period and treatment.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Clinically significant abnormalities/outliers as per the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials will additionally be listed separately. Clinically significant values will be defined as values with toxicity grading of grade 2 or higher.

'Baseline' refers to the last scheduled measurement before administration of cladribine or placebo on Day 9 of each period. I.e. 'baseline' for period 1 refers to assessments on Day 21 of the run-in period.

Shift tables for post-dose shift (Low, Normal, High, Missing) will also be presented. The shift tables will be presented for follow-up versus screening.

See Appendix 5 of the clinical study protocol for a table of the safety laboratory evaluations.

Safety laboratory values are separated into:

- Hematology

- Biochemistry

- Urinalysis

- Other tests

Descriptive statistics shift tables and box plots will be created only for hematology and biochemistry results.

15.4 Vital Signs

The following treatment labels will be used in tables and listings:

- Screening: During the screening period

- Run-in Period: During run-in period

- Microgynon + Placebo or Microgynon + Cladribine: For each measurement from Day 9 on until Day 14

- Follow-up: During follow-up/end of study period

Vital signs will be listed by subject and time-point and summarized for absolute values and changes-from-baseline by treatment sequence, period, treatment and visit using descriptive statistics. Descriptive statistics tables will start at baseline.

15.5 ECG Evaluation

The following treatment labels will be used in tables and listings:

- Screening: During the screening period

- Microgynon + Placebo or Microgynon + Cladribine: For each measurement on Day 9 and Day 14

- Follow-up: During follow-up/end of study period

ECG data will be summarized for absolute values and changes-from-baseline by treatment sequence, period, treatment, and visit using descriptive statistics. Descriptive statistics tables will start at baseline. Clinically significant ECG findings for individual subjects will be listed and summarized.

The time intervals (PR, QRS, RR, QT and corrected QT intervals [based on Fridericia's formula, QTcF]) will be summarized descriptively by treatment sequence, period, treatment and visit.

The Fridericia's Correction (QTcF) is derived as follows:

Fridericia's Correction (QTcF) $$QTc_f = \frac{QT}{\sqrt[3]{RR}}$$

where: RR = RR-interval measured in seconds.

Baseline for ECG is defined as Day 9 pre-dose (for each period).

Observed QTcF values will be categorized according to their absolute values into the categories

- $\leq$ 430 ms,

- $>$ 430 and $\leq$ 450 ms,

- > 450 and ≤ 470 ms,
- > 470 and ≤ 500 ms, and
- > 500 ms,

and categorized according to their absolute change from baseline into the categories

- ≤ 30 ms,
- > 30 and ≤ 60 ms, and
- > 60 ms.

The number and percentage of subjects by these categories at any post-dose assessment (post-dose to intake of placebo or cladribine) will be tabulated by treatment sequence, period and treatment.

All ECG measurements will be listed, with investigator reported abnormalities indicated.

Investigator reported interpretation results will also be listed and tabulated by treatment sequence, period and treatment using the number and percentage of subjects for each interpretation category (Normal, Abnormal Not Clinically Significant [NCS], Abnormal Clinically Significant [CS].

15.6 Sensitivity Analysis

Due to a dispensation error at the study site, the treatment sequence for patient [redacted] needed to be unblinded (only Sponsor Medical Responsible and Medical Monitor were unblinded) so that appropriate further subject treatment could be ensured. This happened during the development of the iAP.

Following the "for cause" unblinding, in a study team call between vendor and CRO on CCI [redacted], the actual assignment of the patient was revealed, to avoid communication errors regarding the treatment sequence to which this patient was initially randomised, and which treatment sequence the patient actually received. This discussion took place after the patient had completed her last treatment as per protocol and her treatment assignment was unblinded according to study protocol, to determine whether or not she may require a second cladribine treatment course after conclusion of the study.

The sponsor statistician at the time, who should not have been informed of the treatment assignment, was present and consequently unblinded regarding the treatment sequence of a single patient.

To this end, a sensitivity analysis will be performed by excluding the affected patient from the analysis. This additional analysis will be done for AEs. An overview table of treatment emergent AEs as mentioned Section 15.1 will be provided.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

The following treatment labels will be used in tables and listings:

Run-in Period: During run-in period (for EE and LNG only)

Microgynon + Placebo or Microgynon + Cladribine.

General Specifications for Plasma Concentration Data

PK concentration data will be presented in tables and descriptively summarized by treatment and nominal time point using n, arithmetic mean, SD, median, minimum, maximum, and CV%. Values below the LLOQ will be taken as zero for descriptive statistics of PK concentrations.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data, and rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PK concentration data:

Mean, Min, Median, Max:	3 significant digits
SD:	4 significant digits
CV%:	1 decimal place

For final evaluations values greater than the upper limit of quantification (ULOQ) are not accepted and should be replaced by valid numeric values from dilution measurement. Missing concentrations (e.g. no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as "N.R.". Pre-dose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study drug administration.

General Specifications for PK Parameter Data

PK parameter data will be descriptively summarized: n, arithmetic mean, SD, median, minimum, maximum, CV%, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%), and the 95% CI for the GeoMean.

