CLINICAL STUDY PROTOCOL

Primary Study Intervention(s)	GSK3036656
Other Study Intervention(s)	Microgynon
Study Identifier	220104
EU CT Number	2023-507839-38-00
Approval Date	23 Apr 2024
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.
Compound Number/Name	GSK3036656
Brief Title	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	GSK Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
Sponsor signatory	Amanda Oliver Head of Clinical Development, Global Health Medicines R&D

Medical monitor name and contact can be found in local study contact information document

Protocol Investigator Agreement

I agree:

- **To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.**
- **To assume responsibility for the proper conduct of the study at this site.**
- **That I am aware of and will comply with GCP and all applicable regulatory requirements.**
- **That I will comply with the terms of the site agreement.**
- **To comply with local bio-safety legislation.**
- **To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.**
- **To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.**
- **To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.**
- **To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.**
- **To ensure that no clinical samples (including serum samples) are retained on-site or elsewhere without the approval of GSK and the express physical informed consent of the participant and/or the participant's LAR.**
- **To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).**
- **To co-operate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.**
- **To have control of all essential documents and records generated under my responsibility before, during, and after the study.**
- **That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.**

Hence, I:

- **Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).**
- **Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.**
- **Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.**
- **Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.**

Study identifier	220104
EU CT number	2023-507839-38-00
Approval date	23 Apr 2024

Title

Investigator name _____

Signature _____

Date of signature

(DD Month YYYY) _____

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 01	23 Apr 2024
Original Protocol	06 November 2023

Amendment 1

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This study will only recruit women of non-childbearing potential, with the majority of them being postmenopausal. Following an extensive review of the database that includes potential participants, it has been recognized that the majority of these women may be taking medication for concurrent conditions that are common in postmenopausal women. To minimise risk to participants by asking them to stop any medication that they require to manage these concurrent conditions, it has been determined that the use of concomitant omeprazole or levothyroxine will be permitted during the study. This would not impact any of the pharmacokinetic endpoints in the study, providing participants have been on a stable dose for at least one month prior to Treatment Period 1, and the dose is maintained throughout the study. In addition, minor typographical errors and inconsistencies have been corrected.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Assessments	Note added to clarify that outpatient visits would take place on Days 8,10 and 12.	Added for better understanding
Section 1.3, Schedule of Assessments, Physical examination	Added weight to list of assessments included as part of full and brief physical exam, for consistency with Section 8.3.1	Added for better understanding
Section 1.3, Schedule of Assessments, Serial PK for EE/LNG	Note added to clarify that serial PK predose sample for EE/LNG should be taken within 30 minutes prior to dose administration. Also, for any unscheduled visit, a predose EE/LNG PK sample should only be collected during Treatment Periods 1 or 3.	Added for better understanding
Section 1.3, Schedule of Assessments, trough GSK3036656 PK	For any unscheduled visit, predose GSK3036656 PK sample should only be collected during Treatment Periods 2 or 3.	Added for better understanding

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion criteria #2, Type of participants and disease characteristics	Clarified that participants should be healthy and compensated. Added a time period of at least 30 days prior to Treatment Period 1 for discontinuation of any HRT to allow confirmation of postmenopausal status before study enrollment. Also, clarified that, in women with less than 12 months of amenorrhea, the FSH measurement should be repeated and confirmed within the Screening period.	To allow participants to be treated with protocol-permitted medications if required. To ensure any prior HRT use has washed out prior to baseline PK assessments, and to confirm timing for any repeat FSH measurement.
Section 5.2.3, prior/concomitant therapy, exclusion criterion #1	Clarification that levothyroxine and omeprazole may also be used during the study providing the participant has been on a stable dose for at least one month prior to the start of Treatment Period 1 and they maintain the same dose throughout the study. The dose of Microgynon should be administered at least one hour after the dose of levothyroxine or omeprazole. Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor.	In WONCBP, the majority of this population are postmenopausal. These women are healthy but be compensated and require use of concomitant medication for common concurrent conditions. Use of levothyroxine and omeprazole and any other concomitant medications approved by the medical monitor will not impact the PK endpoints in this study.
Section 5.2.5, Diagnostic Assessments, Exclusion criteria #18	Footnote 1 expanded to confirm that a QTcF interval between 450 and 460msec can be rechecked by ECG within 30 minutes to verify eligibility	To provide clarification to the investigator on when a repeat ECG should be considered at screening
Section 6.8, Prior and Concomitant Therapy	Clarification that levothyroxine and omeprazole may also be used during the	In WONCBP, the majority of this

Section # and Name	Description of Change	Brief Rationale
	study providing the participant has been on a stable dose for at least one month prior to the start of Treatment Period 1 and they maintain the same dose throughout the study. The dose of Microgynon should be administered at least one hour after the dose of levothyroxine or omeprazole.	population are postmenopausal. These women are healthy but be compensated and require use of concomitant medication for common concurrent conditions. Use of levothyroxine and omeprazole and any other concomitant medications approved by the medical monitor will not impact the PK endpoints in this study.
Section 7.1.2, QTc stopping criteria	Added reference to Section 8.3.3, Electrocardiograms, for clarification on the time period over which any repeat ECGs should be performed.	Clarification for the investigator
Section 7.1.3, Haematology stopping criteria	Added clarification that second sample should be taken within 24 hours of the first sample	Clarification for the investigator
Section 7.2, Participant discontinuation/withdrawal from the study	Deleted the sub-reasons of “Unsolicited AE” and “Solicited AE” from Table 2	These are not applicable for this study.
Section 10.4, Appendix 4, Liver safety: suggested actions and follow-up assessments	Table title corrected to read “Liver safety: Required and suggested actions and follow-up assessments” and missing table footnotes have been added.	Clarification for the investigator.
Section 8.3.5, Pregnancy testing	Deletion of option to only perform pregnancy test in females with doubt about reproductive status as protocol requires that all participants must perform a highly sensitive blood or urine pregnancy test before the administration of any dose of study intervention	Correction of inconsistency between this section and the schedule of asssessments
Section 6.4, Study intervention compliance	Added text to state that a participant diary will be provided to capture dosing compliance.	Additional detail for investigator
Section 6.1, Table 4	Update NIMP by AxMP	To reflect a change in

Section # and Name	Description of Change	Brief Rationale
		nomenclature to ensure consistency across all study documentation

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
AUC	Area under the Plasma Concentration Time Curve
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum Observed Plasma Concentration
COC	Combined Oral Contreceptive
CONSORT	Consolidated Standards of Reporting Trials
CRF/eCRF	Case report form/electronic case report form
CSR	Clinical study report
Ct	Trough Concentration
CV	Cardiovascular
DDI	Drug Drug Interaction
ECG	Electrocardiogram
ED	Early discontinuation
EE	Ethinyl Estradiol
EMA	European Medicines Agency
EoS	End-of-study
FDA	Food and Drug Administration, United States of America
FSFV	First subject first visit
FSH	Follicle Stimulating Hormone
GCP	Good clinical practices
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus

Abbreviation	Definition
HIV	Human Immunodeficiency Virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICSR	Individual case safety reports
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
LNG	Levonorgestrel
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
Mtb	*Mycobacterium tuberculosis*
NIMP	Non-investigational medicinal product
NOAEL	No observed adverse effect level
NQ	Non-quantifiable
OC	Oral contraceptive
od	Once a day
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PK	Pharmacokinetic
QTc	Corrected QT Interval

Abbreviation	Definition
QTL	Quality tolerance limit
SAE	Serious adverse event
SAP	Statistical analysis plan
SERM	Safety Evaluation and Risk Management
SHBG	Sex hormone binding globulin
SmPC	Summary of product characteristics
SoA	Schedule of activities
SRT	Safety Review Team
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Tmax	Time at which Cmax is Observed
UNITE4TB	Academia and Industry United Innovation and Treatment for Tuberculosis
WBC	White blood cell
WHO	World Health Organisation
WOCBP	Woman of childbearing potential
WONCBP	Woman of nonchildbearing potential

Term	Definition
Adverse Drug Reaction (ADR)	An adverse event where a causal relationship between a medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. a. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorized.
Auxillary Medicinal Product (AxMP) a. Authorized AxMP b. Unauthorized AxMP	Medicinal products used in the context of a clinical trial but not as investigational medicinal products, such as medicinal products used for background treatment, challenge agents,, rescue medication, or used to assess end-points in a clinical trial. Auxillary medicinal products should not include concomitant medications, that is medicationsunrelated to the clinical trial and not relavant for the design of the clinical trial. Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. 1. Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC. a. Medicinal product not authorized in accordance with Regulation (EC) No 726/2004 1. Safety reporting for unauthorised auxiliary medicinal products will follow the same processes and procedures as SUSAR safety reporting

Term	Definition
Background treatment	Type of medicinal product administered to each of the clinical trial participant, regardless of randomization group, to treat the indication that is the object of the study. Background treatment is generally considered to be the current standard care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared with an active comparator or with placebo plus background treatment
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Challenge agents	A product given to trial participants to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed.
Co-administered (concomitant) products	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Comparator	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).

