Protocol

Title: A Phase 3, Open-label, Multi-center, Single-arm Study to Assess Contraceptive Efficacy and Safety of the Nomegestrol Acetate + 17β-estradiol Combined Oral Contraceptive (OG-8175A) in Premenopausal Females Aged 14 to 35 Years (Inclusive)

NCT Number: NCT05264506

Document Date: 30 August 2022

TITLE PAGE

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Protocol Number: OG-8175A-023

Amendment Number: Amendment 2

Product: OG-8175A (Nomegestrol acetate and 17β-estradiol)

Short Title: Contraceptive Efficacy and Safety of the NOMAC-E2 Combined Oral Contraceptive

Study Phase: Phase 3

Sponsor Name: Organon LLC., a subsidiary of Organon & Co.

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Regulatory Agency Identifying Number(s): [redacted]

Date of Protocol: 30 August 2022

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Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

This document is signed electronically. See the last page of the protocol for Sponsor signature.

[redacted] **Date**

Investigator Agreement Page is provided in Appendix 7. The Investigator should retain the original in the study site study files and return a copy to the Sponsor or Contract Research Organization for archiving.

Each Investigator should be sent a copy of the Investigator Agreement Page for completion. Signatures are obtained after the Sponsor has finalized and approved the protocol.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Table 1 Document History

Document	Date	Substantial	Region
Amendment 2	30 August 2022	No	Global
Amendment 1	01 December 2021	Yes	Global
Original Protocol	28 July 2021	-	-

Amendment 2 (30 August 2022)

Rationale for the Amendment: This amendment was prepared to describe the potential splitting of Visit 1 into two separate days, to clarify study procedures for pregnancy testing and reporting in relation to the first tablet intake, the starting advice for non-users of hormonal contraception, the PAP test exclusion criterion #7, tests to be done at local and/or central laboratory, and to add tablet-intake advice in case of gastrointestinal disturbance.

Table 2 Description of Changes in Amendment 2

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema	Schema updated.	To include an additional phone visit before treatment and a minimum visit window for screening.
Section 1.3 Schedule of Activities	Added phone visit (P1) before the start of treatment.	To inform the participant of the results of the serum β-hCG test performed at the V2 visit and to review e-Diary instructions.
	Added AE assessment for P1 Visit.	To collect pre-treatment AEs.
	Additional assessment added at V2 for contraception history.	Contraception status to be evaluated at V2 before treatment is allocated.
	Footnote 'a' added to clarify that the screening visit can be split into two separate days, if required, and to clarify the duration between V1 and V2.	To allow the participant to complete the Screening Visit if they cannot complete all assessments on the same day and to prevent enrollment of participants without all the eligibility criteria confirmed.
	Footnote 'b' added.	To clarify the purpose of phone contact P1.
	Footnote 'f' revised.	To indicate that drug intake will not occur at V2.
	A new footnote 'h' was added corresponding to the row for serum β-hCG.	To reference that the V2 serum β-hCG test result will be communicated to the participant at P1 and that a negative V2 serum β-hCG test result and a negative urine

Section # and Name	Description of Change	Brief Rationale
		home pregnancy test result on the intended day of tablet intake are both required prior to the first tablet intake.
	Footnote 'i' revised.	To clarify that urine pregnancy tests must be performed at the site before treatment allocation and at all other visits as well as at home just before the intake of the first tablet of study drug and before the start of all subsequent blisters.
	Footnote 'k' revised.	P5 changed to P6 due to additional phone contact P1 being added to the schedule.
	Footnote 'n' revised.	To add that BMI should also be calculated at enrollment, in addition to the Screening Visit, and that cm and kg should be used as measurement units.
	The following text was added to footnote 'p': "Testing for STIs must be performed by a local laboratory."	To clarify that STI panel must be tested in a local laboratory.
	Deleted superscript associated with urinary pregnancy test for assessments corresponding to V3, V4, V5, V6. EOT and V7.	Footnotes reordered.
Section 1.1 Synopsis (Objectives and Endpoints) Section 3.0 (Objectives and Endpoints) Section 8.2.3.2 Study Treatment Compliance Section 9.3.4 Per-Protocol Analysis and Protocol Deviations	Rephrased the following wording: "protocol violations" changed to "protocol deviations".	For consistency.
Section 1.1 Synopsis (Overall Design) Section 4.1 Overall Design	Text added to clarify the time to schedule V2 (between 7 and 42 days after V1) andclarify that the screening visit can be split into two separate days, if required.	To allow the participant to complete the Screening Visit if they cannot complete all assessments on the same day.
	A paragraph was revised, and the following text was added: "Participants will also receive urine home pregnancy tests, the first of which should be performed just before the first study drug intake of the first cycle. A serum pregnancy test will also be performed at V2,	To describe that negative urine pregnancy tests will be required for the first study drug intake and at the beginning of each subsequent treatment cycle, to reference that the V2 serum β-hCG test result will be communicated to the participant at P1, and that a negative V2 serum β-hCG test result and a negative

Section # and Name	Description of Change	Brief Rationale
	and the results will be communicated to the participant via phone contact (P1). Before participants may begin study drug, a negative V2 serum β-hCG test result, in combination with a negative urine home pregnancy test result just before the first tablet intake, are both required. At P1 the e-Diary instructions will be reviewed too, in particular to ensure adequate recording of the home pregnancy test and start of the first blister at first tablet intake. […] Participants must also perform a urine home pregnancy test at the beginning of each subsequent treatment cycle, which must be negative in order to continue tablet intake.”.	urine home pregnancy test result on the intended day of tablet intake are both required prior to the first tablet intake.
	On-treatment phone contact visits were updated from “P1 to P5” to “P2 to P6”.	Text correction to incorporate additional phone contact (P1) before treatment.
Section 5.2. Exclusion Criteria	The following text was added to exclusion criterion #7: “The presence of atypical squamous cells of undetermined significance (ASCUS) will require HPV reflex testing; ASCUS in an HPV-negative patient is not exclusionary.”.	To clarify the interpretation of PAP results with respect to trial eligibility.
Section 5.4 Screen Failures Table 8 8.2.1.2 Pregnancy	Rephrased the following wording: “data entry guidelines” changed to “eCRF completion guidelines”.	For accuracy.
Section 6.4.1 Timing of the first dose	The bold text was added: “Before participants can begin study drug**, a negative Visit 2 serum β-hCG test result, in combination with a negative urine home pregnancy test result, are both required. The urine home pregnancy test must be performed on the same day as the (intended) first tablet intake and must be performed before the first tablet intake of study drug.”.**	To clarify the importance of the serum pregnancy test performed at V2.
	The following advice was added: “If the first dose is delayed until the start of a subsequent menstrual cycle, a condom must be used until start of study drug on Day 1 of the	To clarify the requirements and timing of first dose.

Section # and Name	Description of Change	Brief Rationale
	subsequent menstrual period.". Note revised (bold text was added): "Participants using a non-hormone medicated intrauterine device should have the device removed prior to starting study drug. **They should start the study drug on the first day of the next menstrual period. A condom must be used until start of study drug. Starting between Days 2 and 5 of the next menstrual period is also allowed, but in this case a condom must be used until the participant has completed 7 days of uninterrupted active study treatment**".	
Section 6.4.2 Management of Missed NOMAC-E2 Tablets	Advice was added for GI disturbances.	To provide guidance for managing a condition that was not yet described in the protocol.
Section 6.7 Treatment After the End of Study	Sentence rephrased (text added in **bold** and deletions in strikethrough): An additional barrier method **(ie, condoms)** or abstinence is recommended ~~(ie, condoms)~~ for 1 week (or longer if indicated by the labeling of the newly started method) to minimize risk of conception during the switch in methods of contraception.	For clarity.
Section 8.1.5.1 Prior Medications	Updated the definition of prior medications (text added in **bold** and deletions in strikethrough): All prior medication taken by the participant **(defined as any medications reported up to the first study drug intake)** ~~within the 2 months before V2~~ should be recorded.	For correction.
Section 8.2.1.2 Pregnancy	The following sentence was edited (text added in **bold** and deletions in strikethrough): ~~Information~~ **Data** should be recorded on the **Pregnancy Report** ~~appropriate pregnancy~~ eCRF. Strikethrough text was deleted: Any AE related to the infant must be reported on the eCRF ~~for capturing these data, not in the AEs eCRF for~~	For accuracy. For correction. There is no specific AE eCRF for infants.

Section # and Name	Description of Change	Brief Rationale
	~~participants.~~	
8.2.3.1 Participant e Diary	Moved the following text about data to be collected in the e-Diary from 'optional information' to 'monthly information': "Start of a new blister, triggering recording of the information below".	Correction.
8.2.3.1.2 Monthly e Diary Questions (Before Starting a New Blister)	The following sentence was deleted: "The e Diary will allow these additional questions to be answered for a period of 4 days, after which, data entry will be locked out.".	Correction.
8.2.3.3 Monitoring "at-risk" Cycle Compliance	Revised sentence (text added in bold and deletions in strikethrough): "Sites will be notified if participants are non-compliant with the protocol (ie, cycles not at risk or entries missing such that a cycle is considered not at risk) **on a per cycle basis** ~~for 2 consecutive cycles~~ and are expected to contact the participant to reinforce compliance with the study protocol".	Correction. Sites are being contacted on a per cycle basis when issues with study compliance are identified.
8.3.2 Gynecologic and Breast Examinations	Strikethrough text was deleted: "Only abnormal findings should be recorded on the appropriate eCRF~~; either as medical history (if obtained at screening and before treatment allocation [V2]) or an AE (if reported after treatment allocation [V2])~~".	Correction to be consistent with the current record period of AEs which will be from the time of signing ICF (not screening).
8.3.4 Clinical Safety Laboratory Assessments	Sentence revised (text added in bold and deletions in strikethrough): "Screening may be performed **between 7 days and 42 days** ~~up to 6 weeks~~ before V2".	To add a minimum visit window for the Screening Visit.
8.4 Adverse Events	Revised paragraphs (text added in bold and deletions in strikethrough): "The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE**s and** SAE**s**, ~~and other reportable safety event reports~~ can be found in	For consistency with the standard process of AE classification and reporting.

Section # and Name	Description of Change	Brief Rationale
	Appendix 4". "The Investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE ~~as well as other reportable safety events~~ with respect to seriousness, intensity/toxicity and causality".	
Section 8.4.1 Time Period and Frequency for Collecting AE and SAE information	Revised text to clarify that the AE reporting period begins with 'signing of ICF' and not 'screening (V1)' since the screening visit may be split into 2 days, if required. Revised the AE reporting period in Table 8.	To clarify the reporting time period for adverse events.
	Deleted 'study drug' from the reporting criteria for AEs for V1 or V2 visit from Table 8. Added 'or'.	There is no study drug administration at V1 or V2; therefore, there will be no AEs due to study drug on these visits.
Section 9.4.3 Safety Analysis	Text in strikethrough was deleted: "The on-treatment period will be defined as the period from the day of first tablet intake up to and including the day of last active study drug intake, extended by 14 days. However, any delayed events or diagnoses judged by the Investigator ~~as well as Sponsor~~ to be related to study drug will also be considered to have occurred on-treatment and will be included in the safety analysis".	To clarify that Sponsor's assessments of delayed events or related events is not necessary for statistical analysis of safety.
Section 9.4.3.2 Laboratory Parameters	Bold text added: "Routine hematology and biochemistry parameters measured at V1 (screening) and V7 (EOS or ET) will be determined by a central laboratory, **unless the central laboratory results are not available in time for either starting study treatment administration and/or response evaluation. The sexually transmitted infections (STI) panel testing will be performed by a local laboratory".**	To accommodate sites' request for documentation in protocol of laboratory assessments required to be performed locally.

Section # and Name	Description of Change	Brief Rationale
Appendix 3	Text was added to clarify that STI testing will be performed locally, and that urine pregnancy tests will be performed on-site or at the participant's home. The sentence "The results of each test must be entered into the eCRF" was deleted. Table 12 was updated to indicate the STI assessment.	To accommodate sites' request for documentation in protocol of laboratory assessments required to be performed locally. Correction, since not all laboratory test results will be entered into the eCRF.
Appendix 4	A paragraph was added as an additional example of events not meeting the AE definition. 'Assessment of Intensity' was changed to "Assessment of Severity", and the text was revised accordingly. The text regarding SAE reporting to Sponsor via an Electronic Data Collection System or via Paper SAE Report Form was revised for clarity.	For consistency with the standard process of AE classification and reporting.
Appendix 5	The following text was added:"In addition to the negative Visit 2 serum β-hCG test result, it is required to have a negative urine home pregnancy test result on the day of the intended first tablet intake, just prior to the actual first tablet intake".	To clarify the importance of the serum pregnancy test performed at V2.
Signature Page	Updated the sponsor signatory.	Administrative update.
	Deleted the text "Medical Monitor name and contact information can be found in Appendix 2".	Correction.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore, have not been summarized.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Open-label, Multi-center, Single-arm Study to Assess Contraceptive Efficacy and Safety of the Nomegestrol Acetate + 17β-estradiol Combined Oral Contraceptive (OG-8175A) in Premenopausal Females Aged 14 to 35 Years (Inclusive).

