Statistical Analysis Plan

Study ID: 220104

Official Title of Study: A Phase 1, open-label, fixed sequence, 1-way drug-drug interaction study to investigate the pharmacokinetics, of GSK3036656 and an oral contraceptive containing ethinyl estradiol and levonorgestrel when the oral contraceptive is administered alone and in combination with GSK3036656 in healthy female participants of non-childbearing potential aged 18-65 years of age

NCT number: NCT06354257

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TITLE PAGE

Protocol Title:	A Phase 1, open-label, fixed sequence, 1-way drug-drug interaction study to investigate the pharmacokinetics, of GSK3036656 and an oral contraceptive containing ethinyl estradiol and levonorgestrel when the oral contraceptive is administered alone and in combination with GSK3036656 in healthy female participants of non-childbearing potential aged 18-65 years of age.
Study Number:	220104
Compound Number:	GSK3036656
Abbreviated Title:	PH1, A study to investigate the pharmacokinetics of a combined oral contraceptive when given alone and in combination with GSK3036656 in female participants of non-childbearing potential aged 18 to 65 years of age.

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s).

Registry	**ID**
Clintrials.gov	*Not Available*

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	28 Mar 2024	Protocol Version 1 (06 November 2023)	Not Applicable	Original version

1. INTRODUCTION

- The purpose of this SAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 220104.
- This SAP is intended to describe the full analyses required for the study.
- This SAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

1.1. Objectives, Estimands and Endpoints

The study objectives and endpoints are presented in Table 1

Table 1: Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of steady state exposure of GSK3036656 on the single dose PK of EE and LNG in healthy female participants of non-childbearing potential	• Area under the plasma concentration-time curve to infinity $AUC_{(0\text{-}inf)}$ and maximum observed concentration (C_{max}), after a single dose of EE and LNG (EE $AUC_{(0\text{-}inf)}$, EE C_{max}, LNG $AUC_{(0\text{-}inf)}$, LNG C_{max})
Secondary	
• To characterize the steady state PK of GSK3036656 in the presence of EE/LNG	• $AUC_{(0\text{-}\tau)}$, C_{max}, C_{τ} (Day 8, 10, 12, 15 and 16) and time of maximum observed concentration (T_{max}) for GSK3036656
• To characterize the single dose PK of EE/LNG alone and in the presence of GSK3036656	• $AUC_{(0\text{-}t)}$, T_{max} and $t_{1/2}$ for EE and LNG, in Treatment Period 1 and Treatment Period 3.
• To assess the safety and tolerability of GSK3036656 and Microgynon when given alone or in combination in healthy female participants of non-childbearing potential	• Incidence of SAEs within each treatment period. • Incidence of AEs of grade 3 severity or higher within each treatment period. • Incidence of AEs considered by the investigator to be possibly, probably, or definitely related to study drug within each treatment period (overall and separately for relationship to Microgynon and to GSK3036656). • Incidence of participants withdrawn from the treatment/study due to adverse events within each treatment period. • Incidence of ECG values of PCI within each treatment period.

Objectives	Endpoints
	• Incidence of clinical chemistry laboratory values of PCI within each treatment period. • Incidence of hematology laboratory values of PCI within each treatment period. • Incidence of vital signs parameters of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) of PCI within each treatment period.

PRIMARY ESTIMAND

The primary clinical question of interest is:

What is the effect of treatment with GSK3036656, estimated by the point estimate and 90% confidence interval (CI) for the ratio of the geometric mean of Microgynon+GSK3036656 compared to Microgynon (within participant comparison), on the exposure ($AUC_{(0\text{-}inf)}$ and C_{max}) of EE and LNG in healthy female participants who are missing no more than one 20 mg dose of GSK3036656 in treatment period 2 and are 100% compliant with study treatments in treatment periods 1 and 3?

The estimand is described by the following attributes:

- Population: Healthy female participants of non-childbearing potential aged 18 to 65 years.
- Endpoints: Plasma PK parameters of EE and LNG: $AUC_{(0\text{-}inf)}$ and C_{max}.
- Treatments: single dose Microgynon +14 days GSK3036656 (Treatment Period 3) Vs single dose Microgynon alone (Treatment Period 1)
- Strategy for intercurrent event: The intercurrent events of interest are participants missing dose of Microgynon in treatment periods 1 and 3, missing dose of GSK3036656 in treatment period 3, or missing more than one 20 mg dose of GSK3036656 in treatment period 2. The strategy for handling all of these intercurrent events will be a Principal Stratum Strategy, where we are only interested in the strata of participants who are missing no more than one 20 mg dose of GSK3036656 in treatment period 2 and are 100% compliant with study treatments in treatment periods 1 and 3.
- Population-level summary: The point estimate and 90% CI for the ratio of the geometric mean for each of EE $AUC_{(0\text{-}inf)}$, LNG $AUC_{(0\text{-}inf)}$, EE C_{max} and LNG C_{max}, for Microgynon+GSK3036656 (Treatment Period 3) compared to Microgynon alone (Treatment Period 1) (within participant comparison).

Rationale for estimand: Interest lies in estimating the effect of GSK3036656 on the pharmacokinetics of Microgynon, which cannot be accurately assessed in the situation where participants are missing more than one 20 mg dose of GSK3036656 in treatment period 2 and are not 100% compliant with study treatments in treatment periods 1 and 3.

Primary estimands of secondary Pharmacokinetic endpoints

Steady State PK of GSK3036656

The clinical question of interest is:

What are the estimates (mean/ median and variability) of steady state PK parameters ($AUC_{(0-\tau)}$, C_{max}, C_τ and T_{max}) of GSK3036656 in the presence of EE/LNG in healthy female participants, who are missing no more than one 20 mg dose of GSK3036656 in treatment period 2 and are 100% compliant with study treatments in treatment period 3?

The Primary Estimand is described by the following attributes:

- Population: Healthy female participants of non-childbearing potential aged 18 to 65 years.
- Endpoints: $AUC_{(0-\tau)}$, C_{max}, C_τ and T_{max} for GSK3036656
- Treatments: single dose Microgynon+14 days GSK3036656
- Strategy for intercurrent event: The intercurrent events of interest are participants missing their dose of Microgynon during treatment period 3, or missing a dose of GSK3036656 in treatment period 3, or missing more than one 20 mg dose of GSK3036656 in treatment period 2. The strategy for handling all of these intercurrent events will be a Principal Stratum Strategy, where we are only interested in the strata of participants who are missing no more than one 20 mg dose of GSK3036656 in treatment period 2 and are 100% compliant with study treatments in treatment period 3.
- Population-level summary:
  - For $AUC_{(0-\tau)}$, C_{max}, and C_τ of GSK3036656: Descriptive Statistics (including n, Arithmetic means with 95% CI, Geometric means with 95% CI, CV%, SD, Median with Min, Max);
  - for T_{max} of GSK3036656: Descriptive Statistics (including n, Median with Min, Max).