Term	Definition
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Investigational medicinal	An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form. Medicinal products with a marketing authorization are IMPs when they are to be used as the test substance, reference substance, or comparator in a clinical study, provided the requirement(s) in the definition is/are met.
Investigational Product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication , or when used to gain further infirmation about the authorised form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions
Medicinal products used to assess end-points	A product given to the participant in a Clinical Trial as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.

Term	Definition
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Rescue Medication	Medicines identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

Term	Definition
Standard of Care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. 1. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: “Study intervention” and “study treatment” are used interchangeably unless otherwise specified.
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
SUSAR	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All ADRs that are both serious and unexpected are subject to expedited reporting.

1. PROTOCOL SUMMARY

1.1. Synopsis

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.

Brief Title: 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.

Rationale: Refer to Section 2.1.

Objectives, Endpoints, and Estimands: Refer to Section 3.

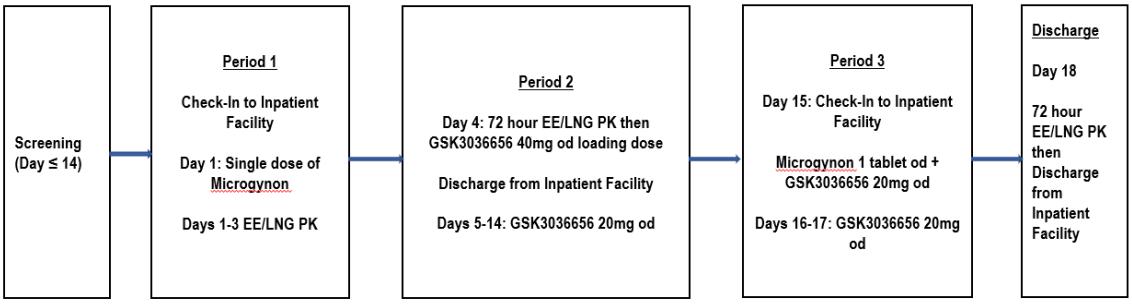
Overall Design: Refer to Section 4.1.

Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Study Schema

Figure 1 Study design overview



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

1.3. Schedule of activities (SoA)

The Schedules of Activities are presented in the following table.

Table 1 Schedule of Activities

Procedure	Screening	Treatment Period 1			Treatment Period 2		Treatment Period 3			Early Withdrawal	Unscheduled	Notes
	D -14 to -1	D 1	D 2	D 3	D 4	D 5-14	D 15	D 16-17	D 18			
Outpatient visit◦	X					X						Outpatient visits would occur on Days 8, 10 and 12
Informed consent•	X											Refer to Section 10.1.3 for details.
Inclusion and exclusion criteria•	X											Refer to Sections 5.1and 5.2 for Inclusion and Exclusion criteria.
Demography•	X											Refer to Section 8.1.1 for more information.
Admit to clinic and inpatient stay◦		X◦◦	X	X			X◦◦	X	X			
Discharge from clinic◦					X*				X			Discharge after 72 hour EE/LNG PK sample taken. *Participants progress immediately from the end of Treatment Period 1 to Treatment Period 2, with no washout required in between
Evaluation of childbearing potential◦	X											Evaluation of childbearing potential includes: – Menstrual history (to confirm no menses) – Documentation of past surgical history – FSH test to confirm ovarian reserve status (for participants who were not surgically sterilized)

Procedure	Screening	Treatment Period 1			Treatment Period 2		Treatment Period 3			Early Withdrawal	Unscheduled	Notes
	D -14 to -1	D 1	D 2	D 3	D 4	D 5-14	D 15	D 16-17	D 18			
Pregnancy Test•		X							X	X	X	A highly sensitive pregnancy test (urine or serum) to be performed on Day 1 prior to dosing with Microgynon and again on Day 18 prior to discharge.
Medication/drug/alcohol history◦	X											Refer to Section 8.1.2 for more information.
Past and current medical conditions•	X											
Drug, alcohol, and cotinine screen◦	X											See Table 10 for specific tests to be performed.
HIV, hepatitis B and C◦	X											
Sex hormone binding globulin (SHBG)◦	X											
Physical examination◦	X*	X			X				X	X		Full physical exam at Screening* and brief physical examination at all other scheduled timepoints. A full physical examination includes at a minimum, weight, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Brief exam includes, at a minimum, weight, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Procedure	Screening	Treatment Period 1			Treatment Period 2		Treatment Period 3			Early Withdrawal	Unscheduled	Notes
	D -14 to -1	D 1	D 2	D 3	D 4	D 5-14	D 15	D 16-17	D 18			
Vital signs•	X	X			X		X		X	X	X	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. On days where the following assessments are done the order should be vital signs before blood draws for PK or safety assessments.
12-Lead ECG•	T	X			X		X		X	X	X	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. On days where the following assessments are done the order should be: ECGs before blood draws for PK or safety assessments.
Meals at inpatient facility•		X	X	X	X		X	X	X			Meals will be served during in patient stay across days 1 to 4 and 15 to 18. Water is permitted as desired.

Procedure	Screening	Treatment Period 1			Treatment Period 2		Treatment Period 3			Early Withdrawal	Unscheduled	Notes
	D -14 to -1	D 1	D 2	D 3	D 4	D 5-14	D 15	D 16-17	D 18			
Laboratory assessments (haematology, chemistry, urinalysis tests) •	X	X			X		X		X	X	X	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. See Table 10 for specific tests to be performed.
Echocardiogram	X											Screening echocardiogram to be performed at Screening (day -14 to -1). Echo should be repeated on participants with changes in clinical status warranting a follow up echo in the opinion of the investigator.
Study treatment: Microgynon (0.03 mg EE/ 0.15 mg LNG) •		X					X					Single dose of Microgynon on Day 1 of Treatment Period 1 and day 15 of Treatment Period 3.
Study treatment: GSK3036656 20 mg od•					X*	X	X	X				*Loading dose of GSK3036656 40 mg on Day 4

Procedure	Screening	Treatment Period 1			Treatment Period 2		Treatment Period 3			Early Withdrawal	Unscheduled	Notes
	D -14 to -1	D 1	D 2	D 3	D 4	D 5-14	D 15	D 16-17	D 18			
Serial PK sampling: EE and LNG•		X	X	X	X		X	X	X		X*	PK samples collected predose and after dosing with Microgynon at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24, 48 and 72 hours relative to Day 1 dosing of Treatment Period 1 and Day 15 dosing of Treatment period 3. The predose sample to be taken within 30 minutes prior to dose administration. Blood is drawn for PK analysis at 0.25-4 hours ±5 minutes after dosing. Blood is drawn for PK analysis at 6-12 hours ±20 minutes after dosing. Blood is drawn for PK analysis at 24-72 hours ±60 minutes after dosing The Day 72 h sample must be taken prior to GSK3036656 dosing on Day 4. *At any unscheduled visit, only collect a predose EE/LNG PK sample if it occurs during Treatment Periods 1 or 3.
Trough PK sampling: GSK3036656•						X					X*	Samples to be taken 24 hours post the previous dose and within 30 minutes prior to the next dose of GSK3036656 on Days 8, 10 and 12. * At any unscheduled visit, only collect a GSK3036656 PK sample if it occurs during Treatment Periods 2 or 3.

Procedure	Screening	Treatment Period 1			Treatment Period 2		Treatment Period 3			Early Withdrawal	Unscheduled	Notes
	D -14 to -1	D 1	D 2	D 3	D 4	D 5-14	D 15	D 16-17	D 18			
Serial PK sampling: GSK3036656•							X	X				PK samples collected predose (GSK3036656) and after dosing at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours relative to Day 15 dosing in Treatment Period 3. The Day 15 24 h sample must be taken prior to GSK3036656 dosing on Day 16. The predose sample to be taken within 30 minutes prior to dose administration. Blood is drawn for PK analysis at 0.5-4 hours ±5 minutes after dosing. Blood is drawn for PK analysis at 6-12 hours ±20 minutes after dosing. Blood is drawn for PK analysis at 24 hours ±1 hours after dosing.
AE review•		←==========							==========→			AEs collected from the start of study intervention until day 18 of Treatment Period 3.
SAE review•	←==========								==========→			SAEs collected from the signing of the ICF until Day 18 of Treatment Period 3.
Concomitant medication review•		←==========							==========→			

AE = adverse event; D = Day; ECG = electrocardiogram; EE = ethinyl estradiol; LNG = levonorgestrel; PK = pharmacokinetic; SAE = serious adverse event.
Assessments performed predose on Day 4 of Treatment Period 2 were considered baseline for GSK3036656 dosing.