Short Title: Contraceptive Efficacy and Safety of NOMAC-E2 Combined Oral Contraceptive

Rationale:

Nomegestrol Acetate + 17β-estradiol (NOMAC-E2; OG-8175A) is a monophasic combined oral contraceptive (COC) containing nomegestrol acetate (NOMAC), a nor-progesterone-derived progestogen, and 17β-estradiol (E2), an estrogen that is identical to the predominant endogenous human estrogen (E2). NOMAC is a highly selective progestogen derived from, and structurally similar to, the naturally occurring steroid hormone, progesterone. NOMAC has a strong affinity for the human progesterone receptor and has strong anti-gonadotropic activity, moderate anti-androgenic activity, and is devoid of any estrogenic, androgenic, glucocorticoid, or mineralocorticoid activity. The estrogen contained in NOMAC-E2 is 17β-estradiol, an estrogen identical to the predominant endogenous human estrogen. This estrogen differs structurally from the estrogen ethinylestradiol (EE) used in other combined hormonal contraceptives (CHC) by the lack of the ethinyl group in the 17-α position.

Phase 2 and 3 clinical studies have shown that NOMAC-E2 has robust contraceptive efficacy, a stable vaginal bleeding profile, and a good overall safety and tolerability profile, as compared with the COC containing drospirenone (DRSP) 3.0 mg and EE 30 µg. NOMAC-E2 has less pronounced effects on metabolic parameters than the levonorgestrel (LNG)-EE 150/30 µg COC. NOMAC-E2 was first registered in July 2011 and is currently registered and marketed in over 50 countries worldwide, including the member states of the European Union, the United Kingdom, and Australia. [redacted]. Mainly, this is a single-arm clinical study that will include the following:

- A total of 1,878 participants to yield: a) >1,000 participants who will complete 1 year (thirteen 28-day cycles) of treatment and b) >16,500 28-day cycles of exposure to assess the safety and contraceptive efficacy of NOMAC-E2.
- The demographic characteristics (age, weight, body mass index [BMI; see exclusion criterion #15], racial distribution, etc.) as per inclusion/exclusion criteria are targeted to be representative of females of childbearing potential in the US.
- The study assessments are designed to capture all information related to the concomitant use of condoms and other forms of contraception during the Treatment Period.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the contraceptive efficacy of the NOMAC-E2 COC based on the number of on-treatment pregnancies	• [redacted]
• To assess the safety and tolerability of the NOMAC-E2 COC	• [redacted] • [redacted] • [redacted]
Secondary	
• To assess the perfect use contraceptive efficacy of the NOMAC-E2 COC based on the number of on-treatment pregnancies conceived during perfect use	• [redacted]
• To assess the typical use contraceptive efficacy of the NOMAC-E2 COC based on the number of on-treatment pregnancies conceived during typical use	• [redacted]
• To assess the contraceptive efficacy of the NOMAC-E2 COC based on the number of on-treatment pregnancies by BMI subgroup	• [redacted]
• To assess the cumulative 1-year pregnancy rates of the NOMAC-E2 COC under at-risk, perfect use, and typical use circumstances, using Life Table Analysis	• [redacted]
• To describe the bleeding profile associated with the use of the NOMAC-E2 COC, assessed by cycle analysis	• [redacted] • [redacted] • [redacted]
• To describe the bleeding occurrence associated with the use of the NOMAC-E2 COC, assessed by 91-day Reference Period Analysis	• [redacted] • [redacted]

Objectives	Endpoints
	[redacted]
• To determine the effects of covariates (body weight and BMI) on the PK of NOMAC	• [redacted]

Abbreviations: BMI=body mass index; COC=combined oral contraceptive; NOMAC-E2=nomegestrol acetate + 17β-estradiol; PI=Pearl Index; PK=pharmacokinetic/s.

Overall Design:

This is an open-label, single-arm, multi-center study to assess the contraceptive efficacy and safety of the NOMAC-E2 COC in postmenarcheal premenopausal women aged 14 to 35 years (inclusive) at the time of study entry. Potential participants must be sexually active and engage in heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile, sterilized, or infertile, and should not routinely use any other form of contraception. [redacted]. It is estimated that 2,680 women need to be screened. Additionally, primary and secondary contraceptive efficacy endpoints will be analyzed [redacted]. To evaluate the potential for body weight and/or BMI to influence NOMAC exposure, contraceptive efficacy, and safety endpoints, the population pharmacokinetics (PK) of NOMAC will be investigated in a subset of participants, including covariate and exposure-response analyses.

During the Screening Visit or Visit 1 (V1), after written informed consent has been obtained, participants will have their relevant medical history assessed; undergo a focused physical examination as well as breast and gynecological examinations, including sexually transmitted infection testing (specifically, gonorrhea and chlamydia, as per guideline recommendations, and trichomonas and bacterial vaginosis if clinically indicated) and a PAP smear if indicated. In addition, participants will have their height, body weight, and vital signs (heart rate, blood pressure) checked; a blood sample taken for evaluation of pregnancy, blood biochemistry and hematology; and a urine sample taken for urinalysis. Participants will also be instructed on the use of the electronic diary (e-Diary), which will have to be completed on a daily basis, to document their vaginal bleeding experience and their intake of study drug (to be documented after treatment allocation). Participants' compliance to complete the e-Diary daily will be monitored for at least 7 days prior to treatment allocation to determine their ability to complete the e-Diary daily. Depending on receipt of laboratory results and the participants' current contraceptive method or the timing of the participants' menstrual cycle, eligible participants will visit the site for allocation to treatment, which is to be scheduled between 7 and 42 days after V1. The Screening Visit may be split into 2 separate days if the participant is not able to complete all assessments on the same day.

At the Treatment Allocation Visit (V2), the participant will receive the study drug after a negative on-site urine pregnancy test and if she meets eligibility criteria related to e-Diary completion (see inclusion criterion #6). Participants will also receive urine home pregnancy tests, which should be

performed just before the first study drug intake of each cycle. A serum pregnancy test will also be performed at V2, and the results will be communicated to the participant via phone contact (P1). Before participants may begin study drug, a negative V2 serum β-hCG test result, in combination with a negative urine home pregnancy test result just before the first tablet intake, are both required. At the beginning of each subsequent treatment cycle, participants must document in the e-Diary whether they have been involved in heterosexual vaginal intercourse during the preceding cycle and whether contraceptive methods other than the study drug have been used. Participants must also perform a urine home pregnancy test at the beginning of each subsequent treatment cycle, which must be negative in order to continue tablet intake. A urine home pregnancy test should also be performed within 48 hours after the last tablet from the last blister of study drug has been taken.

During the Treatment Period, participants will visit the site shortly following completion of Cycles 1, 4, 7, 10 and 13 (V3-V7). At each of these visits, a blood sample for serum β-hCG will be taken, body weight and vital signs will be measured, and the use of concomitant medication and occurrence of adverse events (AEs) will be assessed. Testing for gonorrhea and chlamydia will be conducted at V6 (in addition to V1). Testing for trichomonas and bacterial vaginosis may be repeated during the study, if clinically indicated (ie, if abnormal vaginal discharge is present). Pre- and post-dose PK samples will be taken in a subset of the study population (approximately 200 participants) during V3 and V4 and are to be scheduled between Day 7 and Day 12 of the corresponding cycle (ie, within the +5-day window for Cycle 2 and Cycle 5, respectively).

Sufficient amount of study drug will be provided to cover treatment until one cycle after the next scheduled study visit. In addition, compliance with e-Diary entries and study drug use will be reviewed, and additional training provided as needed for participants who continue to incorrectly or incompletely fill out the e-Diary or who use the study drug incorrectly. Participants who are repeatedly non-compliant with study drug use or with e-Diary entries may be discontinued at the discretion of the Investigator. Phone contacts (P2 to P6) between the on-site visits are planned to monitor the participants' compliance with the use of study drug and completion of e-Diaries, assess the at-risk status of their cycles, provide additional training when needed, and answer any questions.

The Post-Treatment Visit (Visit 7/End of Study [EOS]) is the last site visit and includes the EOS assessments and is conducted either at study completion or after Early Termination (ET), 14 days after completion of the last treatment cycle. Participants will undergo a focused physical examination as well as breast and gynecological examinations, have their body weight and vital signs measured, and have a blood sample taken for evaluation of blood biochemistry including β-hCG, and hematology. The use of concomitant medication, including the initiation of post-study contraception, and occurrence of AEs will be assessed.

The total duration of study participation will be up to 60 weeks, which includes a Pre-treatment Period of maximally 6 weeks, a Treatment Period of 52 weeks, and a Follow-up Period of 2 weeks after the last intake of study drug.

Key Inclusion/Exclusion Criteria

Healthy, postmenarcheal, premenopausal female, aged 14 to 35 years (inclusive) at the time of informed consent signing who is at risk for pregnancy (heterosexual vaginal intercourse at least once a month and not sterilized), with a partner who is not known to be subfertile, sterilized, or infertile, and who does not desire a pregnancy within 1 year following screening and is not

intending to use any other form of contraception (eg, condoms) including withdrawal, during the study. Participants must have a history of regular menstrual cycles of 21 to 35 days prior to the use of any hormonal contraceptive.

Number of Investigators and Study Sites:

Approximately 120 Investigators and study sites are expected to participate in this study.

Number of Participants:

A total of 2,680 fertile premenopausal women aged 14 to 35 years (inclusive) will be screened to achieve about 1,878 being allocated to study treatment. Over 1,000 total participants are expected to complete 1 year of treatment (13 cycles).

Treatment Groups and Duration:

All participants will receive the NOMAC-E2 COC. Participants will take one tablet of study drug per day for a period of thirteen 28-day treatment cycles. Each 28-day treatment cycle consists of 24 days of active medication intake, followed by 4 days of placebo. The total duration of study participation will be up to 60 weeks, which includes a Pre-treatment Period of maximally 6 weeks, a Treatment Period of 52 weeks, and a Follow-up Period of 2 weeks after the last intake of study drug.

Statistical Methods:

[redacted]

A PI of 3.0 is assumed for the NOMAC-E2 COC, which is similar to the values observed for low dose COCs such as LoLoestrin™ (norethindrone/EE) and Quartette™ (LNG/EE). This is considered to be a conservative estimation, as previous clinical study data suggest that the NOMAC-E2 COC is associated with a lower PI than higher dosed COCs such as DRSP/EE 3.0 mg/30 µg (Yasmin™), while recent large scale observational study data suggest that the NOMAC-E2 COC may also have a PI much lower than the LNG/EE 150/30 µg COC (eg, Levora).

[redacted]

[redacted] (see Section 9.2).

Primary and Secondary Efficacy Analyses:

Contraceptive Efficacy:

The estimated PI with associated 95% CI will be calculated for the primary and secondary contraceptive efficacy endpoints of on-treatment pregnancies PI $_{\text{at-risk}}$, PI $_{\text{perfect use}}$, and PI $_{\text{typical use}}$. The PIs will be estimated by means of the maximum likelihood estimate of the mean parameter in a Poisson distribution. The PIs will also be summarized by BMI subgroup.

A time-to-pregnancy analysis under at-risk, perfect use, and typical use circumstances will be performed using the Kaplan-Meier approach. Participants who do not become pregnant will be censored at the last day of the on-treatment period. The cumulative probabilities of in-treatment pregnancies after thirteen 28-day treatment cycles will be estimated.

Bleeding Profile:

The main vaginal bleeding endpoints in the Cycle Control Analysis are:

- Proportion of participants who experienced unscheduled bleeding-spotting
- Proportion of participants who experienced absence of scheduled bleeding-spotting
- Proportion of participants who experienced no scheduled or unscheduled bleeding-spotting at all

Point estimates with associated 95% CIs will be estimated for these main vaginal bleeding outcome proportions and presented by treatment cycle. The 95% CIs will be based on the method of Clopper and Pearson.

Additional vaginal bleeding endpoints in the Cycle Control Analysis include:

- Number of bleeding days
- Number of spotting days
- Number of bleeding-spotting days
- Mean duration of bleeding-spotting episodes

Frequency tables and/or summary statistics for continuous variables will be calculated for all primary and secondary parameters and presented per cycle. The number and percentage of participants with a bleeding day and the number and percentage of participants with a bleeding/spotting day will be presented per cycle and within cycle per cycle day, with a denominator based on the number of participants who are considered evaluable for the complete cycle.

Reference Period Analysis will be also conducted on the following vaginal bleeding endpoints:

- Number of bleeding days, spotting days, and bleeding-spotting days
- Proportion of participants with the following:

  - Amenorrhea;
  - Infrequent, frequent, or normal frequency bleeding-spotting; and
  - Prolonged bleeding-spotting.

- Mean duration of bleeding-spotting episodes defined as abnormal uterine bleeding that occur between periods.

Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized with counts and percentage for each category.

Primary Safety Analyses:

The proportions of participants who experienced

- A treatment-emergent AE,
- Abnormalities in clinical laboratory assessments, vital signs, or physical examination during the on-treatment period.

The proportion of participants who prematurely discontinued study treatment due to an AE will be presented along with a corresponding 95% CI.