Rationale for estimand: Interest lies in estimating the pharmacokinetics of GSK3036656 in the presence of Microgynon, which cannot be accurately assessed in the situation where participants are missing more than one 20 mg dose of GSK3036656 in treatment period 2 and are not 100% compliant with study treatments in treatment period 3.

Pharmacokinetics of EE/LNG

The clinical question of interest is:

What are the estimates (mean/ median and variability) of the PK parameters ($AUC_{(0-t)}$, T_{max} and $t_{1/2}$) of EE and LNG with and without GSK3036656 in healthy female participants, who, for the estimates with GSK3036656 are missing no more than one 20 mg dose of GSK3036656 in treatment period 2 and are 100% compliant with doses of GSK3036656 in treatment period 3? For the estimates of PK parameters of EE and LNG taken alone, no intercurrent events are defined.

The Primary Estimand is described by the following attributes:

- Population: Healthy female participants of non-childbearing potential aged 18 to 65 years.
- Endpoints: $AUC_{(0-t)}$, T_{max} , and t1/2 for EE and LNG
- Treatments: single dose Microgynon+ 14 days GSK3036656 and single dose Microgynon

Strategy for intercurrent event: The intercurrent events of interest, applicable to estimates of PK parameters for EE and LNG with GSK3036656 only, is participants missing one or more doses of GSK3036656 in treatment period 3, or missing more than one 20 mg dose of GSK3036656 in treatment period 2. The strategy for handling this intercurrent events will be a Principal Stratum Strategy, where we are only interested in the strata of participants who are missing no more than one 20 mg GSK3036656 dose in treatment period 2 and are 100% compliant with doses of GSK3036656 in treatment period 3. For the estimates of PK parameters of EE and LNG taken alone, no intercurrent events are defined.

- Population-level summary:
  - For $AUC_{(0-t)}$ and $t_{1/2}$ (h) of EE and LNG: Descriptive Statistics (including n, Arithmetic means with 95% CI, Geometric means with 95% CI, CV%, SD, Median with Min, Max);
  - for T_{max} of EE and LNG: Descriptive Statistics (including n, Median with Min, Max).

Rationale for estimand: Interest lies in estimating the pharmacokinetics of Microgynon, with and without GSK3036656. The PK of Microgynon taken with GSK3036656 cannot be accurately assessed in the situation where participants are missing more than one 20 mg dose of GSK3036656 in treatment period 2 or are not compliant with doses of GSK3036656 in treatment period 3.

Primary estimand of secondary Safety endpoints

For all secondary safety endpoints the primary clinical question of interest:

Are GSK3036656 and Microgynon, taken separately or together, safe and well tolerated in healthy female participants of non-childbearing potential aged 18 to 65 years, regardless of study treatment discontinuation and the level of compliance of either treatment?

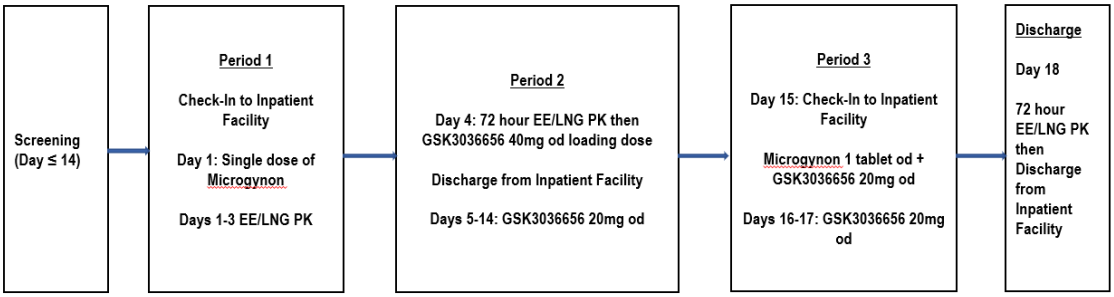
The primary estimands for Safety are described by the following attributes:

- Population: Healthy female participants of non-childbearing potential aged 18 to 65 years.
- Endpoints:
  - Incidence of serious adverse events within each treatment period.
  - Incidence of adverse events of grade 3 severity or higher within each treatment period.
  - Incidence of adverse events considered by the investigator to be possibly, probably or definitely related to study drug (overall and separately for Microgynon and GSK3036656) within each treatment period.
  - Incidence of participants withdrawn from the treatment/study due to adverse events within each treatment period.
  - Incidence of ECG values of PCI within each treatment period.
  - Incidence of clinical chemistry laboratory values of PCI within each treatment period.
  - Incidence of haematology laboratory values of PCI within each treatment period.
  - Incidence of vital signs parameters of SBP, DBP and HR of PCI within each treatment period.
- Treatments: single dose Microgynon, once daily GSK3036656 and single dose Microgynon +once daily GSK3036656
- Strategy for intercurrent event: The intercurrent events of interest are participants missing the dose of Microgynon, missing one or more doses of GSK3036656 or discontinuing GSK3036656 early due to any reason. The strategy for handling these intercurrent events will be a Treatment Policy Strategy, where all safety data after the intercurrent event will be included.
- Population-level summary: Frequency and percentage of participants; with the denominator for percentages being the number of participants entering the treatment period.

Rationale for estimand: It is important to document all safety issues that could potentially be attributable to the regimen, regardless of treatment non-compliance/discontinuation.

1.2. Study Design

Overview of Study Design and Key Features



Participants progress immediately from the end of Treatment Period 1 to Treatment Period 2, with no washout required in between.

Design Features	• A Phase 1, open-label, fixed-sequence, 1-way DDI study. • Participants will be screened within 14 days before the start of Treatment Period 1. The treatment periods are then as follows: – Treatment Period 1: Microgynon only – Treatment Period 2: GSK3036656 only – Treatment Period 3: Microgynon + GSK3036656 • Approximately 20 participants will be enrolled to ensure at least 16 participants provide evaluable data in both test and reference periods.
Study intervention	• Treatment Period 1: Microgynon (0.03 mg EE/0.15 mg LNG) single dose on Day 1 of the treatment period. • Treatment Period 2: A loading dose of GSK3036656 40 mg on Day 4 then GSK3036656 20 mg od from Day 5 to Day 14. • Treatment Period 3: Microgynon (0.03 mg EE/0.15 mg LNG) single dose co-administered with GSK3036656 20 mg on Day 15, then GSK3036656 20 mg od alone from Day 16 to Day 17.
Study intervention Assignment	• This is an open-label study. All eligible participants will receive the same treatments.
Interim Analysis	• No interim analysis is planned for this study.