● Is used to indicate a study procedure that requires databasing (either in eCRF, laboratory or other third-party vendor).
○ Is used to indicate a study procedure that does not require databasing (in source only).
○○ Participants may be admitted the night before Day 1 and Day 14, but study procedures will commence on the morning of Day 1 and morning of Day 15.

2. INTRODUCTION

2.1. Study rationale

GSK3036656 is being developed for TB and a Phase 2B/C regimen building and duration ranging study conducted under the UNITE4TB consortium is planned to start in 4Q2023.

GSK3036656 was teratogenic in rats and rabbits. In rats (most sensitive species) the NOAEL for embryofetal effects was CCI mg/kg/day, with an exposure (AUCtlast) at this dose level of CCI µg.h/mL which is at parity with the CCI mg clinical dose. Precautions will therefore be required prior to starting WOCBP on GSK3036656. The nature of these precautions will be subject to discussion with the external TB community, patient groups and regulators at the time of file.

Of the 10.6 million TB patients diagnosed each year, approximately twenty percent are WOCBP. Therefore, there exists the potential for broad use and impact of GSK3036656 containing regimens regardless of any label restrictions. In addition, several potential combination TB drugs carry label restrictions for pregnancy and WOCBP, whilst TB itself poses risks in pregnancy to both the mother and the developing foetus.

Based on the in-vitro data, GSK3036656 does not exhibit any induction or inhibition of key cytochrome P450s (CYPs). To minimize any risk due to the teratogenicity observed in rats and rabbits, ongoing and planned clinical development studies including GSK3036656 currently mandate use of non-user dependent contraception (intrauterine contraceptive device, or implantable or depot injectable progesterone) during the study for female study participants of childbearing potential, or recruitment of women of non-childbearing potential. In addition, highly sensitive pregnancy testing must be performed prior to dosing and throughout the studies. The recommended population to be enrolled into clinical drug interaction studies with combined oral contraceptives are postmenopausal and premenopausal females (if studying PD endpoints) [FDA, 2023] Taking into account the unknown DDI interaction between GSK3036656 and Microgynon, contraception should not be considered as effective, therefore enrollment of only WONCBP in this study is a safety pregnancy-specific risk minimization measure [EMA, 2022].

FDA guidance states that if an investigational drug shows any nonclinical reproductive and developmental toxicity, then an OC clinical DDI study waiver would be unlikely to be granted by regulators, meaning that an OC DDI study would be required for GSK3036656 as part of the marketing authorization submission. In addition, as non-user-dependent contraceptive measures may not be available or culturally acceptable in some of the participating countries in the Phase 2B/C study, there is a risk that recruitment will be negatively affected, and WOCBP who need access to TB treatment will not be eligible for the study. Hence the opportunity of user dependent contraception with an OC could exclude fewer WOCBP with TB by offering more choice.

Conducting an OC DDI study in parallel with Phase 2B could be beneficial as this could potentially generate data that could allow the use of less restrictive contraceptive measures during Phase 2C, which would have a positive impact on recruitment. There are other regimens within the study that do not require these stringent contraception restrictions and these are only being imposed because of GSK656-containing regimens.

CCI [redacted]

2.2. Background

TB remains a concerning health problem, with *Mycobacterium tuberculosis* (Mtb) now causing more deaths than HIV/ AIDS. In 2021, 1.6 million people died from TB, making it the leading bacterial infectious disease killer in the world [EMA, 2022;FDA, 2023; WHO, 2022] The current long-standing first-line antituberculosis agents are relatively ineffective in controlling the TB epidemic in high-burden countries. Treatment takes 4-18 months to complete (depending on drug sensitivities of the isolated strain and availability of shorter regimens) and is associated with side effects resulting in poor compliance which leads to treatment failure and an increased likelihood of developing drug-resistance.

The development of new drug combinations that are effective against drug-resistant strains of Mtb, and that have the potential to shorten the duration of TB treatments offers the hope of tackling the TB pandemic. A new treatment regimen requires at least three different drugs to which no clinical resistance exists. This highlights the need for the development of additional new chemical entities that strike an appropriate balance between antituberculosis activity and safety profiles, a balance that will enable new future drug combinations that make the optimal use of previously developed entities.

GSK3036656 is a compound with a novel mechanism of action under development for the treatment of TB. It suppresses protein synthesis in Mtb by selectively inhibiting the enzyme Leucyl t-RNA synthetase.

CCI [redacted] and the drug shows potent activity in animal models, resulting in very low predicted efficacious human doses. *In vitro* data show that the risk of drug-drug interactions with GSK3036656, either as perpetrator or victim, is low. These factors make GSK3036656 an attractive potential candidate for the treatment of tuberculosis.

Conducting this OC DDI study will provide data showing if there is any pharmacokinetic effects of GSK3036656 on a combined oral contraceptive, which, in conjunction with cultural sensitivities in specific regions, will help inform future studies on suitable contraceptive measures to be used.

A description of the chemistry, nonclinical and clinical data generated to date for GSK3036656 is provided in the IB.

2.3. Benefit/risk assessment

Data described in the IB support the safety profile of the selected dose of GSK3036656 in patients with newly-diagnosed TB and healthy volunteers. The known potential risks associated with GSK3036656 can be appropriately mitigated by the careful selection of study participants and the proposed safety monitoring procedures. Routine safety and tolerability will be evaluated from reported AEs, scheduled physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory test results as well as observation by clinical staff. The potential risks associated with the administration of GSK3036656 are considered to be justified by the potential benefits that may be afforded to patients with TB if this and future studies with GSK3036656 are deemed successful for the participants from the study treatment. More detailed information about the known and expected benefits and risks and reasonably expected AEs of GSK3036656 may be found in the IB.

2.3.1. Risk assessment

The Sponsor's assessment of known and potential risks of GSK3036656 is summarized in Table 2.

Table 2 Summary of Potential Risks of Clinical Significance

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) GSK3036656		
Reduction in red blood cell count	**Non-Clinical** In a 4-week rat study (doses CCI mg/kg/d) - dose-dependent decline in reticulocytes (by up to 52% in males and 62% in females) at day 7 followed by normal levels by day 14 and increased levels by day 29/30 compared to controls. Hgb levels decreased by 10-13% compared to controls on day 14 and day 29/30. In a 4 week dog study (doses CCI mg/kg/d) - mild dose-dependent decrease in Hgb on day 14 (by about 10% compared to controls) with recovery by week 4. Reticulocyte counts unaffected. Dogs not bled on day 7. No histopathological changes in bone marrow or other relevant histopathology in the 4-week studies.	Standard safety haematology and clinical chemistry assessments will be performed and both trends and changes outside normal range will be monitored as part of laboratory safety assessments. Participants whose haemoglobin drops below pre-specified limits will be withdrawn from study intervention (Section 7.1.3). Haematology Stopping Criteria have been implemented as described in Section 7.1.3:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical In the study 201040 (FTIH) a possible trend of decreased haemoglobin from baseline to follow-up was noted in aggregate haematology data. The mean change from baseline to follow-up was -4.9 g/L in the CCI mg repeat dose cohort, compared to -1.5 g/L in the placebo group. None of the values hit PCI criteria, and declines were not clinically relevant. No clinically significant trends in reticulocyte values were observed, and there were no values of potential clinical importance reported for reticulocytes. In the Study 201214 no significant trends in the haemoglobin level or reticulocytes count were observed.	
Reduction in white blood cell count	**Non-Clinical** In the 4-week rat study, decrease of up to 37% in total leucocyte count on day 29/30 compared to controls. In the 4-week dog study, no reported effects on white blood cells. **Clinical** In the study 201040 (FTIH) - No clinically significant trends in leukocyte or neutrophil count values were observed. Two	White blood cell count will be monitored as part of laboratory safety assessments. Any clinically significant changes will be followed up until levels are not clinically significant. Participants developing neutrophil counts <500/mm^3 (0.5x10^9/L) will be withdrawn from the study (Section 7.1.3).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	participants showed PCI values. One participants had low neutrophil count (normal range 1.57-6.81 × 10^9/L) from screening (1.38) until follow-up (1.41), and also showed low leukocyte count (normal range 3.3-9.8 × 10^9/L) on Day 4 (2.5), Day 10 (2.6) and Day 14 (2.9) and was within normal range at follow-up. Given the low screening values, this observation was considered likely related to the subject's PPD [redacted] A second subject had a single low neutrophil count at follow-up (1.48). In the Study 201214 – in a 1 subject on [redacted]mg dose drug-related neutropenia was registered.	
Heart valvular and vascular pathology	**Non-Clinical** In a 7-day dog dose range finding study – minimal focal subendocardial haemorrhage on the atrial surface of the left atrioventricular valve observed in both animals at the top dose of [redacted] mg/kg/d. In a 10-day dog investigative study at [redacted] mg/kg/d – vascular lesions (including minimal focal necrosis and inflammatory infiltrate) in 3 out of 8 dogs. In the 4-week dog GLP study - no heart or valve changes were observed up to the top dose of	Valvular pathology can be monitored in humans with non-invasive echocardiography, these will be performed at screening. Vascular pathology is not readily monitorable in humans. Subjects with history of known cardiac valve abnormalities, any significant arrhythmia or ECG finding are not eligible for the study. To avoid risk to study participants, dosing will be limited to doses at which individual exposures do not exceed AUC0-24 and Cmax to [redacted] µg.h/mL and [redacted] µg/mL, respectively.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI mg/kg/day and there was no increase in inflammatory markers. In the 17-week GLP dog study there were no heart or valve changes up to the top dose of CCI mg/kg/day. In the 17-week rat study there were no changes in cardiac pathology up to the top dose of CCI mg/kg/day. Valvular or vascular pathology were not observed in rats. This pathological change is not commonly seen in animals, and its mechanism and significance to humans are not clear. A correlation between the presence of hemodynamic changes and the presence of this pathology is suspected, but currently unproven. **Clinical** Echocardiograms were performed at screening and follow up in the 201040 FTIH study in order to exclude participants with pre-existing valve or other cardiac abnormalities from the study, and to detect the presence of abnormalities after completion of the study. No abnormalities were detected. No SAEs, or AEs of cardiovascular nature were reported. There was no change from baseline in	These exposures are 10-fold below the lowest NOAEL achieved in the 17-week studies (rat) QTc stopping criteria have been implemented as described in Section 7.1.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	heart rate observed at any dose. No trends in blood pressure change were observed. Cardiac telemetry and echocardiogram-related interpretations were within normal range. There were no clinically significant ECG observations. There were no troponin I abnormalities in participants after receiving study drug. In Study 201214, one subject (dose CCI mg) had drug-related ventricular hypokinesia. One subject (dose CCI mg) had decreased ejection fraction. None of the participants met the QTcF stopping criteria. No SAEs of cardiovascular nature were reported.	
Hemodynamic changes	**Non-Clinical** Hemodynamic changes in several studies at ≥CCI mg/kg in rats and ≥CCI mg/kg in dogs - increased heart rate (rats and dogs), increased (rats) or decreased (dogs) blood pressure. **Clinical** Data from the 201040 (FTIH) and 201214 studies showed no significant changes in vital signs assessments during the study, and no clinically significant changes in ECG or telemetry assessments including QTc and PR intervals.	Vital signs will be monitored throughout the study as described in Section 8.3.2. ECGs will be monitored throughout the study as described in Section 8.3.3. QTc stopping criteria have been implemented as described in Section 7.1.2