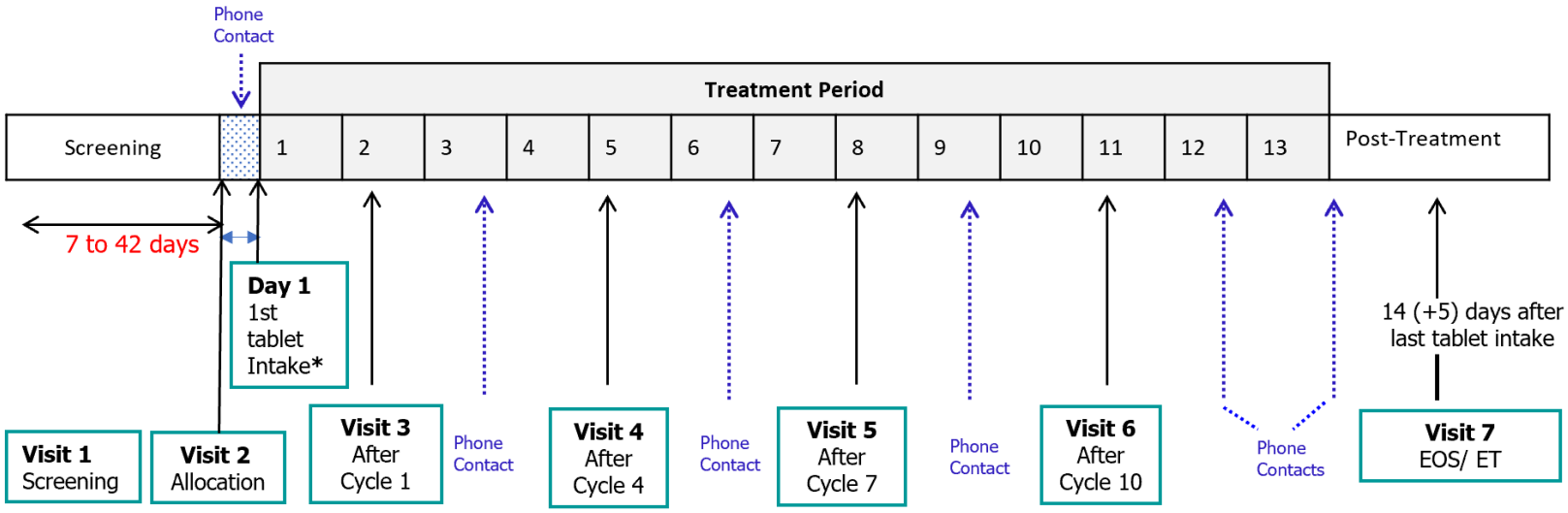
Pharmacokinetic Analysis:

Sparse sampling and population PK modeling will be used to estimate the effect of covariates (body weight and BMI) on NOMAC PK in premenopausal women aged 14 to 35 years (inclusive) after 1.5 mg E2 and 2.5 mg NOMAC. Results will be reported separately from the clinical study report.

Data Monitoring Committee: No

1.2 Schema

Figure 1 Study Schema



Abbreviations: EOS=End of Study; ET=Early Termination;
* Time between Visit 2 and Day 1 will depend on the onset of menstruation or the completion of the pre-study contraceptive.

Abbreviations: EOS=End of Study; ET=Early Termination; Min=minimum; Max=maximum.
* Time between Visit 2 and Day 1 will depend on the onset of menstruation or the completion of the pre-study contraceptive.

1.3 Schedule of Activities

The Schedule of Activities (SoA) is presented in Table 3.

Table 3 Schedule of Activities

Study Period	Pre-treatment[a]			Treatment: 52 weeks									Follow-up 2 weeks
Study Visit	Screening	Treatment Allocation	Before Cycle 1	After Cycle 1		After Cycle 4		After Cycle 7		After Cycle 10		After Cycle 13 EOT	V7/EOS or ET
	V1	V2	P1[b]	V3	P2	V4	P3	V5	P4	V6	P5	P6	
Timing				1st week Cycle 2	3rd week Cycle 3	1st week Cycle 5	3rd week Cycle 6	1st week Cycle 8	3rd week Cycle 9	1st week Cycle 11	3rd week Cycle 12	1st day after Cycle 13	14 days after last intake of study drug
Window (days)				+5	+/-3	+5	+/-3	+5	+/- 3	+5	+/- 3	+3	+5
Informed consent	X												
Inclusion/exclusion	X	X											
Treatment allocation		X											
Demographics	X												
Medical history[c]	X												
Contraceptive history	X	X											
Gynecological and obstetric history[d]	X												
Prior/concomitant medication	X	X		X	X	X	X	X	X	X	X	X	X
Dispense/collect e-Diary	X												X
e-Diary (re-) training[e]	X	X		X	X	X	X	X	X	X	X		

Study Period	Pre-treatment[a]			Treatment: 52 weeks									Follow-up 2 weeks
Study Visit	Screening	Treatment Allocation	Before Cycle 1	After Cycle 1		After Cycle 4		After Cycle 7		After Cycle 10		After Cycle 13 EOT	V7/EOS or ET
	V1	V2	P1[b]	V3	P2	V4	P3	V5	P4	V6	P5	P6	
Timing				1st week Cycle 2	3rd week Cycle 3	1st week Cycle 5	3rd week Cycle 6	1st week Cycle 8	3rd week Cycle 9	1st week Cycle 11	3rd week Cycle 12	1st day after Cycle 13	14 days after last intake of study drug
Window (days)				+5	+/-3	+5	+/-3	+5	+/- 3	+5	+/- 3	+3	+5
e-Diary compliance		X		X	X	X	X	X	X	X	X		X
Dispense study drug[f]		X[f]		X		X		X		X			
Study drug accountability						X		X		X			X
Study drug compliance[g]				X	X	X	X	X	X	X	X	X	X
Post-study contraceptive counseling										X		X	X
Serum β-hCG	X	X[h]		X		X		X		X			X
Urinary pregnancy test		X[i,j]		X		X		X		X		X[kk]	X
Check cycles at risk[l]				X	X	X	X	X	X	X	X	X	X
Vaginal bleeding	X	X		X	X	X	X	X	X	X	X	X	X
Physical examination[m]	X												X
Height	X												
Body weight[n]	X	X		X		X		X		X			X
Vital signs (HR, BP)	X	X		X		X		X		X			X

Study Period	Pre-treatment[a]			Treatment: 52 weeks									Follow-up 2 weeks
Study Visit	Screening	Treatment Allocation	Before Cycle 1	After Cycle 1		After Cycle 4		After Cycle 7		After Cycle 10		After Cycle 13 EOT	V7/EOS or ET
	V1	V2	P1[b]	V3	P2	V4	P3	V5	P4	V6	P5	P6	
Timing				1st week Cycle 2	3rd week Cycle 3	1st week Cycle 5	3rd week Cycle 6	1st week Cycle 8	3rd week Cycle 9	1st week Cycle 11	3rd week Cycle 12	1st day after Cycle 13	14 days after last intake of study drug
Window (days)				+5	+/-3	+5	+/-3	+5	+/- 3	+5	+/- 3	+3	+5
Gynecological exam	X												X
Breast exam	X												X
PAP test[o]	X												
STI panel[p]	X									X			
Routine laboratory[q]	X												X
Urinalysis	X												X
Pharmacokinetics[r]				X		X							
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: β-hCG=β-human chorionic gonadotropin; ACOG=American Congress of Obstetricians and Gynecologists; BMI=body mass index; BP=blood pressure; e-Diary=electronic diary; EOS=End of Study; EOT=End of Treatment; ET=Early Termination; HR=heart rate; P=phone contact; PK=pharmacokinetic/s; STI=sexually transmitted infections; V=visit.

a. The Screening Visit may be split into 2 separate days if the participant is not able to complete all assessments on the same day. The duration between V1 and V2 should be no less than 7 days and no greater than 42 days.
b. The purpose of the phone contact (P1) is to communicate the results of the serum β-hCG test performed at V2 and to reinforce e-Diary instructions.
c. Includes medical history regarding illicit drugs, alcohol, and tobacco use.
d. Includes pregnancy history and menstrual bleeding history (6 months prior to V1).

e. Participants will use the e-Diary for at least 1 week during screening to conduct daily assessments of vaginal bleeding/spotting. Participants will receive e-Diary training at V1. Investigators or designees should explain the importance of completing the e-Diary daily. Investigators are to evaluate participant compliance with the e-Diary during screening to assess eligibility. Additional study visits may also be scheduled to provide additional training as needed for participants who continue to fill out the e-Diary incorrectly or incompletely. Participants who are not compliant should be re-trained.
f. Dispensing only; the first dose will actually be taken at home after Visit 2 (see Section 6.4.1).
g. See Section 6.4 for information regarding timing of the first dose and management of missed study drug doses.
h. A negative Visit 2 serum β-hCG test result, to be communicated at P1, in combination with a negative urine home pregnancy test result on the intended day of tablet intake, are both required prior to the first tablet intake.
i. Urine pregnancy test must be performed at the site before treatment allocation and at all other visits. Urine pregnancy tests must also be performed at home just before the intake of the first tablet of study drug and before the start of all subsequent blisters. Participants must document a negative home pregnancy test in the e-Diary prior to starting each blister.
j. Additional urine pregnancy tests to be conducted at home as needed for suspected pregnancies. If a positive result is obtained with a urine pregnancy test, a confirmatory serum β-hCG test must be performed within 24 hours. Note, a local laboratory can perform the serum pregnancy test used to confirm a positive urine pregnancy test.
k. The scheduled urine pregnancy test indicated at P6 is to be conducted by the participant at home, within 48 hours after the last tablet intake.
l. Assess for heterosexual vaginal intercourse during that cycle and whether contraceptive methods other than the study drug have been used.
m. At a minimum, examination for abnormalities of the heart, lungs, abdomen, and extremities should be performed.
n. Participants' BMI should be calculated at screening and enrollment (using cm and kg as measurement units).
o. In the absence of a documented result within the timeline per current ACOG standard of care guidelines.
p. All participants must be tested for gonorrhea and chlamydia. Testing for trichomonas and bacterial vaginosis will only be required if abnormal vaginal discharge is present, and may be repeated during the study as needed. Testing for STIs must be performed by a local laboratory.
q. Includes biochemistry and hematology. Liver function testing may be repeated once prior to V2 at the discretion of the Investigator if results are inconsistent with the participant's clinical status or recent laboratory results.
r. Sparse sampling for PK analysis to be performed in a subset of the study population during V3 and V4, to be scheduled between Day 7 and Day 12 of the corresponding cycle (ie, within the +5-day window for Cycle 2 and Cycle 5, respectively). At each visit, 2 PK plasma samples will be taken; the first sample within 1 hour prior to, and the second sample between 1 and 2 hours after, the observed dose administration. The dosing date and time for the doses administered prior to and during the V3 and V4 visits will be recorded in the respective electronic case report form (eCRF) pages.

2.0 INTRODUCTION

2.1 Study Rationale

Nomegestrol Acetate + 17β-estradiol (NOMAC-E2; OG-8175A) is a monophasic combined oral contraceptive (COC) containing nomegestrol acetate (NOMAC), a nor-progesterone-derived progestogen, and 17β-estradiol (E2), an estrogen that is identical to the predominant endogenous human estrogen. NOMAC is a highly selective progestogen derived from, and structurally similar to, the naturally occurring steroid hormone, progesterone. NOMAC has a strong affinity for the human progesterone receptor and has strong anti-gonadotropic activity, moderate anti-androgenic activity, and is devoid of any estrogenic, androgenic, glucocorticoid, or mineralocorticoid activity. The estrogen contained in NOMAC-E2 is E2, an estrogen identical to the predominant endogenous human estrogen. This estrogen differs structurally from the estrogen ethinylestradiol (EE) used in other combined hormonal contraceptives (CHC) by the lack of the ethinyl group in the 17-α position.

Phase 2 and 3 clinical studies have shown that NOMAC-E2 has robust contraceptive efficacy, a stable vaginal bleeding profile, and a good overall safety and tolerability profile, as compared with the COC containing drospirenone 3.0 mg and EE 30 µg. NOMAC-E2 has less pronounced effects on metabolic parameters than the levonorgestrel (LNG)-EE 150/30 µg COC. NOMAC-E2 was first registered in July 2011 and is currently registered and marketed in over 50 countries worldwide, including the member states of the European Union (EU), the United Kingdom (UK), and Australia.

A large post-authorization safety study ([redacted]) has been conducted in over 50,000 women having been prescribed NOMAC-E2 in comparison to an equally sized group having been prescribed LNG-EE. The study has been conducted in 12 countries (Australia, Austria, Colombia, France, Germany, Hungary, Italy, Mexico, Poland, Russia, Spain, and Sweden). A pre-final interim analysis has shown that after women had been followed for up to 24 months, NOMAC-E2 is safe and well tolerated, associated with a numerically lower risk of venous thromboembolism (VTE) than LNG-EE (hazard ratio: 0.6; 95% confidence interval [CI], 0.2 – 1.5) and with a statistically significantly lower pregnancy rate than LNG-EE, ie, 0.13 per 100 woman-years (WY) (95% CI, 0.10 – 0.17) for NOMAC-E2 versus 0.39 per 100 WY (95% CI, 0.33 – 0.45) for LNG-EE.