2. STATISTICAL HYPOTHESES

The primary objective, as outlined in Section 1.1, is planned to be addressed using formal hypothesis testing. For the primary estimand, the following (confirmatory) two 1-sided hypothesis is planned to be tested for Microgynon+GSK3036656 (Treatment Period 3) versus Microgynon alone (Treatment Period 1):

H_0: $\mu_{test}/\mu_{ref} < 0.8$ or $\mu_{test}/\mu_{ref} > 1.25$

H_a: $0.8 \leq \mu_{test}/\mu_{ref} \leq 1.25$

Where μ_{test} is the geometric least squares (LS) mean for PK parameters ($AUC_{(0\text{-inf})}$ and C_{max}) of EE/LNG when coadministered with GSK3036656 and μ_{ref} is the geometric LS mean for PK parameters of EE/LNG when administered alone. The hypothesis test will be assessed using Schuirmann's two 1-sided t-test procedure with α=0.05 for each test [D. J Shhuirmann, 1987]. Each ratio will be compared to 0.8 and 1.25 as described above. Lack of effect (i.e. lack of a drug-drug interaction) will be demonstrated if the 90% confidence intervals (CIs) for both PK parameters ($AUC_{(0\text{-inf})}$ and C_{max}) for both EE and LNG are within 0.8 and 1.25 (four parameters in total).

2.1. Multiplicity Adjustment

Not applicable. Although there are four comparisons, the null hypothesis must be rejected in all four cases, so no adjustment to the type 1 error is required.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who signed the ICF and were screened for eligibility. • This population will be used for screen failure listing and summary.	Study Population
Enrolled	• All participants who entered the study (who received study intervention or underwent a post screening study procedure). • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Safety	• All participants who received at least 1 dose of study medication. • Participants will be analyzed according to the actual study intervention.	Safety

Analysis Set	Definition / Criteria	Analyses Evaluated
	• This population will be used for all demographic and safety summaries and listings.	
PK	• All participants in the Safety analysis set who had at least 1 non-missing PK assessment (NQ values will be considered as non-missing values). • Data will be reported according to the actual study intervention. • This population will be used for PK summary tables, statistical analysis tables, figures, and listings.	PK

4. STATISTICAL ANALYSES

4.1. General Considerations

Plasma EE, LNG, and GSK3036656 concentration-time data will be analyzed by the Clinical Pharmacology Modelling & Simulation department, Parexel, using noncompartmental methods with Phoenix WinNonlin Version 8.3 or higher.

Statistical analysis will be performed by Clinical Statistics, GSK.

4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced.

Confidence intervals will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, endpoints defined in Section 1.1 will be summarized using descriptive statistics and graphically presented (where appropriate). In summary tables, results will be presented by treatment periods (Microgynon only, GSK3036656 only, and Microgynon + GSK3036656).

Unless otherwise specified, continuous data will be summarized using descriptive statistics: N, n, mean, standard deviation (std), median, minimum and maximum; for PK concentration data, No. Imputed, between-subject CV (%CV_b) and 95% CIs, will also be reported along with above mentioned summary statistics; categorical variables will be summarized using n and percentage of participants in each category; for T_{max}, only N, n, median, minimum, and maximum values will be presented; log_e-transformed plasma concentration and PK parameters will be summarized using geometric mean, 95% CI, SD (logs) and the geometric %CV_b based on geometric mean.

To assess primary endpoint, log_e-transformed PK parameters will be statistically analyzed separately using Analysis of covariance (ANCOVA) Model to report point estimate for the ratio of the geometric means of treatment groups under comparison along with 90% CIs.

Further details of analysis, including the full list of data displays to be produced, will be provided in the Output & Programming Specification (OPS).

4.1.2. Baseline Definition

For all endpoints the baseline value (derived for each period) will be the latest pre-dose assessment of respective period with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1, Day 4 and Day 15 assessments are assumed to be taken prior to first dose of the respective period and will be used as baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Table 2: Baseline Assessment

Parameter	**Study Assessments**					**Baseline Used in Data Display**		
	Screening	**D 1**	**D 4**	**D 15**	**D 18**	**Treatment Period 1**	**Treatment Period 2**	**Treatment Period 3**
12-Lead ECG#	T#	X	X	X	X	D 1 (Pre-Dose)	D 4 (Pre-Dose)	D 15 (Pre-Dose)
Clinical chemistry^	X	X	X	X	X	D 1 (Pre-Dose)	D 4 (Pre-Dose)	D 15 (Pre-Dose)
Hematology^	X	X	X	X	X	D 1 (Pre-Dose)	D 4 (Pre-Dose)	D 15 (Pre-Dose)
Vital signs*	X	X	X	X	X	D 1 (Pre-Dose)	D 4 (Pre-Dose)	D 15 (Pre-Dose)

T = Triplicate At Screening, triplicate ECGs are taken. Single ECGs will be taken on other scheduled days.

On Day 1, day 4 and day 15 ECG should be performed within 15 minutes before dosing and recorded in the eCRF.
^ Laboratory assessments to be performed at Screening, and prior to dosing on Day 1 of Treatment Period 1, Day 4 of Treatment Period 2 and Day 15 of Treatment Period 3.
* To be performed within 4 hours prior to the first dosing on Day 1 of Treatment Period 1, Day 4 of Treatment Period 2 and Day 15 of Treatment Period 3. Where a measurement is abnormal or significantly different from previous measurements, a further 2 readings will be taken. When vital signs are measured in triplicate, values should be taken at least 1 minute but not more than 5 minutes apart and recorded in the CRF.

4.2. Primary Endpoint(s) Analyses

The primary objective of this study is to assess the effect of steady state exposure of GSK3036656 on the single dose PK of EE and LNG in healthy female participants of non-childbearing potential aged 18 to 65 years, who are missing no more than one 20 mg dose of GSK3036656 in treatment period 2 and are 100% compliant with study treatments in treatment periods 1 and 3. For the analyses planned in the following section, the potential intercurrent events that will be considered are participants missing a dose of Microgynon in treatment periods 1 and 3, or missing dose of GSK3036656 in treatment period 3, or missing more than one 20 mg dose of GSK3036656 in treatment period 2. Events leading to missing data are: participant withdrawal from study/ loss to follow-up, or missing PK assessments.