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GSK3036656 is cleared through the kidneys	Analysis of the 201040 FTIH study data showed the main route of clearance for GSK3036656 is renal and there is therefore a risk that participants with low creatinine clearance may accumulate GSK3036656 and exceed predefined exposure limits. Participants with creatinine clearance less than 75 mL/min were excluded from the 201214 study.	Participants with an estimated creatinine clearance less than 75 mL/min will be excluded.
Skin depigmentation	**Non-Clinical** In a 17-week dog toxicology study (doses CCI CCI mg/kg /day): loss of pigmentation on the eyelids, nose or muzzle of all animals at 45 mg/kg/day group CCI µg.h/mL) and most animals in the CCI mg/kg/day group CCI µg.h/mL). PNL-2 (a melanocyte marker) immunohistochemistry staining demonstrated moderate cytoplasmic positivity in a population of cells in the basal region of the epidermis (interpreted to be melanocytes). The decreased pigmentation was therefore not associated with a loss of melanocytes in affected animals on immunohistochemistry. Depigmentation was not observed in the CCI mg/kg/day group (CCI ug/h/mL). Depigmentation was not observed in the two previous 4 week dog toxicology studies up to CCI mg/kg/day CCI ug.h/mL).	The duration of dosing in this study (14 days) is shorter than that used in the dog toxicology study and the maximum exposure (AUC0-24) has been capped at CCI ug.h/mL (10-fold below effect level for loss of pigment in the 17-week dog study). The physical examination of study participants will include visual examination of the skin. Participants with vitiligo will be excluded from the study to avoid confounding skin assessment at baseline and follow-up physical examinations.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical No adverse events were reported in the 201040 (FTIH) and 201214 studies that would be considered consistent with an asset-related depigmentation.	
Developmental toxicity	**Non-Clinical** Embryofetal developmental effects were observed in both rat and rabbit. In the rat, reduction in fetal viability and malformation, including skeletal malformations, ventricular septal defects and cleft palate were observed from CCI mg/kg/day. The NOAEL for embryofetal effects in the rat is CCI mg/kg/day, the exposure (AUC_{tlast}) at this dose level is CCI µg.h/mL which is at parity with the CCI mg clinical dose. In the rabbit, the only test article-related fetal abnormality was an increase in the incidence of full thoracolumbar ribs. The NOAEL for effects on rabbit embryofetal development was CCI mg/kg/day, and the AUC_{tlast} at this dose was CCI µg.h/mL. **Clinical** Studies 201040 (FTIH) and 201214 excluded females.	For the study, only WONCBP will be eligible: • Particpants with documented infertility (hysterectomy, bilateral salpingectomy, bilateral oophorectomy, other alternative documented) • Postmenopausal females (no menses for 12 months without an alternative medical cause + high FSH) Pregnancy testing has been implemented as described in Section8.3.5.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Blood draws	Venous access in some participants may be problematic and the needles used may cause bruising (ecchymosis) around the access site.	A maximum of approximately 160 mL of whole blood will be collected over the course of the study. At visits to collect whole blood samples, one or more samples of sufficient volume will be collected and divided into suitable portions for the various analyses. Whole blood samples will be collected by site personnel experienced in phlebotomy.
MICROGYNON 30 (Microgynon) [Microgynon, 2023]**. Summary of Product Characteristics, 2023**		
Circulatory disorders: risk of venous thromboembolism (VTE) and arterial thromboembolism (ATE)	Epidemiological studies have suggested an association between the use of COCs containing ethinyloestradiol and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely in average-risk women. The use of any combined hormonal contraceptive increases the risk of VTE compared with no use. Data from a large, prospective 3-armed cohort study (EURAS1 and LASS2) suggest that this increased risk is mainly present during the first 3 months. VTE	For the study, eligible participants who are healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring (history and ECG), non-obese, non-smokers, which exclude presence of major risk factors for both VTE and ATE. Eligible subjects > 35 years old will be more carefully monitored for clinical symptoms of ATE.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	may be life-threatening or may have a fatal outcome (in 1-2% of cases). Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (e.g. myocardial infarction, angina pectoris, stroke or TIA). Arterial thromboembolic events may be fatal.	Echocardiography has been implemented at screening as defined in Section 8.3.6. Full physical examination with vital signs, ECG and laboratory tests have been implemented as described in Section 8.3.
Tumors	A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently taking COCs. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs.	Exclusion criteria have been added to exclude subject with major health conditions (including tumors) as described in Section 5.2. Full clinical examination is a part of the standard safety monitoring for the study. Short duration of dosing by COCs mitigates this risk.
Metabolic problems: lipid and glucose abnormalities	Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when taking COCs. Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in women with	Subjects with baseline problems are eligible if relevantly compensated. Lipid and glucose metabolism safety monitoring have been implemented as described in Section 10.2 Appendix 2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	diabetes taking low dose COCs (containing < 50 µg ethinylestradiol). However, women with diabetes should be carefully observed while taking COCs.	
Hypertension	Small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC, it is prudent for the doctor to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy	Vital signs monitoring have been implemented as described in Section 8.3.2
Gastrointestinal tract problems	Nausea, diarrhoea, abdominal pain and vomiting were reported in COCs users	Full clinical examination and vital signs are a part of the standard safety monitoring as described in Section 8.3.
Liver problems	Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs	Exclusion criteria have been added to exclude participants with hepatitis B, C, impaired LFTs (ALT and Bilirubin >1.5 × ULN) and those with the history of regular alcohol consumption within 6 months. LFT is a part of the standard safety monitoring as described in Section 10.2 Liver stopping criteria have been implemented as described in Section 7.1.1.

2.3.2. Benefit assessment

This study is being conducted in healthy female participants of non-childbearing potential with no significant medical history. Participants will not receive benefit from this study.

2.3.3. Overall benefit-risk conclusion

Overall, the available data from non-clinical and clinical studies has not identified prohibitive risks associated with GSK3036656 at the exposures planned for this study. While there are a number of important potential risks identified for GSK3036656, these can be addressed in clinical trials with proper participant selection, close safety monitoring, and specific risk characterization and mitigation.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

The study objectives and endpoints are presented in Table 3

Table 3 Objectives and Endpoints

Objective(s)	Endpoint(s)
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-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-τ), Cmax, Cτ (Day 8, 10, 12, 15 and 16) and time of maximum observed concentration (Tmax) for GSK3036656
To characterize the single dose PK of EE/LNG alone and in the presence of GSK3036656	AUC(0-t),Tmax and t1/2 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.