Post-marketing surveillance data collected from more than 4 million WY of exposure have confirmed the favorable benefit-risk profile of NOMAC-E2.

[redacted]

[redacted] Mainly, this is a single-arm clinical study that will include the following:

- A total of 1,878 participants to yield: a) >1,000 participants who will complete 1 year (thirteen 28-day cycles) of treatment and b) >16,500 28-day cycles of exposure to assess the safety and contraceptive efficacy of NOMAC-E2.
- The demographic characteristics (age, weight, body mass index [BMI; see exclusion criterion #15], racial distribution, etc.) as per inclusion/exclusion criteria are targeted to be representative of females of childbearing potential in the US.
- The study assessments are designed to capture all information related to the concomitant use of condoms and other forms of contraception during the Treatment Period.

2.2 Background

Combined hormonal oral contraceptives are one of the most common birth control methods used by women. Most COCs in use today are a combination of a synthetic progestin, which is most commonly a 19-nortestosterone derivative, and a synthetic estrogen, EE.

The main goal of the development of CHCs is the demonstration of inhibition of ovulation, good vaginal bleeding pattern, and safety. The first contraceptives had a relatively high steroid content, the preparations showed good contraceptive efficacy, but also produced some rare but serious adverse events (SAEs). Based on laboratory and epidemiological findings of the association between the estrogen dose and the risk of thrombosis, the dose of EE has been progressively reduced over the years and most pills now contain 20 µg to 35 µg of EE. A further reduction is considered not possible without compromising the vaginal bleeding pattern. Furthermore, a new generation of selective progestins has been introduced with the goal of maximizing progestational effects and minimizing symptoms or metabolic effects associated with androgenic activity. The use of highly selective progestogens might also allow the replacement of EE by the predominant endogenous human estrogen, E2. It is generally perceived that an E2 containing CHC will be associated with a more favorable safety profile than EE containing COCs (1-3). In the past, several attempts have been made to replace EE in COCs by E2. However, for a long time E2-containing combinations or regimens have been explored but have not resulted in an acceptable clinical profile, ie, providing both contraceptive efficacy and an acceptable vaginal bleeding pattern for the target population.

Nonclinical and clinical studies that have been conducted with NOMAC-E2 are outlined in the Investigator's Brochure (IB) (4) and Summary of Product Characteristics (5). A brief summary of the clinical studies is provided below.

Dose-finding studies were initially performed with NOMAC alone and identified 2.5 mg NOMAC as the minimum effective dose for ovulation inhibition [redacted]. Subsequently, 2 dose finding studies were performed with combinations of 1.5 mg E2 and 3 doses of NOMAC, with the meanwhile established minimum effective dose of NOMAC as the highest dose ([redacted]. These studies led to the selection of NOMAC-E2 (2.5 mg-1.5 mg), being the combination providing the optimum balance between ovulation inhibition and cycle control. Finally, the selected dose combination was investigated in a study comparing a 21/7 regimen to a 24/4 regimen for 3 cycles ([redacted]). On the basis of a better bleeding profile as judged by a shorter duration of withdrawal bleeding and a lower overall number of days with vaginal bleeding over 3 cycles of use and increased contraceptive robustness, the 24/4 regimen was selected for further development in Phase 3 studies.

The clinical Phase 3 program was initiated in May 2006. The program included 2 (twin) pivotal efficacy and safety studies, [redacted]. These 2 studies together provided a sufficient number of at-risk cycles of exposure to obtain evidence of contraceptive efficacy and sufficient general safety data (6-9). In addition, the clinical Phase 3 program included 3 clinical pharmacology studies, ie, one metabolic safety study of NOMAC-E2 versus LNG-EE that evaluated effects on hemostasis, lipid metabolism, carbohydrate metabolism, adrenal function, thyroid function, and androgens (10, 11); a pharmacodynamic study into the contraceptive mechanism of action of NOMAC-E2 versus drospirenone (DRSP)-EE (12); and a bone mineral density study (13).

Six additional Phase 1 clinical pharmacology studies within the Phase 3 development program were initiated to complete the clinical development for the contraceptive application of NOMAC-E2. These 6 studies were: (1) a study to establish pharmacokinetics of NOMAC and E2 after single and repeated dose administration (14), (2) a study to compare the pharmacokinetics of NOMAC after single-dose oral administration of different NOMAC-E2 batches [redacted], (3) a study to compare the pharmacokinetics of NOMAC after single-dose administration of NOMAC-E2 between healthy female adolescents and female adults (15), (4) a study to investigate the effect of multiple therapeutic and supra-therapeutic oral doses of NOMAC-E2 on the QT/QTc interval in healthy women (16), (5) a bioequivalence study comparing the batches used in the pivotal studies with the batch prepared using the commercial production process [redacted], and (6) a food effect study to complete the characterization of the commercial film-coated tablet formulation [redacted].

In addition to the studies above, this Phase 3 study will provide 1 year of efficacy and safety data for NOMAC-E2 and will support the regulatory submission for NOMAC-E2 in the US.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of a study drug. The NOMAC-E2 COC has demonstrated contraceptive efficacy and is generally well tolerated. Eligible participants in this study will be monitored for safety throughout their participation.

Participants may benefit from 12 months of contraception and from the clinical care provided as part of study participation, including gynecologic and breast examinations, screening for gonorrhea/chlamydia, and trichomonas, bacterial vaginosis, and cervical cytology (if indicated).

As with all contraceptives, there is a risk of getting pregnant, but this risk is considered small if the NOMAC-E2 COC is used according to the instructions. Participants may experience discomfort during the gynecological and breast examinations. Participants may have bruising, experience lightheadedness, and rarely, infection, from drawing blood.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the IB and informed consent/assent documents.

3.0 OBJECTIVES AND ENDPOINTS

This is an open-label, single-arm, multi-center study aimed to assess the contraceptive efficacy and safety of the NOMAC-E2 COC in postmenarcheal premenopausal women aged 14 to 35 years (inclusive). The study objectives and endpoints are outlined in Table 4.

Table 4 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the contraceptive efficacy of the NOMAC-E2 COC based on the number of on-treatment pregnancies	• [redacted]
• To assess the safety and tolerability of the NOMAC-E2 COC	• [redacted] • [redacted] • [redacted]
Secondary	
• To assess the perfect use contraceptive efficacy of the NOMAC-E2 COC based on the number of on-treatment pregnancies conceived during perfect use.	• [redacted]
• To assess the typical use contraceptive efficacy of the NOMAC-E2 COC based on the number of on-treatment pregnancies conceived during typical use	• [redacted]
• To assess the contraceptive efficacy of the NOMAC-E2 COC based on the number of on-treatment pregnancies by BMI subgroup	• [redacted]
• To assess the cumulative 1-year pregnancy rates of the NOMAC-E2 COC under at-risk, perfect use, and typical use circumstances, using Life Table Analysis	• [redacted]
• To describe the bleeding profile associated with the use of the NOMAC-E2 COC, assessed by cycle analysis	• [redacted] • [redacted] • [redacted]

Objectives	Endpoints
• To describe the bleeding occurrence associated with the use of the NOMAC-E2 COC, assessed by 91-day Reference Period Analysis	• [redacted] • [redacted] • [redacted] • [redacted]
• To determine the effects of covariates (body weight and BMI) on the PK of NOMAC	• [redacted]

Abbreviations: BMI=body mass index; COC=combined oral contraceptive; NOMAC-E2=nomegestrol acetate + 17β-estradiol; PI=Pearl Index; PK=pharmacokinetic/s.

4.0 STUDY DESIGN

4.1 Overall Design

This is an open-label, single-arm, multi-center study to assess the contraceptive efficacy and safety of the NOMAC-E2 COC in postmenarcheal premenopausal women aged 14 to 35 years (inclusive) at the time of study entry. Potential participants must be sexually active and engage in heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile, sterilized, or infertile, and should not routinely use any other form of contraception. [redacted] It is estimated that 2,680 women need to be screened. Additionally, primary and secondary contraceptive efficacy endpoints will be analyzed [redacted]. To evaluate the potential for body weight and/or BMI to influence NOMAC exposure, contraceptive efficacy, and safety endpoints, the population pharmacokinetics (PK) of NOMAC will be investigated in a subset of participants, including covariate and exposure-response analyses.

During the Screening Visit or Visit 1 (V1), after written informed consent has been obtained, participants will have their relevant medical history assessed; undergo a focused physical examination as well as breast and gynecological examinations, including sexually transmitted infection testing (specifically, gonorrhea and chlamydia, as per guideline recommendations (17, 18), and trichomonas and bacterial vaginosis if clinically indicated) and a PAP smear if indicated. In addition, participants will have their height, body weight, and vital signs (heart rate, blood pressure) checked; a blood sample taken for evaluation of pregnancy, blood biochemistry and hematology; and a urine sample taken for urinalysis. Participants will also be instructed on the use of the electronic diary (e-Diary), which will have to be completed on a daily basis, to document their vaginal bleeding experience and their intake of study drug (to be documented after treatment allocation). Participants' compliance to complete the e-Diary daily will be monitored for at least 7 days prior to treatment allocation to determine their ability to complete the e-Diary daily. Depending on receipt of laboratory results and the participants' current contraceptive method or the timing of the participants' menstrual cycle, eligible participants will visit the site for allocation to treatment, which is at the latest 6 weeks after V1. The screening visit may be split into 2 separate days if the participant is not able to complete all assessments on the same day.

At the Treatment Allocation Visit (V2), the participant will receive the study drug after a negative on-site urine pregnancy test and if she meets eligibility criteria related to e-Diary completion (see inclusion criterion #6). Participants will also receive urine home pregnancy tests, the first of which should be performed just before the first study drug intake of the first cycle. A serum pregnancy test will also be performed at V2 and the results will be communicated to the participant via phone contact (P1). Before participants may begin study drug, a negative V2 serum β-hCG test result, in combination with a negative urine home pregnancy test result just before the first tablet intake, are

both required. At P1 the e-Diary instructions will be reviewed too, in particular to ensure adequate recording of the home pregnancy test and start of the first blister at first tablet intake. At the beginning of each subsequent treatment cycle, participants must document in the e-Diary whether they have been involved in heterosexual vaginal intercourse during the preceding cycle and whether contraceptive methods other than the study drug have been used. Participants must also perform a urine home pregnancy test at the beginning of each subsequent treatment cycle, which must be negative in order to continue tablet intake. A urine home pregnancy test should also be performed within 48 hours after the last tablet from the last blister of study drug has been taken.

During the Treatment Period, participants will visit the site shortly following completion of Cycles 1, 4, 7, 10 and 13 (V3-V7). At each of these visits, a blood sample for serum β-human chorionic gonadotropin (β-hCG) will be taken, body weight and vital signs will be measured, and the use of concomitant medication and occurrence of adverse events (AEs) will be assessed. Testing for gonorrhea and chlamydia will also be conducted at V6 (in addition to V1). Testing for trichomonas and bacterial vaginosis may be repeated during the study as needed, if clinically indicated (ie, if abnormal vaginal discharge is present). Pre- and post-dose PK samples will be taken in a subset of the study population (approximately 200 participants) during V3 and V4 and are to be scheduled between Day 7 and Day 12 of the corresponding cycle (ie, within the +5-day window for Cycle 2 and Cycle 5, respectively).

Sufficient amount of study drug will be provided to cover treatment until one cycle after the next scheduled study visit. In addition, compliance with e-Diary entries and study drug use will be reviewed, and additional training provided as needed for participants who continue to incorrectly or incompletely fill out the e-Diary or who use the study drug incorrectly (see Section 8.2.3 for more information; per-protocol defined use of study drug is outlined in Section 9.3.4). Participants who are repeatedly non-compliant with study drug use or with e-Diary entries may be discontinued at the discretion of the Investigator. Phone contacts (P2 to P6) between the on-site visits are planned to monitor the participants' compliance with the use of study drug and completion of e-Diaries, assess the at-risk status of their cycles, provide additional training when needed, and answer any questions.

The Post-Treatment Visit (Visit 7/End of Study [EOS]) is the last site visit and includes the EOS assessments and is conducted either at study completion or after Early Termination (ET), 14 days after completion of the last treatment cycle. Participants will undergo a focused physical examination as well as breast and gynecological examinations, have their body weight and vital signs measured, and have a blood sample taken for evaluation of blood biochemistry including β-hCG and hematology. The use of concomitant medication, including the initiation of post-study contraception, and occurrence of AEs will be assessed.

The total duration of study participation will be up to 60 weeks, which includes a Pre-treatment Period of maximally 6 weeks, a Treatment Period of 52 weeks, and a Follow-up Period of 2 weeks after the last intake of study drug.

4.2 Scientific Rationale for Study Design

This is a Phase 3, single-arm, multi-center, open-label study to assess the contraceptive efficacy and safety of the NOMAC-E2 COC. The study has been designed to meet the regulatory requirements for registration within the US in accordance with the 2019 FDA Guidance Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy (19) and it has also taken into account multiple interactions between the FDA and the Sponsor (ie, incorporation of FDA's recommendations into the study design and assessments).