4.2.1. Definition of endpoint(s)/estimands

The primary pharmacokinetic endpoints and attributes of the estimand are detailed in Section 1.1. and Section 4.2.1.1

4.2.1.1. Pharmacokinetic Parameters

The PK parameters will be provided by CPMS group, Parexel. The PK parameters will be calculated by NCA methods from the concentration-time data using Phoenix® WinNonlin® Version 8.3 or later following these guidelines:

- Actual time from dose will be used in the calculation of all derived PK parameters.
- There will be no imputation of missing data.
- Handling of NQ samples for derivation of plasma PK parameters after each dose administration
  - NQs at the beginning of a participant profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero.
  - NQs at the end of a participant profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
  - Single NQs which fall between two measurable concentrations will be set to missing.
  - Consecutive NQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive NQs will also be set to missing.

If a participant experiences emesis, the data for the affected period will be excluded from summary statistics and statistical analysis if vomiting occurs at or before 2 times median T_{max}

The primary and secondary PK parameters (see Section 1.1 and Section 4.3.1) will be estimated according to the guidelines presented in Table 3.

Table 3: Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation	Analyte
C_{max}, T_{max}, C_{τ},	Obtained directly from the observed concentration-time data.	• C_{max} and T_{max}: EE and LNG (Treatment Periods 1 and 3) and GSK3036656 (Treatment period 3) • Cτ: GSK3036656 (at Day 8, 10, 12, 15 and 16).
$AUC_{(0-t)}$	The AUC from zero time (predose) to the time of last quantifiable concentration will be calculated by a combination of linear and logarithmic trapezoidal methods. The linear up/log down trapezoidal method will be employed. $AUC_{l(0-t)}=\int_0^t C(x)dx$	EE and LNG (Treatment Periods 1 and 3)
$AUC_{(0-\tau)}$	The AUC over the dosing interval will be determined for multiple dose studies using the same trapezoidal rule as for $AUC_{(0-t)}$. If extrapolation is required for $AUC_{(0-\tau)}$ calculation and it is not possible to derive an acceptable λz value, then AUC up to the time of last quantifiable concentration ($AUC_{(0-t)}$) will be used as approximate estimate of $AUC_{(0-\tau)}$. This imputation will be considered reliable only if the time of last measurable concentration is close to the end of the dosing interval.	GSK3036656 (Treatment Period 3)
$AUC_{(0-inf)}$	The area from zero time extrapolated to infinite time will be calculated as follows: $AUC_{(0-inf)} = AUC_{(0-t)} + Clast/\lambda z$ where C_{last} is the last observed quantifiable concentration.	EE and LNG (Treatment Periods 1 and 3)

Parameter	Guideline for Derivation	Analyte
$\%AUC_{ex}$	The percentage of $AUC_{(0\text{-}inf)}$ obtained by extrapolation will be calculated as follows: $\%AUCex = (AUC(0\text{-}inf) - AUC(0-t))/AUC(0\text{-}inf)x100$ If the $\%AUC_{ex}$ is greater than 20% the value, $\%AUC_{ex,}$ and all dependent parameters will be flagged in listings. It is acceptable to include data from profiles with >20% extrapolated area if at least 80% of the profiles in the study have <20% of the $AUC_{(0\text{-}inf)}$ as extrapolated area. Unless otherwise determined by PK scientist's best knowledge and judgement, it is unacceptable to use $AUC_{(0\text{-}inf)}$ data if >40% of the AUC has been extrapolated: in this case, $\%AUC_{ex,}$ and all dependent parameters will be flagged in listings and might be excluded from summary tables and statistical analysis of PK parameters. The reason for exclusion will be listed/footnoted in parameter listings.	EE and LNG (Treatment Periods 1 and 3)
λ_z and $t_{1/2}$	The apparent terminal phase rate-constant (λ_z) will be estimated by linear regression of concentration versus time data presented in a log-linear scale (with uniform weighting). Only those data points that are judged to describe the terminal log-linear decline will be used in the regression. Data points may be dropped from the linear regression if the PK Scientist considers the reported values to be anomalous. Any data points so designated should remain in the listings with a footnote and be identified in the study report with a rationale for exclusion. A minimum number of three data points in the terminal phase will be used in calculating λ_z with the line of regression starting at any post-C_{max} data point (C_{max} will not be part of the	EE and LNG (Treatment Periods 1 and 3)

Parameter	Guideline for Derivation	Analyte
	regression slope). Based on the PK Scientist's best knowledge and judgment, if the adjusted coefficient of determination (R^2 adjusted) is <0.85, then λ_z and all the λ_z dependent parameters (i.e. $t_{1/2}$, $AUC_{(0\text{-inf})}$) will be flagged in listings and might be excluded accordingly from summary tables and statistical analysis of PK parameters. The reason for flagging/ exclusion will be listed/footnoted in parameter listings. The interval used to determine λ_z should be equal or greater than 2-fold the estimated $t_{1/2}$, and if less than 2-fold, λ_z will be flagged in listings. All the derived parameters (i.e. $t_{1/2}$, $AUC_{(0\text{-inf})}$) will also be flagged in listings. The reason for flagging will be listed/footnoted in parameter listings. The $t_{1/2}$ will be calculated as follows: $t_{1/2} = \ln 2/\lambda_z = 0.693/\lambda_z$	

4.2.2. Main analytical approach

The primary analysis for the primary PK endpoints will be performed for the strata of participants able to adhere to treatment as defined in primary estimand framework, and included in the PK analysis set. τ

- Based on the individual concentration-time data the following primary plasma parameters will be estimated, refer Section 4.2.1.1. Pharmacokinetic Parameters for more details:
  - EE (separately for Microgynon+GSK3036656 and Microgynon alone): $AUC_{(0\text{-inf})}$ and C_{max}
  - LNG (separately for Microgynon+GSK3036656 and Microgynon alone): $AUC_{(0\text{-inf})}$ and C_{max}

- Analyses will be performed on the natural logarithms of $AUC_{(0\text{-}inf)}$ and $C_{max,}$ for EE and LNG, separately using linear mixed effect models with treatment as a fixed effect and subject as a random effect. Effects will be estimated, and CIs will be constructed for the following treatment comparison:
  - Microgynon+GSK3036656 (Treatment Period 3) versus Microgynon alone (Treatment Period 1)
- Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale.

Summary statistics for plasma EE and LNG PK parameter values will be presented by treatment, refer to Section 4.1.1 General Methodology and Section 4.3.1.2.5 Pharmacokinetic Parameter Summary Tables for more details.