Objective(s)	Endpoint(s)
	• Incidence of ECG values PCI within each treatment period. • 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-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-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-inf) , LNG AUC(0-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-τ), C_{max}, Cτ and Tmax) 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-τ), Cmax, Cτ and Tmax 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-τ), Cmax, and Cτ of GSK3036656: Descriptive Statistics (including n, Arithmetic means with 95% CI, Geometric means with 95% CI, CV%, SD, Median with Min, Max);
    - for Tmax 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 ($AUC_{(0-\tau)}$, 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), Tmax, C_{max} and t1/2 for EE and LNG
- Treatments: single dose Microgynon+ 14 daysGSK3036656 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 t1/2 (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 Tmax 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:

Adverse Events/ Serious Adverse Events, Clinical laboratory assessments, ECG, and Vital Sign measurements:

- 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.

4. STUDY DESIGN

4.1. Overall design

This is a Phase 1, open-label, fixed-sequence, 1-way DDI study designed to assess the PK, safety, and tolerability of GSK3036656 and an oral contraceptive containing EE/LNG (Microgynon) when the oral contraceptive is administered alone and in combination with GSK3036656 in healthy female participants of non-childbearing potential.

The study consists of a screening period, check-in to the inpatient facility for a single dose treatment period with Microgynon given alone followed by PK assessments for 72 hours, then discharge. The participant immediately starts a 14-day treatment period with GSK3036656 and is readmitted to the clinic on Day 15 where they receive a single dose of Microgynon in combination with GSK3036656. The participant is discharged from the clinic on Day 18 following completion of the 14-day GSK3036656 treatment period and the 72 hour EE/LNG PK assessments.

Participants will be screened within 14 days before the start of Treatment Period 1. The treatments are as follows:

- 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 coadministered with GSK3036656 20 mg on Day 15 of Treatment Period 3, then GSK3036656 20 mg od alone from Day 16 to Day 17.

Participants will take the single dose of Microgynon in the morning after an overnight fasting (at least 8h) at approximately the same time in Treatment Periods 1 and 3. Participants should remain fasted until at least 4 hours post dose.

Time of dose administration for GSK3036656 should be approximately 24 hours apart.

Blood samples for the analysis of EE, LNG and GSK3036656 will be collected as per SoA.

Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings.

Study assessments will be performed as indicated in the SoA Table 1. Participants will check into the clinic on Day 1 of Treatment period 1 and will remain confined until discharge on Day 4. Participants will be readmitted on Day 15 of Treatment Period 3 and will be discharged 72 hours later on Day 18 of Treatment Period 3. The duration of the study, including Screening, Treatment Period 1, Treatment Period 2, Treatment Period 3 and Discharge, will be approximately 4 weeks.

A study design schematic is presented in Section 1.2.

4.2. Scientific rationale for study design

This study was designed in accordance with the US FDA Guidance for Industry, Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications [DHHS, 2017] to assess the PK, safety, and tolerability of GSK3306656 and EE/LNG when administered alone and in combination.

The study will only recruit WONCBP to reduce any risk to the participants and to remove the need for any additional contraceptive requirements beyond the COC. This will also mean that participants only need to be admitted to the clinic for an inpatient stay during the PK assessment periods, thus reducing burden on the participants.

4.2.1. Participant input into design

As this is a healthy volunteer clinical drug interaction study to assess PK, safety, and tolerability, there was no participant involvement in the study design, which had to conform to FDA requirements. However, every effort has been made to minimize the burden on the participants.

4.3. Justification for dose

The daily clinical dose of 20 mg of GSK3036656 was selected based on evaluation of the final efficacy data from the completed monotherapy early bactericidal activity study with GSK3036656. Exposure-Response analysis was utilised to determine the clinical steady-state exposure associated with >90% of response (change from baseline in logCFU) and this was set as the targeted clinical exposure. Furthermore, a probabilistic analysis (PTA%) using both inter-subject variability and parameters' uncertainty was conducted to ensure that >90% of patients would achieve the targeted clinical exposure.

Based on this, a daily repeat dose of 20 mg of GSK3036656 will be used in the current study with a loading dose of 40 mg on Day 4 administered to ensure a PK profile that closely resembles steady-state by Day 8 of Treatment Period 2, thus allowing one week (from Day 8 to Day 15) for a potential enzyme induction to occur, while maintaining a 14-day cycle of GSK3036656 administration.

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA Table 1

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

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

5.1. Inclusion criteria

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

Age

1. Participant is 18 to 65 years of age, inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy or compensated as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring (history and ECG).
3. A creatinine clearance ≥75 mL/min (Cockroft-Gault formula).
4. Normal echocardiogram or echocardiogram with normal left ventricular function with at most trace to mild valvular regurgitation is allowed and no valvular stenosis.

Weight

5. Body weight ≥45.0 kg (99 lbs) and body mass index within the range 18.5 to 31.0 kg/m^2 (inclusive).

Sex

6. Female of Nonchildbearing Potential

Women in the following categories are considered WONCBP:

1. Permanently sterile due to one of the following procedures:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy

For permanently sterile individuals due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry. If reproductive status is questionable, additional evaluation should be considered.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required, within the Screening period.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT at least 30 days prior to the start of Treatment Period 1 to allow confirmation of postmenopausal status before study enrollment

Informed Consent

7. Participant is capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.

5.2. Exclusion criteria

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

5.2.1. Medical History

1. History of known cardiac valve abnormalities

5.2.2. Laboratory Assessments

2. Presence of hepatitis B surface antigen at Screening or within 3 months prior to starting study treatment.
3. Positive hepatitis C antibody test result at Screening or within 3 months prior to starting study treatment AND positive on reflex to hepatitis C RNA.
4. Positive HIV-1 and -2 antigen/antibody immunoassay at Screening.
5. Alanine aminotransferase (ALT) >1.5×ULN. A single repeat of ALT is allowed within a single screening period to determine eligibility.
6. Bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN is acceptable if bilirubin was fractionated and direct bilirubin <35%).

7. Any acute laboratory abnormality at Screening which, in the opinion of the investigator, should preclude participation in the study of an investigational compound.
8. Participants with haemoglobin <8.0 g/dL
9. Any Grade 2 to 4 laboratory abnormality at Screening, with the exception of creatine phosphokinase and lipid abnormalities (e.g., total cholesterol, triglycerides, etc), and ALT (described above), excludes a participant from the study unless the investigator provided a compelling explanation for the laboratory result(s) and has the assent of the sponsor. A single repeat of any laboratory abnormality is allowed within a single screening period to determine eligibility.
10. A positive test result for drugs of abuse (including marijuana), alcohol, or cotinine (indicating active current smoking) at Screening or before the first dose of study treatment.

5.2.3. Prior/Concomitant Therapy

11. Unable to refrain from the use of prescription or non-prescription drugs including vitamins, herbal and dietary supplements (including St John's wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study treatment and for the duration of the study. (Note: acetaminophen/paracetamol at doses of ≤2 grams/day and hydrocortisone cream 1% are permitted for use any time during the study. Levothyroxine and omeprazole may also be used during the study providing the participant has been on a stable dose for at least one month prior to the start of Treatment Period 1 and they maintain the same dose throughout the study. The dose of Microgynon should be administered at least one hour after the dose of levothyroxine or omeprazole). Other concomitant medications may be permitted on a case by case basis on the discretion of the medical monitor and the GSK ganfeborole team.
12. Treatment with any vaccine within 30 days prior to receiving study treatment.
13. Unwillingness to abstain from excessive consumption of any food or drink containing caffeine, grapefruit or grapefruit juice, Seville oranges, blood oranges, or pomelos or their fruit juices within 7 days prior to the first dose of study treatment(s) until the end of the study.
14. The study will exclude participants who have undergone IVF or other assisted reproductive techniques within 9 months prior to screening, or are participating in such programs at the time of screening, or who plan to undergo IVF or other assisted reproductive techniques during the following year.

5.2.4. Prior/Concurrent Clinical Study Experience

15. Participation in another concurrent clinical study or prior clinical study (with the exception of imaging trials) prior to the first dosing day in the current study: 30 days, 5 half-lives plus 10 days, or twice the duration of the biological effect of the investigational product (whichever is longer).