The study has a duration of 1 year (thirteen 28-day cycles) and primarily aims to establish the contraceptive efficacy of the NOMAC-E2 COC in women aged 14 to 35 years (inclusive), at risk of pregnancy. The assessment of efficacy is based on the point estimate and the upper bound of the corresponding 95% CI for the PI. To be considered a very effective COC, the upper bound of the 95% CI for the PI should not exceed 5 in an adequately designed and conducted study. The anticipated exposure of >14,000 cycles at risk in 1,878 participants expected to complete 1 year of treatment (thirteen 28-day cycles) has been calculated to provide a PI conforming to this requirement (see Section 9.4.2 for additional information). In addition to the post-marketing data, the results from this study will also provide additional support to the clinical safety of the NOMAC-E2 COC. This study is open label and does not have a comparator arm, as this is not needed to meet regulatory requirements for registration.

4.3 Justification for Dose

The NOMAC-E2 COC active tablets contain 2.5 mg NOMAC and 1.5 mg E2 and will be used in a 24/4 regimen, ie, 28-day cycles with 24 days of active tablet intake followed by 4 days of placebo tablet intake. The doses and regimen have been selected based on providing strong ovulation inhibition and good cycle control and are currently the marketed approved dose and regimen in countries wherein NOMAC-E2 is approved.

4.4 End of Study Definition

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

A participant is considered to have completed the study if she has completed all phases of the study, including the last scheduled procedure indicated at the EOS Visit shown in the Schedule of Activities (SoA); Section 1.3.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to eligibility 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:

Demographics

1. Is a postmenarcheal, premenopausal female, aged 14 to 35 years (inclusive) at the time of informed consent signing.
2. Is at risk for pregnancy (heterosexual vaginal intercourse at least once a month and not sterilized), with a partner who is not known to be subfertile, sterilized, or infertile.
3. Does not desire a pregnancy within 1 year following screening and is not intending to use any other form of contraception (eg, condoms) including withdrawal.
4. Is in good physical and mental health, based upon the medical judgment of the Investigator.
5. Has a history of regular menstrual cycles of 21 to 35 days prior to the use of any hormonal contraceptive.
6. Is able and willing (in the opinion of the Investigator) to adhere to all required study procedures, including study visits and e-Diary entries, and not planning to relocate during the study (such that the participant would not be able to continue participation at the study site).

   Note: Participants are eligible to participate in the study, if they have demonstrated capability to independently complete the e-Diary and have completed the questions related to bleeding at least 6 out of 7 days of the last week preceding treatment allocation (V2).

Informed Consent

7. The participant (or legally acceptable representative, if applicable) provides written informed consent (and assent, if applicable) for the study.

5.2 Exclusion Criteria

The participant is excluded from the study if the participant:

Recent or Current Pregnancy

1. Has a known or suspected pregnancy.

   Note: A negative serum β-hCG test at V1 and a negative urine pregnancy test at V2 are required for a participant to be eligible in this study.
2. Has a history of subfertility or infertility.
3. Has not had at least 2 normal menstrual cycles following a recent pregnancy regardless of gestational age.

4. Is breastfeeding or has been breastfeeding within 2 months prior to start of study drug.

Gynecologic Conditions

5. Has a known human immunodeficiency virus (HIV) infection.
   Note: This condition requires the use of condoms, which is not allowed per protocol.
6. Has untreated gonorrhea, chlamydia, or trichomonas.
   Note: These conditions require the use of condoms, which is not allowed per protocol. Participants may be rescreened 3 weeks after completing treatment for these conditions if not at risk for reinfection as deemed by the Investigator.
7. Has no documented normal PAP test within the timeline of current standard of care guidelines or has a significantly abnormal PAP test at Screening (V1) (ie, ASC-H, low grade squamous intraepithelial lesion, high grade squamous intraepithelial lesion, atypical glandular cells [any type], squamous cell carcinoma, or adenocarcinoma [in situ or invasive]). The presence of high-risk human papillomavirus (HPV), regardless of PAP result, is exclusionary.
   Note: The presence of atypical squamous cells of undetermined significance (ASCUS) will require HPV reflex testing; ASCUS in an HPV-negative patient is not exclusionary.
8. Has had any unexplained abnormal vaginal bleeding or abnormal vaginal bleeding attributable to underlying pathology (ie, cervical/endometrial polyp, uterine fibroids, endometriosis, etc.) which has not been treated/resolved.

Cardiovascular Risks and Disorders:

9. Has a presence or history of VTE (ie, deep vein thrombosis, pulmonary embolism), a history of arterial thrombotic or thromboembolic events (ATE) (ie, myocardial infarction, stroke, or peripheral arterial disease), or a history of transient ischemic attack, angina pectoris, or claudication.
10. Is at a higher risk of VTE due to major surgery, any surgery to the legs or pelvis, neurosurgery, major trauma, recent prolonged immobilization (within 2 weeks before screening, eg, due to trauma, surgery, or other illness markedly limiting mobility); is planning surgery requiring prolonged immobilization; or has a hereditary or acquired predisposition or elevated risk for venous or arterial thrombosis, such as Activated Protein C resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies (eg, anticardiolipin antibodies, lupus anticoagulant); or has thrombogenic cardiac valve or rhythm abnormalities of the heart associated with thromboembolism (eg, atrial fibrillation).
    Note: Routine screening through laboratory tests for thrombophilia is not required. Exclusion from participation is based on reported medical history.
11. Has uncontrolled or severe hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg) at Screening (V1).
    Note: if hypertension can be controlled with medications and is no longer severe at treatment allocation (V2), the participant may be eligible.

12. Has severe dyslipoproteinemia.

    Note: Routine screening is not required. A lipid panel may be performed at V1 at the discretion of the Investigator.
13. Has a history of migraine with aura or focal neurological symptoms.
14. Has diabetes mellitus with end-organ involvement (nephropathy, retinopathy, neuropathy, or vascular involvement) or has diabetes for >20 years duration.
15. Has multiple cardiovascular risk factors such as obesity (BMI >30 kg/m^2), inadequately controlled hypertension, use of tobacco/nicotine products, or inadequately controlled diabetes which, in the opinion of the Investigator, in composite pose an unacceptable risk of study participation.

    Note: A participant who has a BMI >30 kg/m^2 **only** is not exclusionary. The Investigator should consider the severity of each risk factor in determining whether study participation is appropriate.

Gastrointestinal Disorders:

16. Has a history of pancreatitis associated with severe hypertriglyceridemia.
17. Has a presence or history of clinically significant liver disease, including active viral hepatitis or cirrhosis. Participants with a prior history of liver disease which is now inactive or successfully treated may be eligible if liver function values (ie, aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin) have been normal for the past year and are within the normal range (per central laboratory) at V1. Liver function testing may be repeated once prior to V2 at the discretion of the Investigator if results are inconsistent with the participant's clinical status or recent laboratory results.
18. Has a history of malabsorptive surgical procedures (eg, Roux-en-Y gastric bypass, jejunoileal bypass, biliopancreatic diversion).

Other Medical Disorders:

19. Has a history of malignancy ≤5 years before signing the informed consent except for adequately treated basal cell or squamous cell skin cancer.

    Note: Participants with a history or presence of liver tumors (benign or malignant) or sex steroid-influenced malignancies (eg, genital organs, breasts) are excluded regardless of the interval since the history of the malignancy.
20. Has a history or presence of meningioma.
21. Has any disease that may worsen under hormonal treatment such as disturbances in the bile flow (presence of or history of cholestasis, presence of gallstones), systemic lupus erythematosus, pemphigoid gestationis or idiopathic icterus during a previous pregnancy, middle-ear deafness (otosclerosis), Sydenham chorea, or porphyria.

    Note: History of cholecystectomy does not exclude a participant.
22. Has a current or previous history of medically diagnosed severe depression unless the potential participant is determined to be clinically stable and asymptomatic.

23. Has a known allergy/sensitivity or contraindication to NOMAC-E2.
24. Has a history (current or within the past 2 years) of drug or alcohol abuse or dependence.
25. Has any clinically relevant abnormal laboratory result at Screening (V1) as judged by the Investigator.
26. Has a history or current evidence of any condition, therapy, or other circumstance that in the opinion of the Investigator might confound the results of the study, affect participant's well-being, or interfere with the participant's participation for the full duration of the study (ie, approximately 1 year).

Prior/Concomitant Therapy

27. Has received any treatment listed in Table 6 more recently than the "last allowable use" indicated in Table 6 and/or needs to continue to receive any treatment listed in Table 6.
    Note: Contraceptives are allowed beginning the day following the last placebo tablet intake.

Prior/Concurrent Clinical Study Experience

28. Has used an investigational drug and/or participated in any other clinical study within 2 months before V2.

Other Exclusions

29. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is part of the investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

There are no restrictions related to lifestyles, including diet or alcohol restrictions.

5.4 Screen Failures

Screen failures are defined as participants who consent (and assent, if applicable) to participate in the clinical study, but are not subsequently allocated to treatment in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, and any pre-treatment AEs or SAEs (for definition, see Section 8.4.1) as outlined in the electronic case report form (eCRF) completion guidelines.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened, except for those participants who were diagnosed with chlamydia, gonorrhea, or trichomonas, which may be rescreened once 3 weeks after completing treatment for these conditions if not at risk for reinfection. Rescreened participants retain the same screening number.

If the rescreening is outside the 42-day window since V1, all screening assessments must be repeated.

6.0 STUDY TREATMENT

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

6.1 Study Treatment(s) Administered

All participants will receive NOMAC-E2 COC. Participants will take one tablet of study drug per day for thirteen 28-day treatment cycles. Each 28-day treatment cycle consists of 24 days of active study drug, followed by 4 days of placebo. Details regarding the study drug are provided in Table 5.

Table 5 Study Treatment Details

Study Treatment Name:	Nomegestrol acetate / estradiol Nomegestrol Acetate + 17β-estradiol combined oral contraceptive, NOMAC-E2 COC, OG-8175A
Dosage Formulation:	Film-coated Tablet
Unit Dose Strength:	Nomegestrol acetate (NOMAC) 2.5 mg and estradiol (E2) 1.5 mg; Each blister strip[a] contains 28 tablets: 24 tablets with the active drug (number 1 to 24) and 4 tablets with placebo (number 25 to 28).
Route of Administration	Oral
Dosing Instructions:	Take 1 tablet daily at about the same time as directed.
Packaging and Labeling	Study treatment will be provided in blister strips[a], packaged in tamper sealed boxes. Each box will be labeled as required per country requirement. A day label will be supplied for application to the blister strip[a] to designate the first day of dosing for each cycle and subsequent daily dosing.
Manufacturer	[redacted]

a. Referred to as "blister" throughout protocol.

6.2 Preparation/Handling/Storage/Accountability

The Investigator, a member of the study site staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study drug using the Drug Accountability Form. These forms must be available for inspection at any time.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only eligible participants in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatment 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, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Study site personnel will be responsible for the assessment of drug accountability, by counting returned blisters and unused tablets during on-site visits, which must be documented in the source documents and relevant form.

A record of the quantity of blisters dispensed to and blisters administered by each participant must be maintained and reconciled with study drug records. Study drug start and stop dates will also be recorded in the e-Diary and eCRF.

For reporting of potential quality-related issues with blister, refer to the Pharmacy Manual.

Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual or other specified location.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; however, the treatment to be taken by a participant will be allocated using an Interactive Voice (Web) Response System (IVRS/IWRS). The study site will contact the IVRS/IWRS prior to the start of study treatment administration for each participant.

6.4 Study Drug Intake

6.4.1 Timing of the First Dose

Participants will take their study drug at home. Before participants can begin study drug, a negative Visit 2 serum β-hCG test result, in combination with a negative urine home pregnancy test result, are required. The urine home pregnancy test must be performed on the same day as the (intended) first tablet intake and must be performed before the first tablet intake of study drug. Participants should begin study treatment only after a negative test result is obtained.

The start of the study drug depends on the contraceptive status of the participant at Treatment Allocation Visit (V2), as follows:

- **No preceding hormonal contraceptive use:** Participants not using a hormonal contraceptive should start the study drug on the first day of their menstrual period. Starting on Days 2 to 5 is allowed, but in this case a condom must be used until the participant has completed 7 days of uninterrupted active study treatment.
  - If the first dose is delayed until the start of a subsequent menstrual cycle, a condom must be used until start of study drug on Day 1 of the subsequent menstrual period.

Note: Participants using a non-hormone medicated intrauterine device should have the device removed prior to starting study drug. They should start the study drug on the first day of the next menstrual period. A condom must be used until start of study drug. Starting between Days 2 and 5 of the next menstrual period is also allowed, but in this case a condom must be used until the participant has completed 7 days of uninterrupted active study treatment.