4.2.3. Sensitivity analyses

- Not applicable

4.2.4. Additional estimands

- Not applicable

4.3. Secondary Endpoint(s) Analyses

4.3.1. Secondary Pharmacokinetics Endpoints

Secondary PK objectives for this study are to characterize the steady state PK of GSK3036656 in the presence of EE/LNG and to characterize the single dose PK of EE/LNG alone and in the presence of GSK3036656, in healthy female participants.

4.3.1.1. Definition of [endpoint(s)/estimands]

The secondary Pharmacokinetic endpoints and attributes of the estimands are detailed in in Section 1.1

Refer to Section 4.2.1.1 Pharmacokinetic Parameters for more details.

4.3.1.2. Main analytical approach (Pharmacokinetic analysis)

- The analysis for the secondary PK endpoints will be performed for the participants included in the PK analysis set.
- Based on the individual concentration-actual time data the following secondary plasma parameters will be estimated, as data permits (refer to Section 4.2.1.1 Pharmacokinetic Parameters for more details):
  - EE and LNG (separately for Microgynon+GSK3036656 and Microgynon alone): $AUC_{(0-t)}$, T_{max} and $t_{1/2}$
  - GSK3036656 (Microgynon+GSK3036656): $AUC_{(0-\tau)}$, C_{max}, $T_{max,}$ and C_{τ} (Day 8, 10, 12, 15 and 16).
  - GSK3036656 (GSK3036656 alone): Whilst not defined as a secondary endpoint C_{τ} (Day 8, 10 and 12), will also be analysed to aid in interpretation on achievement of steady state.
    - Analyses will be performed on the natural logarithms of GSK3036656 C_{τ}, separately using mixed effect models with day (include Day 8, 10, 12, and 15 pre-dose concentration) as a fixed effect and subject as a random effect.
    - The coefficients of the slopes for the day effect on log scale, along with corresponding 90% confidence intervals, will be used to determine whether steady state was achieved prior to co-administration with EE and LNG.

Summary statistics for plasma EE, LNG, and GSK3036656 PK parameter values will be presented by treatment, refer to Section 4.1.1 General Methodology and Section 4.3.1.2.5 Pharmacokinetic Parameter Summary Tables for more details.

4.3.1.2.1. Pharmacokinetic Concentrations Listings

The PK concentration data will be listed by analyte (EE, LNG and GSK3036656), treatment, day, time and subject for the PK analysis set. Concentration listings will include nominal PK sampling time, actual sampling times, time deviation, and actual relative time, and concentrations. Plasma concentrations below the lower limit of quantification (LLOQ), i.e. non-quantifiable (NQ), will be presented as NQ in the listings and the LLOQ value presented as a footnote.

4.3.1.2.2. Pharmacokinetic Concentration Summary Tables

PK concentration data will be reported according to GSK data standards.

For summary tables, all NQs will be replaced with zero for the calculation of median and mean profile however for geometric mean and geometric CV% NQ values will be replaced by half the LLOQ value, refer [GSK, VQD-REF-015788] Non-Compartmental Analysis of Clinical Pharmacokinetic Data (Section 7 References) for more details. Summary statistics will not be calculated if there are less than 3 participants with quantifiable concentrations at a scheduled timepoint. The statistics will be reported as NC, with the exception of minimum and maximum; minimum will be reported as “NQ” and in case of all NQ values, the maximum will also be reported as NQ.

Data in concentration summary tables will be reported as per IDSL reporting standards.

4.3.1.2.3. Pharmacokinetic Concentration Figures

Comparative linear and semi-logarithmic plots of the median (range) and mean (±SD) concentration-time data for each analyte will be prepared. A reference line indicating LLOQ will be included on plots.

For median and mean profiles, PK concentrations that are NQ will be handled as follows:

- All NQ values will be set to zero except when an individual NQ falls between two quantifiable values, in which case it will be omitted from the calculation of mean or median profiles.
- Measurable concentrations which follow more than one consecutive mid-profile NQ will be set to missing.

Figures will report mean / median values below the LLOQ of the assay, if obtained. For linear plots, zero concentration value(s) will be included in the plot. For log-linear plots, zero concentration value(s) will be assigned a missing value.

Individual concentration-time time will be plotted vs actual sample times, in linear and log-linear scale. For individual linear and log-linear figures NQ values will be substituted as follows:

- NQs at the beginning of a participant profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero. For linear plots, zero concentration values at the beginning of a participant profile will be included in the plot; when using log-linear scale, zero values will be considered missing.
- NQs at the end of a participant profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
- Single NQs which fall between two measurable concentrations will be set to missing.
- Consecutive NQs which fall between measurable concentrations will be set to zero and for individual subject plots
- Measurable concentrations after consecutive NQs will be retained.

4.3.1.2.4. Pharmacokinetic Parameter Listings

The PK parameters will be listed by participant for the PK analysis set. The PK parameters that will be flagged and/or excluded from summary tables and statistical analyses will be flagged and footnoted in the listing with the reason for flagging/exclusion. In case of C_τ concentrations that are NQ, they will be presented as NQ in parameter listings.

4.3.1.2.5. Pharmacokinetic Parameter Summary Tables:

Biostatistics group will consider the derived PK parameters as source data and will use this data without rounding for calculation of PK parameters summary statistics tables.

The PK parameters will be summarized by analyte, treatment, and day for the PK analysis set; for more details, refer to Section 4.1.1 General Methodology.

PK parameters that are not determined (ND) because the planned calculation could not be adequately performed will be assumed missing in both descriptive and statistical analyses and no imputation will be performed.

In case of C_τ concentrations that are NQ, for PK parameter summary tables they will be handled with the same rules described as for concentration summary tables.

Data in PK parameter summary tables will be reported as per IDSL reporting standards.

4.3.2. Secondary Safety endpoint(s)

A secondary objective of this study is to assess that GSK3036656 and Microgynon taken alone or together are safe and well tolerated in healthy female participants of non-childbearing potential. Safety endpoints assess the incidence of safety events occurring during each treatment period.

4.3.2.1. Definition of [endpoint(s)/estimands]

The secondary safety endpoints and attributes of the estimands are detailed in Section 1.1

4.3.2.2. Main analytical approach

All safety analyses will be performed on the Safety Population. Safety data will be presented in tabular format by treatment groups (Microgynon, GSK3036656 and Microgynon+GSK3036656) and summarized descriptively according to GSK's Integrated Data Standards Library. For each treatment group, the denominator for percentages (N) will be the number of participants entering the associated treatment period. No formal statistical analysis of the safety data will be conducted. Unless otherwise specified, available data will be analyzed as collected regardless of intercurrent events that may occur (treatment policy). Missing data will not be imputed.