16. Where participation in the study results in donation of blood or blood products in excess of 500 mL within 56 days.

5.2.5. Diagnostic Assessments

17. Any significant arrhythmia or ECG finding (e.g., symptomatic bradycardia, non-sustained or sustained atrial arrhythmias, non-sustained or sustained ventricular tachycardia, second-degree atrioventricular block Mobitz Type II, or third-degree atrioventricular block) which, in the opinion of the investigator or GSK Medical Monitor, would interfere with the safety for the individual participant.
18. Exclusion criteria for screening ECG (a single repeat was allowed for eligibility determination):

Heart rate[1]	<50 or >100 beats per minute
QTcF interval[1],[2] (Fridericia's)	>450 ms

1. A heart rate from 100 to 110 beats per minute can be rechecked by ECG or vital signs within 30 minutes to verify eligibility. A QTcF interval between 450 and 460msec can be rechecked by ECG within 30 minutes to verify eligibility.
2. The corrected QT (QTc) is the QT interval corrected for heart rate according to Fridericia's formula (QTcF). It is either machine read or manually over-read. The specific formula used to determine eligibility and discontinuation for an individual participant in this study is Fridericia's formula.

5.2.6. Other Exclusion Criteria

19. Participants with vitiligo.
20. Participants with hypertension or Type 2 diabetes that cannot be controlled with diet and exercise alone.
21. History of regular alcohol consumption within 6 months of the study defined as: an average weekly intake of >14 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
22. Unable to refrain from tobacco- or nicotine-containing products within 3 months prior to Screening.
23. History of sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.

5.3. Lifestyle considerations

5.3.1. Meals and dietary restrictions

- Participants should arrive fasted for the Screening Visit and will be allowed to eat during the Screening Visit after blood draw for clinical chemistry has been completed. Participants should fast overnight(at least 8h) prior to dosing of Microgynon in Treatment Periods 1 and 3 and remain fasted until at least 4 hours post dose.

- Participants must refrain from any food or drink containing grapefruit or grapefruit juice, Seville oranges, blood oranges, or pomelos or their fruit juices within 7 days prior to the first dose of study treatment(s) until the end of the study.

5.3.2. Caffeine, alcohol, and tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 6 hours prior to admittance to the inpatient unit in treatment periods 1 and 3, and during each inpatient period.
- Participants will abstain from alcohol for 24 hours prior to admittance to the inpatient unit in treatment periods 1 and 3, and during each inpatient period.
- Use of tobacco products will not be allowed from 3 months prior to Screening until after the final visit.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 4 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.3.4. Other restrictions

- Participants will be asked to refrain from donating blood for the duration of their study participation.

5.4. Screen failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5. Criteria for temporarily delaying enrollment

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study intervention(s) administered

Study intervention is presented in Table 4

Table 4 Study Intervention(s) Administered

Intervention Name	GSK3036656	Microgynon
Type	Drug	Drug
Dose Formulation	Capsule	Tablet
Unit Dose Strength(s)	20 mg	Not Applicable
Dosage Level(s)		**Treatment Period 1:** Microgynon (0.03 mg EE/0.15 mg LNG) QD on Day 1 of treatment period 1.
	Treatment Period 2 A loading dose of GSK3036656 40 mg on Day 4 of Treatment Period 2, then GSK3036656 20 mg od on Days 5-14 of Treatment Period 2.	
	Treatment Period 3 GSK3036656 20 mg coadministered with Microgynon on Day 15 of Treatment Period 3, then GSK3036656 20 mg od alone on Days 16-17	**Treatment Period 3** Microgynon (0.03 mg EE/0.15 mg LNG) QD coadministered with GSK3036656 20 mg on Day 15 of the treatment period.
Route of Administration	Oral	Oral
Use	Experimental	Background Intervention
IMP and NIMP	IMP	AxMP
Sourcing	Provided centrally by the Sponsor	Commercial material sourced locally by the study site.
Packaging and Labelling	Study intervention will be provided in HDPE bottles. Each HDPE bottle Each HDPE bottle will be labelled as required per country requirement	Microgynon will be labelled as per country requirement
Current/Former Name(s) or Alias(es)]	NA	NA

HDPE = high-density polyethylene; IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

6.2. Preparation, handling, storage, and accountability

- The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the [pharmacy manual or other specified location].
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- A MSDS/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Assignment to study intervention

This is an open label study.

6.4. Study intervention compliance

When participants are dosed at the site during the inpatient stays, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned capsules, and documented in the source documents and relevant form. A participant diary will be provided to capture dosing compliance. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of GSK3036656 and Microgynon dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5. Dose modification

Not applicable

6.6. Continued access to study intervention after the end of the study

There is no continued access to study intervention following the end of this study as these are healthy volunteers. Participants will not require any additional care after they complete or discontinue the study as they are healthy volunteers.

6.7. Treatment of overdose

For this study, any dose of GSK3036656 greater than 20mg within a 24-hour time period, other than the loading dose of 40 mg on Day 4 of Treatment Period 2, will be considered an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until GSK3036656 can no longer be detected systemically (at least 14 days), as medically appropriate.
3. Obtain a plasma sample for PK analysis within 1-2 hours from the time of the last dose of study intervention. Additional samples may be requested by the medical monitor (determined on a case-by-case basis)].
4. Document the quantity of the excess dose as well as the duration of the overdose.

For any GSK3036656 overdose, GSK advises administration of activated charcoal if ingestion in the last 6 hours and supportive care. Any deliberate overdose would be reported as a grade 3 SAE (CTCAE) and would lead to immediate withdrawal from the study and referral to emergency services for charcoal and supportive care as well as review by a mental health professional. The GSK medical monitor should be contacted, and the participant should be observed as described above.

For Microgynon, there is no risk of overdose as this will be administered to the participant on site as a single dose in Treatment Period 1 and a single dose in Treatment Period 3.

6.8. Prior and concomitant therapy

Participants must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol, at doses of ≤ 2 grams/day and hydrocortisone cream 1%, are permitted for use any time during the study. Levothyroxine and omeprazole may also be used during the study providing the participant has been on a stable dose for at least one month prior to the start of Treatment Period 1 and they maintain the same dose throughout the study. The dose of Microgynon should be administered at least one hour after the dose of levothyroxine or omeprazole. Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of the study intervention. In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if possible, continue other study procedures (e.g., safety) planned in the study protocol at the discretion of the investigator. If the participant does not agree to continue in-person visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information (e.g., telephone contact). See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The primary reason for premature discontinuation of the study intervention will be documented in the eCRF based on the list below:

Reasons	Additional items/Sub-reasons
AE	
Lost to follow-up	Subject Relocated Subject was Incarcerated Other, specify Unknown
Participant Reached Protocol-Defined Stopping Criteria	Liver chemistry stopping criteria QTc Stopping criteria Haemotology stopping criteria
Physician Decision	Specify

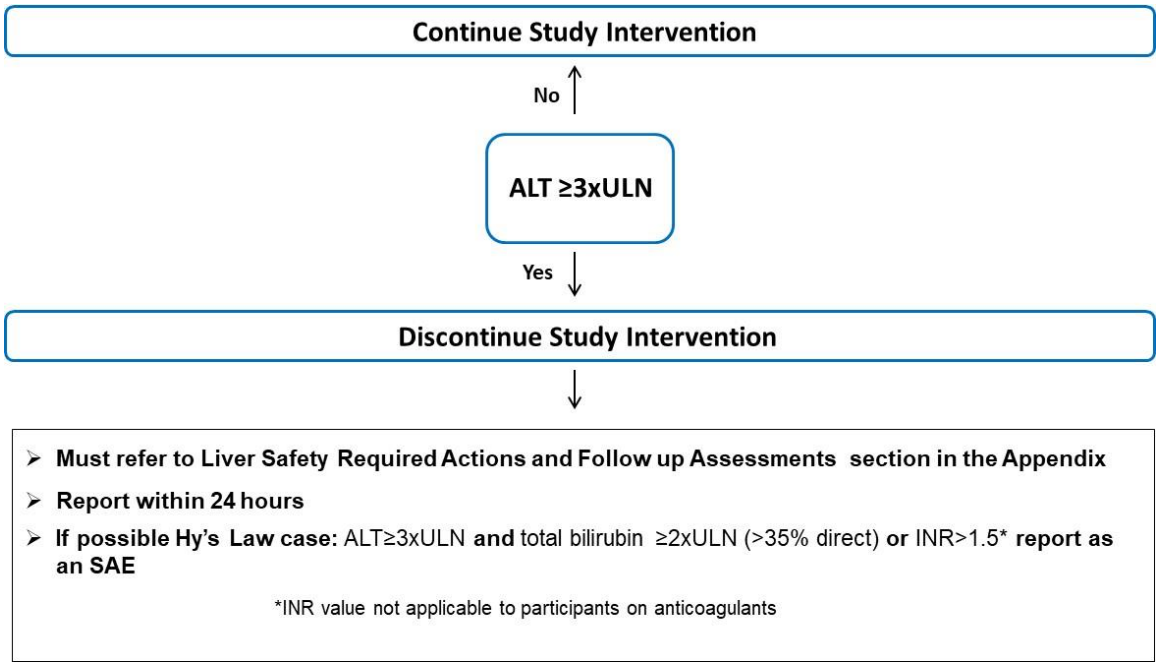
Reasons	Additional items/Sub-reasons
Pregnancy	
Protocol Deviation	Specify
Site Terminated by Sponsor	
Study Terminated by Sponsor	
Withdrawal by Participant	Burden of Procedure Participant Relocated Other
Other	Specify
Death	

If the participant does not agree to continue in-person visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the participant, a contact with a relative or treating physician, or collecting information from medical records. The approach taken should be recorded in the medical records. A participant who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.1.1. Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in the algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Refer to Section 10.4 for required Liver Safety Actions and Follow up Assessments.