- **Changing from a CHC (COC, transdermal patch, or vaginal ring):**
  - Participants switching from a COC should, after having completed at least 14 days of the active treatment phase, start the study drug within 4 or 7 days after the last active tablet, depending on whether the length of the progestin/estrogen active interval of the previous COC is 24 or 21 days, respectively.
  - Participants switching from a weekly transdermal patch should after having completed at least 2 patches (14 days) of a course, start study drug within 7 days after patch removal.
  - Participants switching from a contraceptive vaginal ring should after having completed at least 14 days of uninterrupted ring use, start study drug within 7 days after ring removal.
- **Changing from a progestogen-only method (minipill, implant, intrauterine system):**
  - Participants switching from a progestogen-only pill (POP) should stop taking the POP and start the study drug on the next day (immediate switch).
  - Participants switching from a contraceptive implant or an intrauterine system (IUS) should start on the day of its removal.

  In these cases, a condom must be used until the participant has completed 7 days of uninterrupted active study drug intake.

6.4.2 Management of Missed NOMAC-E2 Tablets

The NOMAC-E2 blister contains 28 tablets: 24 white tablets with the active substances (number 1 to 24) and 4 yellow tablets without active substances (number 25 to 28).

The participant should take one tablet every day at about the same time, without regard to meals and with some liquid if needed and in the order directed on the blister. Stickers marked with the 7 days of the week are provided; the participant should choose the sticker that starts with the day the participant begins taking the study drug.

If a participant misses a dose, the risk of pregnancy increases; this includes starting the pack late. The more tablets missed and the closer the missed tablets are to the 4 yellow placebo tablets, the higher the risk of a pregnancy.

The following advice **applies in case of** missed white active tablets:

1 active white tablet missed
The user should take the last missed tablet as soon as she remembers, even if this means taking 2 tablets at the same time. She then continues to take tablets at her usual time. She does not need any additional contraceptive protection.

2 or more active white tablets missed
The user should take the last missed tablet as soon as she remembers, even if this means taking 2 tablets at the same time. She then continues to take tablets at her usual time. A condom should be used until she has completed 7 days of uninterrupted white active tablet intake. This might continue into the next cycle. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer to the regular placebo tablet interval, the higher the risk of a pregnancy.

Finally, if the participant is not sure what to do about what advice to follow on the number of tablets missed, she should be advised to use a barrier method anytime. If the woman missed active white tablets and subsequently has no withdrawal bleed in the first normal placebo tablet interval, the possibility of a pregnancy should be considered.

If yellow placebo tablets are missed contraceptive protection is not reduced. Yellow tablets from the last (4^{th}) row of the blister can be disregarded. However, the missed tablets should be discarded to avoid unintentionally prolonging the placebo tablet phase.

The following advice **applies in case of** GI disturbances:

In case of severe gastrointestinal disturbances (e.g., vomiting or diarrhea), absorption of steroids from the COC tablet may not be complete and a condom should be used for protection during this timeframe and until the participant has completed 7 days of uninterrupted active study drug intake following the resolution of the severe gastrointestinal disturbance.

If the symptoms persist, the participant should be advised to contact the Investigator.

6.5 Dose Modification

Dose modification is not permitted during the course of the study.

6.6 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of treatment allocation (V2) or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor or appropriate designee should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1 Prohibited Medications

Medications and herbal supplements such as St. John's wort specifically prohibited (see Table 6) are not allowed during the ongoing study, including during time periods specified by this protocol for that medication. Note that contraceptives are allowed beginning the day after the last tablet intake of study drug from the last blister (last cycle). If there is a clinical indication for any medications specifically prohibited, discontinuation from study drug may be required. The Investigator should discuss any questions regarding this with the Sponsor Clinical Director or appropriate designee. The final decision on any supportive therapy rests with the Investigator and/or the participant's primary physician. However, the decision to continue the participant on study drug requires the mutual agreement of the Investigator, the Sponsor, and the participant.

Vaccination with live or non-live vaccines (including SARS-CoV-2 vaccines) can be administered according to local vaccination standards whenever medically appropriate.

As discussed in Section 9.4.2.6, a supportive Reference Period Analysis (RPA) will be performed excluding cycles during which concomitant medications are used for treatment of vaginal bleeding.

Table 6 Prohibited Medications, Supplements, and Other Substances

Prohibited Medications, Supplements, and Other Substances	Last Allowable Use
Sex hormones (other than pre- and post-treatment contraceptives)	2 months before V1
Injectable hormonal contraception with 3-month duration	9 months before V1
Injectable hormonal contraception with 2-month duration	6 months before V1
Injectable hormonal contraception with 1-month duration	3 months before V1
Intrauterine Device, Hormonal Intrauterine System, Contraceptive Implant, Contraceptive Vaginal Ring, Contraceptive Patch	Cycle 1 Day 1
Oral contraceptives (other than study drug)	Day before Cycle 1 Day 1
Injectable gonadotropin-releasing hormone agonist with 1-month duration (eg, leuprolide)	3 months before V1
Injectable gonadotropin-releasing hormone agonist with 3-month duration (eg, leuprolide)	10 months before V1
Oral gonadotropin-releasing antagonist (eg, elagolix)	2 months before V1
Medicines that induce liver enzymes, affecting the bioavailability of steroids, including but not limited to the following: • Anti-epileptics (eg, phenytoin, barbiturates, primidone, carbamazepine, oxcarbazepine, topiramate, and felbamate) • Bosentan • Rifampicin, rifabutin • Anti-HIV or anti- Hepatitis C drugs which decrease serum exogenous hormone levels (eg, ritonavir, nelfinavir, nevirapine, efavirenz, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, tipranavir/ritonavir, boceprevir, telaprevir) • Griseofulvin • Herbal remedies containing Hypericum perforatum (eg, St John's wort)	2 months before study treatment allocation (V2)
Medicines whose action may be affected by the use of CHCs • Lamotrigine	One month prior to V1

Abbreviations: CHC=combined hormonal contraceptive; HIV=Human Immunodeficiency Virus; V=visit.

6.6.2 Rescue Medicine

No rescue or supportive medications are specified for use in this study.

6.7 Treatment After the End of the Study

The Sponsor will not provide any additional care to participants after they leave the study because such care should not differ from what is normally expected. There will be no access to study drug after the participant has completed or discontinued treatment.

Participants who do not wish to conceive after the last tablet intake of study drug should begin a new contraceptive method as soon as possible after the last intake of study drug. Post-study

contraceptive counseling will be provided by study site personnel in accordance with the SoA (Section 1.3).

At V6, Investigators (or their appropriately trained designee) should begin to discuss a participant's preferences for contraception (if desired) after their study participation is complete. The Investigator may provide a referral for continuing care if needed or may elect to prescribe an alternative contraceptive as appropriate.

When scheduling V7 (EOS/ET Visit), the plan for post-study contraception should be confirmed. At V7, the post-study contraceptive medication should be recorded as concomitant therapy in the database. Expenses and procedures related to initiation of a new contraceptive method are not funded by the study.

Participants should start their post-study contraceptive (if applicable), as soon as possible after the last tablet intake of study drug. An additional barrier method (ie, condoms) or abstinence is recommended for 1 week (or longer if indicated by the labeling of the newly started method) to minimize risk of conception during the switch in methods of contraception.

7.0 DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Strategies to Minimize Participant Discontinuation/Withdrawal

To minimize the number of participants who discontinue participation prematurely or are lost to follow-up, the following actions must be taken if a participant fails to return to the clinic for a required study visit:

- As per inclusion criterion #6, participants must be able and willing (in the opinion of the Investigator) to adhere to all required study procedures, including study visits and e-Diary entries, and not planning to relocate during the study (such that the participant would not be able to continue participation at the study site). Additionally, participants are eligible to participate in the study, if they have demonstrated capability to independently complete the e-Diary and have completed the questions related to bleeding at least 6 out of 7 days of the last week preceding treatment allocation (V2).
- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and 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, 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 made at a minimum of at least 3 times and documented in the participant's medical record.
- Study site personnel will remind the participants at each visit the importance of completing their scheduled visit (ie, site and phone call visits) and continuing with study participation. Re-training should be considered for participants who are non-compliant with e-Diary completion.

7.2 Discontinuation of Study Treatment

If a participant who does not meet eligibility criteria is inadvertently included in the study, that participant must be discontinued from study treatment and the Sponsor or Sponsor designee must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the participant to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the participant to continue in the study.

Participants who discontinue study treatment will not be replaced. Discontinuation from study drug is permanent.

Participants who discontinue study drug before completion of the protocol-specified Treatment Period should compleqte all study-related procedures specified for the EOS/ET Visit (V7). See the

SoA (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

Participants may discontinue at any time for any reason or be discontinued from the study drug at the discretion of the Investigator should any untoward effect occur. In addition, a participant may be discontinued from study drug by the Investigator or the Sponsor if study drug is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study drug for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- The participant has experienced a VTE or ATE (including myocardial infarction, stroke, or peripheral arterial events).
- The participant has had or is likely to have prolonged immobilization due to illness, injury, major trauma, surgery to the legs, or any other major surgery(ies) known to have an elevated risk of thromboembolism.
- The participant has a sufficiently significant adverse reaction to the NOMAC-E2 COC that, in the opinion of the Investigator and/or Sponsor, places the participant at unnecessary risk from continued study participation.
- The participant has a medical condition or personal circumstance, which in the opinion of the Investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study drug.
- The participant has a confirmed pregnancy (ie, positive serum pregnancy test or ultrasound). See Section 8.2.1.1 for further details.
- The participant has a need for continued use (>1 month) of any of the medications listed in Table 6 including any sex steroids.

  Note: Interactions between hormonal contraceptives and enzyme-inducing drugs may lead to breakthrough bleeding and/or contraceptive failure. A back-up nonhormonal contraceptive method is recommended when enzyme inducers are used with hormonal contraceptives and should be continued for 28 days after discontinuing the enzyme inducer.

- The participant is persistently not at risk for pregnancy (see Section 8.2.3.3).

For participants who are discontinued from study drug, all procedures for V7 should be completed.

Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.3. Contraceptive counseling, as applicable, should be performed (see Section 6.7). The participant will be permanently discontinued both from the study drug and from the study at that time.

The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.4.

7.3 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent (or assent, if applicable) from the study.

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, she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

At the time of withdrawal participants should be encouraged to complete the applicable activities scheduled for the EOS/ET Visit (V7). See the SoA (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

A participant who discontinues from study drug or withdraws from the study will not be replaced.

7.4 Lost to Follow-up

Strategies to minimize participant discontinuation/withdrawal are outlined in Section 7.1. A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

After employing the strategies outlined in Section 7.1, should the participant continue to be unreachable, she will be considered to have withdrawn from the study.

The missing data for the participant will be managed via the prespecified statistical data handling and analysis considerations.

Discontinuation of specific study sites or of the study as a whole are handled as part of Appendix 2.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

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. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each participant is displayed in Table 7. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 7 Blood Volume

Sample Type	Screening	Treatment Period		Number of Collections	Volume (mL)/Collection	Total Volume (mL)/Test
	V1	V2 to V6	V7 to EOS/ET			
Laboratory Safety Tests – Hematology	1	-	1	2	2	4 mL
Laboratory Safety Tests – Chemistry	1	-	1	2	3.5	7 mL
Serum β-hCG	1	5	1	7	3.5	24.5 mL
Plasma PK	-	2[a]	-	4	5	20 mL
Total Blood Volume per Participant						35.5 mL
Total Blood Volume per Participant in the PK subset[a]						55.5 mL

Abbreviations: β-hCG=beta human chorionic gonadotropin; EOS=end of study; ET=early termination; PK=pharmacokinetic/s; V=visit.

a. Samples collected from participants in the PK subset only, during V3 and V4.

8.1 General Assessments

8.1.1 Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee at Screening (V1) and treatment allocation(V2) to ensure that the participant qualifies for the study. Prior to treatment allocation, the participant's BMI will be calculated via IVRS/IWRS and participants will be categorized as having BMI <30 kg/m^2 or ≥30 kg/m^2.

8.1.2 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The Investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent (and assent, if applicable). At the time of treatment allocation, site personnel will add the treatment number to the participant identification card.

8.1.3 Assignment of Screening Number

All participants who consent (and assent, if applicable) will be given a unique screening number (also referred to as participant number) that will be used to identify the participant for all procedures that occur prior to treatment allocation (V2). Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is rescreened will retain the original screening number assigned at the initial Screening Visit. Specific details are provided in Section 5.4.

8.1.4 Assignment of Treatment Number

All eligible participants will receive a treatment (allocation) number. Treatment numbers cannot be re-assigned to another participant. A single participant cannot be assigned more than one treatment number. In this study, all participants receive the same study drug treatment.

8.1.5 Prior and Concomitant Medications

8.1.5.1 Prior Medications

The Investigator or qualified designee will review current medication use at the time of screening and prior medication use, as applicable based on the time of screening in relation to planned treatment allocation. All prior medication taken by the participant (defined as any medications reported up to the first study drug intake) should be recorded. The medication review should specifically address any treatment that would meet the protocol-specified requirement for prohibited medications (see Table 6).

8.1.5.2 Concomitant Medications

The Investigator or qualified designee will record medication, if any, taken by the participant during the study. Concomitant medications should be reviewed at every study visit or contact. The use of herbal supplements and nonprescription medications should be recorded as concomitant medications. Note, the use of any product containing St. John's wort (*Hypericum perforatum*) must be documented as this prohibited herbal medication may decrease contraceptive efficacy.