4.3.2.2.1. Adverse Events (AEs)

An adverse event (AE) is considered study intervention emergent if the AE onset date is on or after study intervention start date for each treatment period. All AE summaries will be based on study intervention emergent events unless otherwise specified. Serious Adverse Event (SAE) summaries will be based on all SAEs reported regardless of whether they meet the definition of study intervention emergent or not. All AE and SAE summaries will be by System Organ Class and Preferred Term (PT) only unless otherwise specified.

Adverse events will be coded using the latest version of the standard Medical Dictionary for Regulatory Activities (MedDRA dictionary) and graded by the investigator according

to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE version 4.03].

In addition to the summary of all AEs, including counts and percentages of participants with any AE, there will be separate summaries for:

- SAEs
- Severe AEs (AEs with a grade of 3 or higher)
- Drug-related AEs
  - Microgynon
  - GSK3036656
- AEs leading to study withdrawal
- AEs leading to study treatment discontinuation
- Most Common (>=5%) Adverse Events by Overall frequency

4.3.2.2.2. Electrocardiograms (ECGs)

ECG data will include heart rate, PR, QRS, QT, and corrected QT (QTc). The QTc data analysis will use the collected values based on Fridericia formula.

ECG values relative to PCI criteria, will be summarized by treatment group, ECG parameter and category.

4.3.2.2.3. Clinical Laboratory Values

The haematology and clinical chemistry laboratory data, relative to PCI criteria, will be summarized by treatment group, laboratory test and category.

4.3.2.2.4. Vital Signs

Vital sign data include temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and respiratory rate.

Vital sign data (SMP, DBP and HR), relative to PCI criteria, will be summarized by treatment group, vital sign and category. Worst-Case Vital Sign Results Relative to Normal Range Post-Baseline Relative to Baseline will also be summarized.

4.4. Other Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.4.1. Additional Safety Assessments

4.4.1.1. Laboratory Data

In addition to laboratory summaries related to PCI criteria, summaries of worst-case grade increase from baseline will be provided for all the lab tests that are gradable by CTCAE v4.03. These summaries will display the number and percentage of subjects with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia separately.

Change from period baseline values of haematology and chemistry will be summarized using descriptive statistics.

For lab tests that are not gradable by CTCAE v4.03, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the “Decrease to Low” categories and the “Increase to High” categories.

Separate summary tables for haematology and chemistry laboratory tests will be produced. Liver function laboratory tests will be included with chemistry lab tests.

Protocol-required routine urinalysis tests will also be summarized descriptively.

An e-DISH plot of maximum post baseline total bilirubin versus maximum post baseline ALT will be created.

4.4.1.2. Vital Signs

In addition to above summaries of PCI criteria, summary statistics for all results and changes from period baseline will be provided by day of assessment for each test.

4.4.1.3. ECG

ECG findings are defined from best to worst as: “normal”, “abnormal - not clinically significant”, and “abnormal - clinically significant”. The worst finding will be selected at each time point when there is repeat ECG. All ECG findings will be summarized by days.

The QTc data analysis will use the collected values based on Fridericia formula.

The QTc values based on Fridericia formula will be rounded to the integer and the values will be categorized into the following CTCAE grade and ranges: Grade 0 (<450 msec), Grade 1 (450-480 msec), Grade 2 (481-500 msec), and Grade 3 (≥501 msec). Summaries of grade increase will be provided. These summaries will display the number and percentage of subjects with any grade increase, increase to grade 2 and increase to grade 3 for the worst-case post-baseline only. Missing baseline grade will be assumed as grade 0.

The changes in QTc values will be categorized into the clinical concern ranges which are specific to changes in QTc: 31-60 and >60 msec. A summary of change in QTc value will display the number and percentage of subjects with a change within each range for the worst-case post-baseline only. Subjects with missing baseline values will be excluded from this summary.

A figure plotting the baseline QTc and the worst-case post-baseline values will be produced for each period. The figure will have reference lines at 450, 480 and 500 msec for both the x and y axes. There will be diagonal reference lines at equality (i.e. a 45-degree line), at equality plus 30 msec, and at equality plus 60 msec.

4.5. Other Analyses

4.5.1. Subgroup analyses

There will be no subgroup analysis planned.

4.5.2. Analyses to Support Regional Submission

There will be no regional submission planned.

4.6. Interim Analyses

There will be no interim analysis performed.

4.7. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the original version of protocol (Dated: 06 Nov 2023).

5. SAMPLE SIZE DETERMINATION

From the Adjusted gMean ratios and 90% CIs reported in the historical reference [Vonk, 2022], CVw(%) has been obtained using the CVfromCI function from POWERTOST package in R software. The R CVfromCI function uses methodology described in Section 5.1.1. CVw(%) values of 11.5%, 12.5%, 14.9%, 17.9% for EE $AUC_{(0\text{-inf})}$, EE C_{max}, LNG $AUC_{(0\text{-inf})}$ and LNG C_{max} respectively were calculated (Table 4). The largest CVw for the analytes and parameters is 17.9%.

Table 4: Intrasubject Coefficient of Variability (CVw%) for PK Parameters of EE and LNG

Historical Reference	Analyte	Parameter	n	Adjusted gMean ratio	(90% CI)	CVw%
Madelon C. Vonk, et al.	EE	$AUC_{(0\text{-}inf)}$	15	101.2	(94.0, 109.1)	11.5
		C_{max}	15	116.7	(107.6, 126.5)	12.5
	LNG	$AUC_{(0\text{-}inf)}$	15	88.1	(80.0, 97.0)	14.9
		C_{max}	15	100.9	(89.9, 113.2)	17.9

The true ratio of Microgynon+GSK3036646 versus Microgynon alone, is assumed to be 1.0 for all 4 comparaisons, EE $AUC_{(0\text{-}inf)}$, EE C_{max}, LNG $AUC_{(0\text{-}inf)}$ and LNG C_{max}. In order to calculate the joint power for the four comparisons, a conservative between parameter correlation of 0.6 has been assumed; of note considering correlation of 1.0 would increase the joint power by less than 1% for the same sample size. Based on these assumptions an evaluable sample size of 16 provides 92% (Table 5) joint power to ensure that the 90% CIs for the geometric mean ratios for all parameters lie within the range of 0.8 to 1.25. To account for an expected 20% rate of non-evaluable participants, approximately 20 participants will be enrolled to ensure at least 16 participants provide evaluable data in both test and reference periods.