PK parameter C_{max} will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the SDTM PP domain, PK parameters will be provided with full precision, and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values, and rounded for reporting purposes only.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

Mean, Min, Median, Max, GeoMean, 95% CI:	3 significant digits
SD:	4 significant digits
CV%, GeoCV%:	1 decimal place
Ratio of GeoMean and 90% CI	4 decimal places

All statistical analyses and descriptive summaries of pharmacokinetic data will be performed on the PK Analysis Set. All available concentration/PK data will be listed. Data of subjects not in the PK analysis set or invalid data will be flagged accordingly; a reason for exclusion will be detailed in the CSR (e.g. a footnote or a table of exclusions). Any flags should be included in the study specific ADaM data sets**.**

16.1.1 Primary Pharmacokinetic 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 four 90% CIs for the TEST/REFERENCE ratios are fully contained within the [0.8000 to 1.2500] acceptance range.

Scatter plots will be produced for the individual primary PK parameters by treatment indicating the geometric means within each treatment. Boxplots for primary PK parameters by treatment will also be provided.

16.1.2 Secondary Pharmacokinetic Endpoints

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%). Secondary PK parameters calculated for Cladribine: C_{max} and t_{max}.

Secondary parameters will be listed.

Summary statistics will be provided for all secondary PK parameters for EE, LNG and cladribine in plasma by analyte, treatment and day, if applicable.

16.1.3 Plasma Concentration Data

Concentrations of EE, LNG and cladribine will be tabulated and displayed graphically. Summary statistics will be provided by analyte, treatment and nominal timepoint and day.

The following figures will be produced for the EE and LNG plasma concentrations on Day 14:

- Arithmetic mean plasma concentration-time profiles overlaying all treatments on linear and semi-logarithmic scale
- Arithmetic mean plasma concentration-time profiles overlaying all treatments on linear scale including SD error bars
- Individual plasma concentration-time profiles overlaying subjects, for each treatment separately on linear and semi-logarithmic scale
- Individual plasma concentration-time profiles overlaying all treatments, separately for each subject on linear and semi-logarithmic scale

The following figures will be produced for the cladribine plasma concentrations on Days 10, 11, 12 and 13 separately:

- Individual plasma concentration-time profiles on linear and semi-logarithmic scale overlaying subjects, for each treatment separately on linear and semi-logarithmic scale (x-scale: relative actual time related to corresponding cladribine administration)
- Individual plasma concentration-time profiles on linear and semi-logarithmic scale overlaying all treatments, separately for each subjects on linear and semi-logarithmic scale (x-scale: relative actual time related to corresponding cladribine administration)

The following figures will be produced for the cladribine plasma concentrations overlaying Days 10, 11, 12 and 13:

- Individual plasma concentration-time profiles on linear and semi-logarithmic scale separately for each treatment and subjects on linear and semi-logarithmic scale (x-scale: relative actual time related to corresponding cladribine administration)
- Arithmetic mean plasma concentration-time profiles for each treatment separately on linear and semi-logarithmic scale
- Arithmetic mean plasma concentration-time profiles for each treatment separately on linear scale including error bars

The following listing will be produced:

- Plasma concentrations will be listed for each analyte by treatment, subject, and nominal time and day. Excluded plasma concentrations will be flagged.

16.1.4 Estimation of Individual Pharmacokinetic Parameters

The computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA) will be used to derive PK parameters applying Non-compartmental analysis (NCA). The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.1 or higher) may be used to generate additional PK parameters, produce tables, listings and figures.

The following PK parameters will be calculated for Day 14, when appropriate:

Table 2 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)
$C_{av,ss}$	Average plasma concentration at steady state during a complete dosing interval (τ); $C_{av,ss} = AUC_{\tau,ss} / \tau$
PTF %	Peak-to-trough fluctuation over 1 complete dosing interval at steady state

The following PK parameters will be calculated for Days 9, 10, 11, 12 and 13, when appropriate:

Table 3 PK Parameters of cladribine[a]

Parameter	Full description
C_{max}	Maximum observed concentration (Days 10-13 only)
t_{max}	Time to reach the observed maximum (peak) concentration (Days 10-13 only)
C_{pre}	Measured concentration during repeat-dosing taken directly before drug administration (on Day 10-13).

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 cladribine.

Individual PK parameters will be calculated using actual elapsed time since dosing, given with a precision of 14 significant digits or the SAS format Best12. The pre-dose sample will be considered as if it had been taken simultaneously with the administration of study drug. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data.

Samples that are collected outside the specified time windows specified in the CTP will be included in the PK parameter estimation (NCA) but will be excluded from the concentration summary and mean concentration plots.

16.1.5 Sensitivity Analysis

For the same reason mentioned in Section 15.6, a sensitivity analysis will be performed by excluding the subject PPD from the analysis if not excluded from the PK analysis set after BDRM. The same summary tables for the primary parameters of EE and LNG as well as the ANOVA mentioned in Section 16.1.1 above will be provided for this analysis.

[redacted]

17 References

None.

18 Appendices

None.