Participants are required to record in the e-Diary if they used any additional contraception (and specify the type used) at the end of every cycle throughout the study. These questions will be automatically administered by the e-Diary. If the participant indicates use of a hormonal contraceptive other than the NOMAC-E2 COC (eg, emergency contraceptive medication) in the e-Diary or verbally, this medication must be recorded as a concomitant medication in the database.

8.1.6 Medical and Contraceptive History

A medical history, including medical history regarding illicit drugs, alcohol, and tobacco use as well as a contraceptive history will be obtained by the Investigator or qualified designee.

8.1.7 Gynecologic and Obstetric History

A gynecological and obstetric history (including menstrual history, gravidity, and parity) will be obtained by the Investigator or qualified designee for all participants at V1 to ensure the participant meets entry criteria. For eligible (allocated to treatment) participants, the pregnancy history should be reported on the eCRF. Refer to the eCRF completion guidelines for details.

8.2 Efficacy Assessments

8.2.1 Assessment of On-treatment Pregnancy

On-treatment pregnancies are those with an estimated date of conception between the day of first intake of study drug up to and including 7 days after the last intake of active study drug. For more information regarding contraceptive efficacy definitions, see Section 9.4.2.1.1.

The contraceptive efficacy is expressed by the PI defined as the number of pregnancies per 100 WY of study drug exposure. The PI will be calculated for at-risk cycles as well as under perfect and typical study drug use and will be analyzed as described in Section 9.4.2.2 and Section 9.4.2.3, respectively.

8.2.1.1 Pregnancy Testing

Serum β-hCG will be determined at all scheduled study visits and performed by the central laboratory. See the laboratory/procedure manual for sample collection instructions. A negative serum β-hCG test at Screening (V1) and a negative urine pregnancy test at treatment allocation (V2) are both required for a participant to enter the study. Borderline results should be repeated with quantification of the serum results.

If pregnancy is suspected, urine pregnancy tests may be performed either by the participant at home (at any time) or at a study visit to achieve a rapid result; however, results should be confirmed by serum β-hCG within 24 hours. If a pregnancy is confirmed, the participant will be discontinued from study drug and from the study. **Confirmed pregnancies must be reported to the Sponsor within 24 hours.** See Section 8.2.1.2 for further details regarding pregnancy reporting.

A urine pregnancy test must be performed at the site before treatment allocation at V2. Urine pregnancy test kits will be dispensed at V2 and at subsequent visits (as needed) for use by participants at home (see Section 8.2.1.1.1).

8.2.1.1.1 Urine Home Pregnancy Test

Urine pregnancy test kits will be dispensed to all study participants at V2 and at subsequent visits, as needed, for use by participants at home prior to starting each blister, whenever a pregnancy is suspected, and within 48 hours after the last tablet from the last blister of study drug has been taken. Instructions for use should be reviewed with each participant. The lot number and expiration date of the test kit(s) provided to the participant should be documented in the study chart. Additional test kits will be dispensed at subsequent visits, as needed, to replace those that were used and ensure that test kits for future use will not expire between visits.

If a positive result is obtained with a urine home pregnancy test, a confirmatory serum β-hCG test must be performed within 24 hours. Note, a local laboratory can perform the serum pregnancy test used to confirm a positive urine pregnancy test.

The earliest positive pregnancy test should be entered into the e-Diary and into the database (even if performed at home) after confirming the results.

Negative urine home pregnancy tests should be documented within the database when performed due to a missed visit. In the event of a missed visit, the site will contact the participant and request that the visit be rescheduled. If the participant is unable to return to the site, the participant should perform a urine home pregnancy test and results should be documented in the e-Diary.

8.2.1.2 Pregnancy

Pregnancy is not considered an AE. It is an efficacy endpoint. If a pregnancy is confirmed, the participant will be discontinued from study drug and from the study. **Any pregnancy in a participant that occurs during the study is to be reported to the Sponsor within 24 hours of confirmation** and should follow the procedures outlined in Appendix 5. Refer to Section 8.2.1.2.1 for determination of estimated conception date by ultrasound.

Details of all pregnancies will be collected after the start of study treatment. Pregnancies potentially exposed to NOMAC-E2, ie, pre-treatment pregnancies diagnosed after the onset of

treatment and pregnancies with a conception date between first tablet intake and 7 days after the last active tablet intake, must be followed to the delivery/termination of the pregnancy (unless the participant withdraws consent [or assent, if applicable]). The site should obtain the necessary information such as the date of delivery/termination, type of delivery/termination, outcome (health of infant), and birth weight. Data should be recorded on the Pregnancy Report eCRF.

Pregnancy outcomes such as spontaneous abortion, missed abortion, benign or malignant hydatidiform mole, fetal death, intrauterine death, ectopic pregnancy, and stillbirth must be reported as SAEs (important medical events).

Any AE related to the infant must be reported on the eCRF. Refer to the eCRF completion guidelines for details.

Information regarding exposure during breastfeeding is not applicable since participants who are pregnant or lactating would be excluded from study participation.

Pregnancy follow-up and outcomes for participants that have been exposed to treatment may not yet be available at the time of preparing the clinical study report. Any follow-up information not available at the time of preparing the clinical study report will be reported separately. Only information collected up to and including the last assessment 14 days after end of treatment will be reported in the clinical study report.

8.2.1.2.1 Ultrasound Dating of Confirmed Pregnancies

Ultrasound examination should be performed to determine the gestational age and estimated date of conception. First trimester ultrasound results are preferred for dating purposes as they are the most accurate. The estimated date of conception, date of the ultrasound, and gestational age of the fetus (in weeks and days) at the time of the ultrasound, should be recorded on the appropriate eCRF. **This information is very important for determining the on-treatment pregnancies used in the calculation of the PI for the primary efficacy endpoints.** A pregnancy wheel or date of last menstrual period is not acceptable when determining the date of conception. A first trimester ultrasound must be performed to determine the gestational age of the pregnancy. If a first trimester ultrasound is not performed, the earliest available ultrasound should be used to determine the gestational age of the pregnancy.

8.2.2 Vaginal Bleeding Event

The vaginal bleeding events will be assessed and recorded daily in the e-Diary (Section 1.3). Participants are to record the presence of bleeding or spotting daily and any use of sanitary products for this purpose. Sanitary products used for other reasons other than for vaginal bleeding (eg, urinary incontinence or vaginal discharge), are not recorded. Participants will be trained in how to record vaginal bleeding and spotting in the e-Diary as per below:

- No bleeding: no vaginal discharge containing blood.

- Bleeding: vaginal discharge containing blood that requires the use of a sanitary product (ie, pad, panty liner, tampon, or menstrual cup).
- Spotting: vaginal discharge containing blood that requires no use of a sanitary product (ie, pad, panty liner, tampon, or menstrual cup).

See Section 9.4.2.5.1 for definitions of expected (ie, scheduled) bleeding interval. Data will be analyzed according to the definitions noted in Section 9.4.2.5.

8.2.3 Compliance

Participants will be assessed for compliance with the following in accordance to the time points specified in the SoA (Section 1.3):

- e-Diary completion (see Section 8.2.3.1).
- Study drug intake (see Section 8.2.3.2).
- "at-risk" cycles (see Section 8.2.3.3).

8.2.3.1 Participant e-Diary

Access to the e-Diary Application will be made available to participants at V1. Participants should begin using the e-Diary on the same day as V1, at home, and continue to complete the e-Diary at approximately the same time daily until the e-Diary is returned at EOS/ET or at V2 for participants who did not meet inclusion/exclusion criteria. Participants should complete the e-Diary entries before returning their device, if one was provided.

Participants will use the e-Diary for at least 1 week during screening to conduct daily assessments of vaginal bleeding/spotting. Participants will receive e-Diary training at V1. Investigators or designees should explain the importance of completing the e-Diary daily. Investigators are to evaluate participant compliance with the e-Diary during screening to assess eligibility. At V2, participants should complete their e-Diary after the visit has been conducted.

Participants should bring their e-Diary each time they visit the site.

Site staff are responsible for:

- Training participants on how to complete the e-Diary.
- Ensuring participants understand the e-Diary questions.
- Ensuring participants understand the importance of completing the e-Diary every day.
- Contacting participants when alerted to missing e-Diary entries.

See the e-Diary manual for additional information, including e-Diary activation instructions and technical guidance and support.

Data to be collected in the e-Diary include (but are not limited to) the following:

- Daily information:
  - Study drug intake
  - Vaginal bleeding-spotting events and the use of sanitary products.
- Monthly information (to be provided before starting a new blister):
  - Start of a new blister, triggering recording of the information below
  - Pregnancy testing and results
  - Heterosexual vaginal intercourse during previous cycle.
  - Concomitant use of condoms and other forms of contraception during previous cycle
- Optional information:
  - Pregnancy testing and results as applicable.

8.2.3.1.1 Daily e-Diary Questions

Every day, starting at V2, eligible participants are to record the intake of study drug during the past 24 hours.

Every day, starting at V1, participants are to record vaginal bleeding-spotting events that occurred during the past 24 hours. The use of any sanitary products (ie, tampons, pads, panty liners, or menstrual cup), used for vaginal bleeding should be recorded. Other sanitary products that do not permit the estimation of the amount of bleeding (eg, superabsorbent undergarments) should not be used. Sanitary products that are used for any other reason (eg, for urinary incontinence or vaginal discharge) are not recorded in the e-Diary. The questions should be completed EVERY DAY until V7 to also cover the withdrawal period, so that scheduled bleeding after the last cycle can also be determined.

Participants should alert the site immediately if they are experiencing technical difficulties with their e-Diary. The e-Diary will allow daily data entry up to 24 hours late, after which, data entry will be locked out. Participants should complete the e-Diary entry before returning their device at V7.

8.2.3.1.2 Monthly e-Diary Questions (Before Starting a New Blister)

The e-Diary will include additional questions for the participant to answer just before starting a new blister of study drug. These questions ask about the occurrence of heterosexual vaginal intercourse at least once during the preceding cycle and the use of additional contraceptives (eg,

condoms). If additional contraception was used, the participant must specify the type of contraception used.

Note: If additional use of hormonal contraceptives (other than the NOMAC-E2 COC) is recorded, details should be collected at the next study visit and recorded in the database as concomitant medications.

8.2.3.1.3 Monitoring e-Diary Compliance

e-Diary entries will be uploaded daily and monitored for completion. The e-Diary is equipped with a sound alert to daily remind participants to complete the e-Diary. Participants will receive a daily reminder alert to complete the e-Diary. Participants will not receive a daily reminder to take study drug. Compliance will be remotely monitored by study staff on an ongoing basis and will be reviewed at each site visit and phone contact.

Missing daily e-Diary entries will interfere with the interpretation of adherence to study drug intake and the vaginal bleeding profile. Sites will be contacted if 2 consecutive daily e-Diary entries are missing. When alerted to missing entries, the site is expected to contact the participant in a timely fashion and remind the participant to complete the e-Diary. Attempts to contact the participant should be documented within the study record.

As the end of cycle questions (to be answered before starting a new blister) regarding heterosexual vaginal intercourse and additional contraceptive use are crucial to the primary efficacy endpoints (and missing data will result in the exclusion of a cycle from the primary endpoint PI calculation), at the time of the statistical analysis, missing end of cycle e-Diary entries will be imputed by 'No' for heterosexual vaginal intercourse and 'Yes' for use of additional contraception, making the cycle to be considered not at-risk, which will exclude the entire cycle for the primary contraceptive efficacy analysis (unless a pregnancy occurred).

At all site visits, compliance with daily and end of cycle e-Diary entries will be reviewed by site staff. Reinforcement of e-Diary study requirements and additional e-Diary training will be provided to study participants, as needed. Additional study visits may also be scheduled to provide additional training as needed for participants who continue to fill out the e-Diary incorrectly or incompletely. Participants who are not compliant should be re-trained.

8.2.3.2 Study Treatment Compliance

The prescribed dosage and mode of administration may not be changed.

The intake of study drug will be recorded by the study participants daily in the e-Diary. The e-Diary data will be the primary source to measure study treatment compliance. Any deviations from the prescribed dosing regimen will be captured in the e-Diary.

During both on-site and phone visits, compliance will be reviewed by the site using the e-Diary data. Participants exhibiting poor study drug intake compliance should be counseled on the

importance of good compliance to the study drug dosing regimen. These compliance checks by the site and the counseling on the importance of compliance to study drug intake must be documented by site personnel in the source documents.

Non-compliance to study drug intake during the scheduled active cycle period (Days 1 to 24) is defined as 4 or more days with forgotten tablets, or 2 or more consecutive days with forgotten tablets. The remaining treatment cycles will be included in the Per-Protocol (PP) analysis unless excluded by other protocol deviations (see Section 9.3.4 for more information).