Table 5: Estimated Power and Sample Size Table

Analyte	Parameter	n	CVw%	Power
EE	$AUC_{(0\text{-}inf)}$	16	11.5	99.98
	C_{max}	16	12.5	99.87
LNG	$AUC_{(0\text{-}inf)}$	16	14.9	98.66
	C_{max}	16	17.9	92.73
Joint Power for all 4 comparisons		16		91.91

Table 6: provides the 90% CIs for a range of possible observed ratios, for each assumed CVw%, with 16 estimated participants.

Table 6: Sample Size: Estimated Precision for Different Observed Effects

Analyte	Parameter	n	CVw%	Observed Ratio	Estimated 2-sided 90% CI
EE	$AUC_{(0\text{-}inf)}$	16	11.5	0.90	(0.84, 0.97)
				1.0	(0.93, 1.07)
				1.10	(1.02, 1.18)
	C_{max}	16	12.5	0.90	(0.83, 0.97)
				1.0	(0.93, 1.08)
				1.10	(1.02, 1.19)

Analyte	Parameter	n	CVw%	Observed Ratio	Estimated 2-sided 90% CI
LNG	$AUC_{(0\text{-}inf)}$	16	14.9	0.90	(0.82, 0.99)
				1.0	(0.91, 1.10)
				1.10	(1.00, 1.21)
	C_{max}	16	17.9	0.90	(0.81, 1.01)
				1.0	(0.90, 1.12)
				1.10	(0.98, 1.23)

5.1.1. Calculation of CVw from CI:

The point estimate (PE, adjusted geometric mean) and the confidence interval limits have been obtained from historical reference.

The number of subjects / sequence (example 2×2 cross-over), is obtained as follows:

- If total sample size (N) is an even number, assume n1= n2= ½N
- If N is an odd number, assume n1= ½N+ ½, n2= ½N–½ (not n1= n2 = ½N)

The difference between the CL and the PE can be calculated as follows on the log-scale (using the CL which is given with the highest number of significant digits.

$$\Delta_{CL} = \ln\ (CL_{hi}) - \ \ln(PE)\ \ |or|\ \Delta_{CL} = \ln(PE) - \ln\ (CL_{lo})$$

The Mean Square Error (MSE) is then calculated as follows:

$$MSE = 2\left(\frac{\Delta_{CL}}{\sqrt{\left(\frac{1}{n1}+\frac{1}{n2}\right)} \times t_{(1-2\propto,n1+n2-2\ )}}\right)^2$$

And finally, the CVw is calculated from the MSE:

$$CVw\% = 100\ \times \sqrt{(e^{MSE} - 1)}$$

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Enrolled Analysis Set. A summary of the number of participants in each of the participant level analysis set will be provided.

Screen failure participants will be summarized based on Screened analysis set.

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have completed the scheduled study intervention, or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, height/weight at screening and race will be summarized with descriptive statistics based on the Enrolled Analysis Set.

Past medical conditions and current medical conditions as of screening will be summarized respectively. Substance use, including smoking history, tobacco use, alcohol and drug history will be summarized.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised in the protocol deviations ADaM dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using both the GSK Drug and WHO Drug dictionaries. However, the summary will be based on GSK Drug dictionary only. The summary of concomitant medications will be provided by ingredient, i.e. multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients. The summary will be created using ingredient base names, i.e. ingredients with the same base name but different salt will appear under one base name in the summary. Anatomical Therapeutic Chemical (ATC) classifications will not appear in the summary.

For classifying study phase for concomitant medication, use the following definition.

Medication Classification	Definition
Prior	If medication end date is not missing and is on or prior to the date of the screening visit
Concomitant	Any medication that is not a prior
Please refer to Section 6.2.8: for handling of partial end dates for concomitant medication.	

6.1.5. Study Intervention Compliance

A summary of treatment compliance of Microgynon and GSK3036656 based on the exposure data will be produced. Overall compliance categories will also be summarized using descriptive statistics, refer to OPS for more details.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Change from Baseline

The change from baseline will be calculated by subtracting the period baseline values from the subsequent post-baseline values. If either the baseline or post-baseline value is missing, the change from baseline is set to missing as well.

6.2.2. Pharmacokinetic Parameters

For the purposes of calculating summary statistics and for statistical analysis, all PK parameters with the exception of T_{max}, $t_{1/2}$ will be $\log_e$ transformed.

Between subject coefficient of variation $\%CV_b$ will be calculated according to the following methods:

Untransformed Data : $\frac{SD}{mean} \times 100$,

Transformed Data : $\sqrt{e^{S^2} - 1} \times 100$,

where S is the SD of the $\log_e$ transformed data, S^2 = variance of $\log_e$ transformed data.

6.2.3. Criteria for Potential Clinical Importance

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE v4.0.3] will be used to assign grades to the relevant laboratory parameters, blood pressure and QTc.

In addition, the following criteria will be used to flag potential clinical importance (for laboratory data, ECG parameters and vital signs):

6.2.3.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Change from Baseline	Decrease of 0.075	
Haemoglobin	g/L	Male	75	180
		Female	75	180
		Change from Baseline	Decrease of 25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
Red blood cell (RBC) count	million/mcL		4.2	6.1
Mean corpuscular volume (MCV)	fl.		80	100
Mean corpuscular hemoglobin (MCH)	picograms (pg)		27.5	33.2
%Reticulocytes	%		0.5	2
Monocytes	%		2	8
Eosinophils	%		1	4
Basophils	%		0.5	1

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Calcium	mmol/L		2	2.75
Creatinine	%	Change from Baseline		Increase of 30%
Glucose	mmol/L		3	11
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Direct bilirubin	mg/dl		<0.3	<0.3
Total protein	g/dl		6	8.3
Blood urea nitrogen (BUN)/Urea	mg/dl		5	20

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Creatine phosphokinase (CPK)	mcg/l		10	120
Homocysteine	µmol/L		4	14
Antiphospholipid antibodies	MPL		0	39.9
Sex hormone binding globulin (SHBG)	nmol/L		18	144

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT	IU/L	High	≥ 3x ULN
AST	IU/L	High	≥ 3x ULN
T Bilirubin	µmol/L	High	≥ 1.5x ULN

ULN = Upper Limit of Normal; ALT=Alanine Aminotransferase; AST=Aspartate Aminotransferase;
T. Bilirubin=Total Bilirubin

6.2.3.2. ECG Values

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			
Absolute QTcF Interval	msec		>450
Absolute PR Interval	msec	< 110	>220
Absolute QRS Interval	msec	< 75	>110
Change from Baseline			
Increase from Baseline QTcF	msec		>60

QTcF=QT Interval corrected for heart rate (Fridericia); PR=Electrocardiographic PR Interval

6.2.3.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	>160
Diastolic Blood Pressure	mmHg	< 45	>100
Heart Rate	bpm	< 40	>110
Respiratory Rate	Breaths/min	10	28
Temperature	Degrees C	35.0	37.9

6.2.4. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Treatment period 1 ranges from Day 1 dose to Day 4 predose, similarly treatment period 2 ranges from Day 4 dose to Day 15 predose and treatment period 3 ranges from Day 15 dose until Day 18.