7.1.2. QTc Stopping criteria

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

A participant that meets either bulleted criterion below based on average QTc values of triplicate ECGs over a brief recording period (See Section 8.3.3) will discontinue study intervention and will be withdrawn from study intervention.

- QTcF > 500 msec,
- Change from baseline in healthy participants: QTcF >60 msec

7.1.3. Haematology Stopping Criteria

IP will be discontinued for a participant if the following haematology stopping criteria are met (confirmed on two samples taken within 24 hours of each other) or at the discretion of the investigator in consultation with the medical monitor) and participants should be followed up until values are not clinically significant.

- A reduction in haemoglobin to below 8.0 g/dL

- A reduction in neutrophil count to below 500/mm^3 (0.5 × 10^9/L)

7.1.4. Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study are not allowed.

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

At the time of discontinuing from the study, if possible, an ED visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study intervention and the study at that time.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The primary reason for participant discontinuation/ withdrawal from the study will be documented in the eCRF based on the list below:

Reasons	Additional items/Sub-reasons
AE	
Lost to follow-up	Subject Relocated Subject was Incarcerated Other, specify Unknown
Participant Reached Protocol-Defined Stopping Criteria	Liver chemistry stopping criteria QTc Stopping criteria Haemotology stopping criteria
Physician Decision	Specify
Pregnancy	
Protocol Deviation	Specify
Site Terminated by Sponsor	
Study Terminated by Sponsor	
Withdrawal by Participant	Burden of Procedure Participant Relocated Other
Other	Specify
Death	

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.4.5).

7.3. Lost to follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, [3] telephone

calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of activities (SoA) Table 1. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Subjects who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management [(e.g., blood count)] and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 160 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative and baseline procedures

8.1.1. Collection of demographic data

Record demographic data such as date of birth, sex, race, and ethnicity in the participant's eCRF.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1.2. Medical history

Obtain the participant's medical history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study interventionin the eCRF.

8.2. Efficacy assessments

Efficacy assessments are not evaluated in this study.

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.3.1. Physical examination/history directed physical examination

- A complete physical examination will include, at a minimum, assessments of the skin, CV, respiratory, gastrointestinal, and neurological systems. Height (at Screening) and weight (at all scheduled timepoints) will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, CV system, and abdomen [liver and spleen].
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Position of the participant should be consistent across readings (e.g. semi-supine or supine). Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements must be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of at least 1 pulse and 1 blood pressure measurement. 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.

8.3.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, uncorrected QT intervals. QTcF will be calculated using heart rate and QT by Friderica's formula. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- At Screening, ECGs will be measured in triplicate. In the event where triplicate ECG readings are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates

should be completed in less than 10 minutes and the QTc must be based on the average of triplicated ECG readings.

- Stopping criteria are described in Section 7.1.2.
- At all other timepoints, a single ECG measurement should be taken.

8.3.4. Clinical safety laboratory tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3).
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 24 hours after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. Further tests will be performed as required.
    - In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Sections 10.3.1 and Section 10.3.2).
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g, SAE or AE), then the results must be recorded.

8.3.5. Pregnancy testing

- All participants must perform a highly sensitive blood or urine pregnancy test before the administration of any dose of study intervention. The study intervention may only be administered if the pregnancy test is negative.
- Refer to Section 8.4.5for the information on study continuation for participants who become pregnant during the study.

8.3.6. Echocardiogram

Transthoracic echocardiography/echocardiogram will be performed at Screening on all participants who have undergone all other screening assessments, have been found eligible for the study, and are willing to enrol into the study. The echocardiogram is used as a screening tool to assess heart function at baseline and will help assess for valve dysfunction. If the test is abnormal, the participant will be referred to a cardiologist and will be excluded from the study.

8.4. Adverse Events (AEs) serious adverse events (SAEs), and other safety reporting

For definitions relating to safety information see Section 10.3

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study. (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3 and/or Section 10.3.4.

8.4.1. Time period and frequency for collecting AE, SAE, and other safety information

All SAEs will be collected from the signing of the ICF until Day 18 of Treatment Period 3 at the time points specified in the SoA.

SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product (non-IMP) will be recorded from the time a participant consents to participate in the study.

All AEs will be collected from the start of study intervention until Day 18 of Treatment Period 3 at the timepoints specified in the SoA.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 and/or Section 10.3.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section 8.4.1.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.4.5.

8.4.4. Regulatory reporting requirements for SAEs

- **Prompt notification by the investigator to the sponsor of** an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See [Section 8.4.1] for reporting timeframes.
- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.4.6
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IBand will notify the IRB/IEC, if appropriate according to local requirements.

Table 5 Timeframes for submitting SAE and pregnancy reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours* ‡	AEs Report	24 hours*	AEs Report
Pregnancies	24 hours*	Pregnancy Notification/Report	24 hours *	Pregnancy Follow-up Report

*** Timeframe allowed after receipt or awareness of the information by the investigator/site staff.**

‡ Paper AEs Report will be dated and signed by the investigator (or designee)· For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.4.5. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 30 days after the last dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. See Table 6 for reporting timeframes.
- Any post study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.4.6. Contact information for reporting SAEs

Table 6 Contact information for reporting SAEs

Study contact for questions regarding SAEs Contact GSK's local and/or medical contacts
Contacts for reporting SAEs Available 24/24 hours and 7/7 days uk.gsk-rd-gcsp-ctsm-admin@gsk.com

8.4.7. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician, family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up.

- **New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.**

8.5. Pharmacokinetics

Plasma samples will be used to evaluate the PK of GSK3036656, EE and LNG. Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK3036656, EE, and LNG as specified in the SoA (Section 1.3).

Additional timepoints may be added during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection (including the volume to be collected), handling and processing of biological samples will be provided by the sponsor in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

- PK Samples will be analysed using an appropriately validated assay method.
- Each whole blood sample will be processed into plasma and divided into separate aliquots and sent to the appropriate laboratory (pending the analysis required). Additional details for sample collection and processing are provided in the laboratory manual.
- Genetic analyses will not be performed on these whole blood samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

8.6. Pharmacodynamics

There are no pharmacodynamic endpoints in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity assessments

Immunogenicity is not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical hypothesis

The primary objective, as outlined in Section 3, 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: μtest $/\mu_{ref} < 0.8$ 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-inf) and Cmax) 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 [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-inf) and Cmax) for both EE and LNG are within 0.8 and 1.25 (four parameters in total).

9.1.1. 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.

9.2. 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. • This population will be used for all demographic and safety summaries and listings.	Safety
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

9.3. Statistical analyses

9.3.1. General considerations/definitions

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

Statistical analysis will be performed by Clinical Statistics, GSK.

9.3.2. Primary endpoint(s)/estimand(s) analysis

9.3.2.1. Definition of endpoint: Pharmacokinetic 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. Values below limit of quantification for PK should be included and are not considered as missing.

The primary pharmacokinetic endpoints and attributes of the estimands are detailed in Section 3.

9.3.2.2. 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. Plasma concentrations of EE and LNG will be subjected to PK analyses using noncompartmental methods.

- Based on the individual concentration-time data the following primary plasma parameters will be estimated:
  - 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-inf) and Cmax
- Analyses will be performed on the natural logarithms of $AUC_{(0\text{-}inf)}$ and C_{max} 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 (including n, arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma EE and LNG PK parameter values will be presented by treatment.

More details will be included in the SAP.

9.3.2.3. Sensitivity Analysis

Not applicable

9.3.3. Secondary endpoint(s)/estimand(s) analyses

9.3.3.1. 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.

The secondary Pharmacokinetic endpoints and attributes of the estimands are detailed in in Section 3 "OBJECTIVES, ENDPOINTS AND ESTIMANDS".

9.3.3.1.1. Main Analytical Approach

- Plasma concentrations of GSK3036656, EE and LNG will be subjected to PK analyses using noncompartmental methods.
- 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:
  - EE and LNG (separately for Microgynon+GSK3036656 and Microgynon alone): AUC(0-t), Tmax and t1/2
  - GSK3036656 (Microgynon+GSK3036656): AUC(0-τ), C_{max}, Cτ and Tmax.
- Summary statistics (including n, arithmetic mean, geometric mean, 95% CI, median, standard deviation, minimum, maximum, and coefficient of variation as appropriate) for plasma EE, LNG, and GSK3036656 PK parameter values will be presented by treatment.