6.2.5. Study Day, Reference Dates and Period Day

The reference date is the period 1 Microgynon start date and will be used to calculate study day for safety and PK measures.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Reference Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Reference Date + 1

Period day is calculated as the number of days from first treatment start date for the respective period (Period Treatment Start Date):

- Assessment Date = Missing → Period Day = Missing
- Assessment Date < Period Treatment Start Date → Period Day = Assessment Date – Period Treatment Start Date
- Assessment Data ≥ Period Treatment Start Date → Period Day = Assessment Date – (Period Treatment Start Date) + 1

6.2.6. Assessment Window

- Actual times will be used in the derivation of PK parameters and in the individual concentration-time plots. Planned times will be used in the descriptive summaries and in mean and median plots.
- PK concentration listings shall have both the planned and actual times
- Planned time will be used for all other analysis.
- For data summaries by visit, the nominal visit description will be used. The unscheduled assessment will be listed.

6.2.7. Multiple measurements at One Analysis Time Point

When triplicate ECG assessments and triplicate Vitals Sign assessment are taken, mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. This will apply to both baseline and post baseline assessments.

For multiple assessments of the lab tests taken on a study day, the worst case will be used.

6.2.8. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events.
Adverse Events	The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. Unless available data demonstrate that the AE could not have started during treatment period 2, AEs with partial start dates will be assumed to have started in treatment period 2. This is due to participants being in-patients within the clinic during treatment periods 1 and 3, thus partial AE start dates during these periods are highly unlikely. The following rules will be followed: Let • SM_P1=start month of period 1 (month of first treatment in period 1) • SM_P2=start month of period 2 (month of first treatment in period 2) • SM_P3=start month of period 3 (month of first treatment in period 3) • EM_P1=end month of period 1 (month of day prior to first treatment in period 2) • EM_P2=end month of period 1 (month of day prior to first treatment in period 3) • SM_AE=start month of AE • EM_AE=end month of AE • If SM_P1>SM_AE THEN AE start date=1st of the month • If AE end date is complete:

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>1. If EM_P1 ≥ SM_AE ≥ SM_P1 AND
Period 2 start date > AE end date ≥ Period 1 start date
THEN AE start date = start date of treatment period 1
2. If EM_P2 ≥ SM_AE ≥ SM_P2 AND
AE end date ≥ Period 2 start date
THEN AE start date = start date of treatment period 2
3. If SM_AE ≥ SM_P3 AND
SM_AE ≠ EM_P2 AND
AE end date ≥ Period 3 start date
THEN AE start date = start date of treatment period 3
• If AE end date has the day missing:
1. If EM_P1 ≥ SM_AE ≥ SM_P1 AND
SM_P2 > EM_AE ≥ SM_P1
THEN AE start date = start date of treatment period 1
2. If EM_P2 ≥ SM_AE ≥ SM_P2 AND
EM_AE ≥ SM_P2
THEN AE start date = start date of treatment period 2
3. If SM_AE ≥ SM_P3 AND
SM_AE ≠ EM_P2 AND
EM_AE ≥ SM_P3
THEN AE start date = start date of treatment period 3
• Missing Stop Day: Last day of the month will be used
• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
• If month and year of start date = month and year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
– Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
• If year of start date = year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.</td></tr>
</table></td></tr>
</table>

Element	Reporting Detail	
		– Else set start date = study. intervention start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation
Age	• Age will be calculated based on the Screening Visit date • GSK standard IDSL algorithms will be used for calculating age where date of birth (DOB) will be imputed as follows: – Any participant with a missing day will have this imputed as day '15'. – Any participant with a missing day and month will have this imputed as '30th June'. – Birth date will be presented in listings as 'YYYY'. – The Date of Birth will be assumed to be 30 June YYYY and age will be calculated at screening visit using this assumed date of birth.	

6.2.9. List of Abbreviations

Abbreviation	Description
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area under concentration-time curve
$AUC_{(0\text{-inf})}$	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
BMI	Body Mass Index
C	Complement
CI	Confidence Interval
C_{max}	Maximum Observed Concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CSR	Clinical Study Report
Ct	Trough Concentration
CV	Coefficient of Variation

Abbreviation	Description
DDI	Drug Drug Interaction
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EE	Ethinyl Estradiol
GSK	GlaxoSmithKline
ICF	Informed consent form
LNG	Levonorgestrel
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of participants with available data
NCA	Non-compartmental Analysis
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NONMEM	Non-linear Mixed-effects Modelling
NQ	Non-quantifiable
OPS	Output and Programming Specification
PCI	Potential Clinical Importance
PK	Pharmacokinetic
PT	Preferred Term
QTC	Corrected QT Interval
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class

Abbreviation	Description
T_{max}	Time at which Cmax is Observed
WBC	While Blood Cell
WHO	World Health Organisation

6.2.10. Trademarks

Trademarks of the [GlaxoSmithKline] Group of Companies
None

Trademarks not owned by the [GlaxoSmithKline] Group of Companies
NONMEM
SAS
WinNonlin

7. REFERENCES

D. J Shhuirmann. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm 1987 Dec;15(6):657-80. doi: 10.1007/BF01068419.

Vonk MC, Guillén-Del-Castillo A, Kreuter M, et al. A Drug-Drug Interaction Study to Investigate the Effect of Nintedanib on the Pharmacokinetics of Microgynon (Ethinylestradiol and Levonorgestrel) in Female Patients with Systemic Sclerosis-Associated Interstitial Lung Disease. Eur J Drug Metab Pharmacokinet. 2022 Jan;47(1):81-89.

U.S. Department of Health and Human Services; Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov) Version 5.0 Published: November 27, 2017

GSK, VQD-REF-015788, Veeva Vault - Non-Compartmental Analysis of Clinical Pharmacokinetic Data; Version 1.0, Effective: 14 Sep 2022: 3-32.