More details will be included in the SAP.

9.3.4. Safety Endpoints/ Estimand

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 (detailed in Table 3) occurring during each treatment period.

The secondary safety endpoints and attributes of the estimands are detailed in Section 3.

9.3.4.1. 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 standards. 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. The values of PCI for laboratory parameters, ECGs and vital signs will be detailed in the SAP.

9.3.4.1.1. Adverse Events (AEs)

Adverse events will be coded using the MedDRA (Medical Dictionaries for Regulatory Activities) coding system.

Counting of AEs will be based on the number of participants, not the number of AEs. In addition to all adverse events, 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

9.3.4.1.2. Electrocardiograms (ECGs)

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

9.3.4.1.3. Clinical Laboratory Values

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

9.3.4.1.4. Vital Signs

Vital sign data (SBP, DBP and HR), relative to PCI criteria, will be summarized by treatment group, vital sign and category.

The details of the statistical analyses of Safety and tolerability data for adverse events/serious adverse events, observed and change from baseline clinical laboratory assessments, electrocardiograms, and vital sign measurements will be provided in the SAP.

9.4. Interim analyses

There will be no interim analysis performed.

9.5. 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 9.5.1. CVw(%) values of 11.5%, 12.5%, 14.9%, 17.9% for EE AUC(0-inf), EE Cmax, LNG AUC(0-inf) and LNG Cmax respectively were calculated (Table 7). The largest CVw for the analytes and parameters is 17.9%.

Table 7 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
		Cmax	15	116.7	(107.6, 126.5)	12.5
	LNG	$AUC_{(0\text{-}inf)}$	15	88.1	(80.0, 97.0)	14.9
		Cmax	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-inf), EE Cmax, LNG AUC(0-inf) and LNG Cmax. 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 8) 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 8 Estimated Power and Sample Size Table

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

Table 9 provides the 90% CIs for a range of possible observed ratios, for each assumed CVw%, with 16 estimated participants.

Table 9 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)
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)

9.5.1. 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:

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- **Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.**
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation

536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically or digitally sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that physical or digital informed consent was obtained before the participant was enrolled in the study and the date the physical or digital consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical or digital copy of the ICF(s) must be provided to the participant.

In case of unexpected pregnancy, participant must be informed that PI such as date of birth, sex of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Recruitment strategy

Participants will be identified for potential recruitment using clinical database and IEC/IRB-approved advertisements (e.g., newspaper, social media) prior to consenting to take part in this study.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, that their data will be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access**.** GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.n

10.1.6. Committees structure

A SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

10.1.7. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.

- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- **Guidance on completion of eCRFs will be provided in eCRF completion guidelines.**
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the QTL plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan .
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- When copies of source documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g., endpoint adjudication committee; expert reader), documents are stored by the external body for a minimum of 7 years. These documents will be used by the third party solely for the purpose indicated within this protocol.

10.1.9. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRFor entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in source data acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Copies of documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g. endpoint adjudication committee; expert reader). The non-exhaustive list of documents shared to inform the central reader may include, discharge summaries, imaging reports, ECG reports etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the investigator sites prior to transfer. Details of the list of documents and the redaction procedure are provided in the site manual or equivalent. These documents will be used by the third party solely for the purpose indicated within this protocol.

10.1.10. Study and site start and closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as FSFV (first ICF signature date) at a country-level.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication policy

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the sponsor's internal policy. Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.2. Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 10 Protocol-required safety laboratory tests

Laboratory Tests	Parameters
Haematology	Platelet count Red blood cell (RBC) count RBC indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Hemoglobin Hematocrit %Reticulocytes WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry[1]	Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) Alkaline phosphatase2 Total bilirubin Direct bilirubin Total protein Blood urea nitrogen (BUN)/Urea Potassium Creatinine* Sodium Calcium Glucose [indicate if fasting or nonfasting] Creatine phosphokinase (CPK) Homocysteine Antiphospholipid antibodies Sex hormone binding globulin (SHBG)
Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick Microscopic examination (if blood or protein is abnormal) Epithelial cells Red Blood cells WBC Casts Crystals Culture (if positive: specify pathogen)
Pregnancy testing	Highly sensitive [serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP)[3]

Laboratory Tests	Parameters
Other screening tests	Follicle stimulating hormone and estradiol (as needed in WONCBP only) [Serum or urine] [alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, cotinine, opiates, cannabinoids and benzodiazepines)] [Serology [(HIV antibody 4th generation test, HBsAg, and HCV antibody)] SHBG

NOTES:

1. Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 :Liver Chemistry Stopping Criteria and Section 10.4: Liver Safety: Suggested Actions and Follow-up Assessments [and Study Intervention Rechallenge Guidelines]]. All events of ALT [or AST] ≥3× ULN and total bilirubin ≥2×ULN (> 35% direct bilirubin) or ALT [or AST] ≥3×ULN and INR >1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to [sponsor] in 24 hours (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC

* To assess the kidney function, use the eGFR 2021 calculator

10.3. Appendix 3: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of AE

AE definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination.).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. Pre-existing diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.
- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
- The investigator considers that there is a reasonable possibility that the event was related to the administration of the study intervention

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for

observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant
f. Other situations: • Possible Hy's Law case: ALT ≥3×ULN AND total bilirubin ≥2×ULN (>35% direct bilirubin) or INR >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of TEAE

TEAE Definition:
• A TEAE is an event that emerges during treatment, having been absent pre-treatment or worsens relative to the pre-treatment state.

10.3.4. Recording, assessment and follow-up of AE, SAE

10.3.4.1. AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.3.4.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild:
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.3.4.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the

initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.4.4. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

10.3.4.5. Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

After the initial AE/SAE or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other nonserious AEs must be followed until study completion or until the participant is lost to follow-up.

Follow-up during the study

AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the final participant has completed the study.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper pregnancy follow-up report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.4.7

10.3.4.6. Updating of SAE information after removal of write access to the participant's eCRF

When additional SAE information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.3).

10.3.4.7. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, related to any GSK non-IMP they will report these events to GSK

or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

- Contacts for SAE reporting can be found in Section 8.4.6.

SAE Reporting to GSK via Paper Data Collection Tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.4.6.

10.4. Appendix 4: Liver safety: required and suggested actions and follow-up assessments

Phase 1 Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology.

Phase 1 Liver Chemistry Stopping Criteria and Required Follow Up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT≥3×ULN If ALT≥3×ULN AND total bilirubin≥2×ULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5, report as an SAE[1,2].
Required Actions, Monitoring and Follow up Assessments	
Actions	**Follow Up Assessments**
• Immediately discontinue study intervention • Report the event to GSK within 24 hours • Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments as described in the Follow Up Assessment column • Do not restart or rechallenge participant with study intervention • Monitor the participant until liver chemistries resolve, stabilize, or return	• Viral hepatitis serology[3] • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Obtain blood sample for PK analysis, as soon as possible after the most recent dose[4] • Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH) and serum albumin • Fractionate bilirubin, if total bilirubin ≥2×ULN

Liver Chemistry Stopping Criteria	
to within baseline (see MONITORING) **MONITORING:** **If ALT≥3×ULN AND total bilirubin ≥2×ULN or INR >1.5** • **Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within 24 hours** • **Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline** • **A specialist or hepatology consultation is recommended** **If ALT≥3×ULN AND total bilirubin <2×ULN and INR ≤1.5:** • **Perform liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within 24-72 hours** • **Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline**	• **Obtain complete blood count with differential to assess eosinophilia** • **Record the appearance or worsening[5] of clinical symptoms of liver injury, or hypersensitivity, on the liver event form** • **Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications** • **Record alcohol use on the liver event alcohol intake form** **If ALT≥3×ULN AND total bilirubin ≥2×ULN or INR >1.5 obtain the following in addition to the assessments listed above:** • **Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins** • **Serum acetaminophen adduct assay should be done (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout)** • **Liver imaging (ultrasound, magnetic resonance, or computed tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging form.** • **Liver biopsy may be considered and discussed with local specialists if available, for instance:** ○ **In participants when serology raises the possibility of autoimmune hepatitis (AIH)**

Liver Chemistry Stopping Criteria	
	○ **In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention** ○ **In participants with acute or chronic atypical presentation.** • **If liver biopsy is conducted, then complete liver biopsy form**

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. For PK sampling; record the date/time of the PK blood samples* draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Lab Study Manual.*The following samples will be needed:a sample for Microgynon PK and a sample for both Trough and Serial PK of GSK3036656
5. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

10.5. Appendix 5: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

11. REFERENCES

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