8.2.3.3 Monitoring "at-risk" Cycle Compliance

Participants are expected to have heterosexual vaginal intercourse at least once a month and refrain from using additional methods of contraception. Compliance with these instructions are needed for a cycle to be included in the primary endpoint PI calculation. Compliance will be assessed by review of the end of cycle questions (Section 8.2.3.1.2) at study visits and on an ongoing basis by the Sponsor through medical monitoring reports. Sites will be notified if participants are non-compliant with the protocol (ie, cycles not at risk or entries missing such that a cycle is considered not at risk) on a per cycle basis and are expected to contact the participant to reinforce compliance with the study protocol. Additionally, sites will be notified if participants are persistently non-compliant with the protocol (ie, for 3 or more consecutive cycles) such that cycles are not at risk for pregnancy. Participants who are persistently non-compliant will be evaluated for appropriateness to continue in the study.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3). Details regarding specific safety procedures/assessments to be performed in this study are provided below.

8.3.1 Physical Examinations

A focused physical examination will be conducted by an Investigator or medically qualified designee (consistent with local requirements) at the Screening (V1) and EOS (V7) Visits as per institutional standard. At a minimum, examination for abnormalities of the heart, lungs, abdomen, and extremities should be performed. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Gynecologic and Breast Examinations

A gynecological examination (including vulva, vagina, cervix, uterus, and adnexa) and a breast examination will be performed according to the SoA (see Section 1.3) and whenever clinically indicated. These examinations should be conducted by a licensed clinician (ie, Physician, Physician Assistant, or Nurse Practitioner).

Only abnormal findings should be recorded on the appropriate eCRF.

8.3.3 Vital Signs, Body Weight, and Height

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Blood pressure and pulse measurements:

- Should be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Should be performed before performance of any study procedure that may cause discomfort (eg, gynecological examination, venipuncture) and preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

Height and weight will be measured and recorded according to the SoA (see Section 1.3). The BMI will be calculated (weight/height^2 in kg/m^2) at each visit during data analysis. The study site should calculate BMI at the Screening Visit to assess participant eligibility, and the IVRS/IWRS will calculate BMI at baseline (V2) to support treatment allocation targets for BMI <30 kg/m^2 and BMI ≥30 kg/m^2. Baseline BMI subgroups used for primary and secondary contraceptive analyses will be defined based on screening height and baseline weight as captured on the eCRF.

8.3.4 Clinical Safety Laboratory Assessments

See Appendix 3 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The Investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE eCRF. The laboratory reports must be filed with the source documents.

All protocol-required laboratory assessments, as defined in Appendix 3 must be conducted in accordance with the laboratory/procedure manual and the SoA.

If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the Investigator (eg, SAE or AE), then the results must be recorded in the appropriate eCRF.

For any laboratory tests with values considered clinically significantly abnormal during participation up to EOS. Every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the Investigator. If such 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.

Screening laboratory safety tests may be repeated once before treatment allocation (V2) at the discretion of the Investigator if the initial results are inconsistent with the participant's clinical

status or recent laboratory results. Screening may be performed between 7 days and 42 days before V2.

Laboratory safety tests (hematology and biochemistry) are scheduled to be repeated at V7 for all participants. If the participant discontinues early from the protocol-specified Treatment Period, those safety tests specified for the EOS Visit (V7) should be completed.

Details on sampling, processing, and shipping of the materials to the central laboratory will be described in a separate laboratory/procedure manual.

8.4 Adverse Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AEs and SAEs, can be found in Appendix 4.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative).

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The Investigator and any designees remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment or withdraw from the study.

The Investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE with respect to seriousness, intensity/toxicity and causality.

For any guidance regarding AE/SAE reporting, the Investigator should contact the Medical Monitor.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until EOS/ET (Section 1.3).

From the time of signing ICF through EOS/ET(V7), which is 14 to 19 days after last intake of study drug, all AEs, SAEs, and other reportable safety events must be reported by the Investigator. For the analysis of AEs and SAEs, a distinction will be made between:

- **Pre-Treatment AEs**: Events which occur after the ICF (or assent form, if applicable) is signed and before the first intake of study drug.
- **Treatment-emergent AEs**: Events which occur in temporal association with intake of study drug, until 14 days after the last intake of active study drug.

Additionally, any SAE brought to the attention of an Investigator at any time outside the period specified in the previous paragraph must be reported immediately (within 24 hours of learning about the event) to the Sponsor if the event is considered related to study drug.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 8.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

Table 8 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Signing of ICF to First Intake of Study Drug (Day 1)	Reporting Time Period: First Intake of Study Drug (Day 1) through End of Study (V7)	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious Adverse Event (NSAE)	Report if: • Due to protocol-specified procedure, or • Causes exclusion	Report all	Per eCRF completion guidelines
Serious Adverse Event (SAE)	Report if: • Due to protocol-specified procedure, or • Causes exclusion	Report all	Within 24 hours of learning of event
Pregnancy complications and outcomes/ Lactation Exposure	Report if: • Participant has been exposed to any protocol-specified procedure	Report all	Within 24 hours of learning of event
Event of Clinical Interest (ECI)	Report if: • Causes exclusion	Report all	Within 24 hours of learning of event
Tumor	Report if: • Causes exclusion	Report all	Within 5 calendar days of learning of event (unless serious)

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and

non-leading 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 AEs, SAEs, and other reportable safety events, including pregnancy complications/outcomes (see Appendix 5) and exposure during breastfeeding, events of clinical interests (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). In addition, the Investigator will make every attempt to follow all nonserious AEs that occur in eligible (allocated to treatment) participants for outcome. Further information on follow-up procedures is given in Appendix 4.

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 towards the safety of participants and the safety of a study drug under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Events of Clinical Interest

Selected nonserious AEs and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interests for this study that require regulatory reporting **within 24 hours** of learning of the event include:

- An elevated AST or ALT lab value that is greater than or equal to 3 × the upper limit of normal (ULN) and an elevated total bilirubin lab value that is greater than or equal to 2 × ULN and, at the same time, an alkaline phosphatase lab value that is less than 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

***Note:** These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

- ATE (including myocardial infarction, stroke, or peripheral arterial events) and VTE (including pulmonary embolism and deep venous thrombosis).

8.5 Treatment of Overdose

Multiple doses up to 5 times the daily dose of NOMAC-E2 and single doses up to 40 times the daily dose of NOMAC alone have been used in women without safety concern. For this study, any dose of 3 or more tablets per day will be considered an overdose. Based on general experience with COC, symptoms that may occur include nausea, vomiting, and slight vaginal bleeding. There are no antidotes, and further treatment should be symptomatic. See the IB for more information (4).

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

- Contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

8.6 Pharmacokinetics and Pharmacodynamics

Sparse plasma samples for NOMAC PK analysis will be collected in a subset of the study population (approximately 200 participants) during V3 and V4, to be scheduled between Day 7 and Day 12 of the corresponding cycle (ie, within the +5 day window for Cycle 2 and Cycle 5, respectively). The subset will be representative of the study population in terms of BMI distribution.

For each participant in the PK subset, PK plasma samples will be taken during V3 and V4. At each visit, two PK plasma samples will be taken; the first sample within 1 hour prior to, and the second sample between 1 and 2 hours after, the observed dose administration.

Participants must take their daily dose at the visit so it can be observed and recorded by the site staff. The dosing time and date must be correctly recorded for the dose immediately preceding the V3 and V4 clinic visits along with the date and time of the dose administration during the V3 and V4 clinic visits, in the respective eCRF pages. The participant must also enter the dose taken in their e-Diary, as usual. The date and time for all PK samples, along with the corresponding labeled

accession number will be recorded in the eCRF page. This will result in the study participants staying in the clinic a maximum of 3 hours longer for a visit when PK is assessed.

Pharmacokinetic visits must be scheduled to allow 16 to 30 hours between the dose taken by the participant on the day prior to the PK visit, and the dose taken on the day of the PK visit.

The following dosing instructions and visit scheduling relative to PK sampling should be followed:

- If the participant is routinely taking their dose in the morning, the dose should be held until instructed to take the dose during the V3 and V4 clinic visits.

  or

- If the participant is routinely taking their dose in the afternoon or evening, the corresponding V3 and V4 daily dose will be administered in the clinic when instructed. Consequently, no additional dose (after the dose taken in the clinic) should be taken the afternoon or evening of the V3 or V4 clinic visit.

Samples will be kept frozen at -20°C, or colder, prior to shipment. See the Central Laboratory Manual for details on sampling, processing, labeling, storage, and shipment of human biological samples used in the PK evaluation.

Pharmacodynamics are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.9 Changes to Study Procedures Due to COVID-19 Pandemic

The following information provides guidance regarding changes to the study procedures that could be implemented for study participants or study sites affected by the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance takes references from the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency – Guidance for Industry, Investigators, and IRBs, March 2020, updated 03 June 2020, and the European Medicines Agency Guidance on the Management of Clinical Trials During the COVID 19 (Coronavirus) Pandemic, Version 3 (28 April 2020).

As the COVID-19 pandemic may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes

should be made on a case-by-case basis by the Investigator in consultation with the study team and the medical team as needed, while maintaining patient safety and confidentiality as the priority.

Procedural changes due to COVID-19 may include the following:

- All visits except Screening, V2, and EOS/ET (V7) may be converted to virtual visits or phone calls to extend flexibility to participants during the COVID-19 public health emergency. Virtual visits/phone calls will be documented in the study records and eCRF. The data collected from virtual visits/phone calls may be handled differently in the final data analysis, with this documented in the Statistical Analysis Plan (SAP). All other planned in-clinic visits must be done with the participant present at the site. Upon discussion and agreement with the Sponsor, other options besides virtual visits/phone calls may be utilized. Any conversion of visits must be approved by the Sponsor.
- For virtual visits/phone calls, collection of scheduled clinical laboratory samples (blood specimen collection or other diagnostic tests) will be performed by a qualified health care professional who can visit the participant at home. All laboratory samples should still be sent to the designated laboratory as outlined in the Laboratory Manual.
- Missed clinic visits or participant withdrawals due to COVID-19 must be recorded on the eCRF. Participants who discontinued from screening due to COVID-19-related factors but were otherwise qualified to participate in the study may be rescreened. Any rescreening must be approved by Medical Monitor.
- Allow electronic clinical outcomes assessments typically scheduled for completion at the clinic to be completed at home if a site visit cannot occur.
- In specific circumstances and with Sponsor approval, it may be allowed to transfer participants to sites away from risk zones or closer to their homes (either to new sites or sites already participating in the study).
- During the COVID-19 public health emergency, alternative study drug delivery to study participants may be necessary to avoid unnecessary visits to sites while providing needed study drug. If there is a high risk that an upcoming visit may be converted from an on-site to off-site visit, additional study drug may be dispensed during a scheduled study visit. If needed, study drug may also be shipped directly from investigational sites to participants' residences by a contracted logistics provider or distributor (direct-to-participant shipment) in compliance with national laws or temporary national emergency measures and Sponsor processes.

Deviations from the protocol-specified procedures (eg, laboratory assessments) will be recorded as related to COVID-19.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

In this study, point estimates and associated CIs will be calculated. No formal hypothesis tests will be conducted.

9.2 Sample Size Determination

9.2.1 Main Analysis

[redacted]

A PI of 3.0 is assumed for the NOMAC-E2 COC, which is similar to the values observed for low dose COCs such as LoLoestrin (norethindrone/EE) and Quartette (LNG/EE). This is considered to be a conservative estimation, as previous clinical study data suggest that the NOMAC-E2 COC is associated with a lower PI than higher dosed COCs such as DRSP/EE 3.0 mg/30 µg (Yasmin), while recent large scale observational study data suggest that the NOMAC-E2 COC may also have a PI much lower than the LNG/EE 150/30 µg COC (eg, Levora).

[redacted] (19).

A summary of the number of at-risk cycles and number of treated participants required is presented in Table 9 for different scenarios of expected PIs ranging between 2.4 and 3.4 in order to achieve 80%, 85%, or 90% power, respectively.

Table 9 Number of at-risk Cycles and Number of Treated Participants Required Depending on Expected PI to Achieve an Assumed 80%, 85% or 90% Power

PI Expected	Power[a] (%)	Number of At-risk Cycles	Number of Treated Participants
2.4	80	5557	731
2.4	85	5903	776
2.4	90	7060	928
2.6	80	6847	900
2.6	85	7212	948
2.6	90	8307	1092
2.8	80	8417	1107
2.8	85	8825	1160
2.8	90	9890	1300
3.0	80	10717	1409
3.0	85	11643	1531
3.0	90	12708	1671
3.2	80	12695	1669
3.2	85	14941	1964
3.2	90	16481	2167
3.4	80	16469	2165
3.4	85	18629	2449
3.4	90	20997	2760

Abbreviations: CI=confidence interval; PI=Pearl Index.

a. The "probability of success" or "power" represents the probability that the upper CI limit of the PI will be no larger than 5.0, under the various assumptions of the PI and that the number of pregnancies follow a Poisson distribution. The power was derived, based on formula (14) and exact Poisson probabilities, computed in the R software.

[redacted]

9.2.2 Pharmacokinetic Analysis

For the PK evaluation described in Section 8.6, sparse sampling and population PK modeling will be used to estimate the effect of covariates (body weight and BMI) on NOMAC PK in premenopausal women aged 14 to 35 years (inclusive) after 1.5 mg E2 and 2.5 mg NOMAC. A

subset of approximately 200 participants, representative of the study population in terms of BMI distribution, will be selected for inclusion in the NOMAC PK evaluation.

The number of participants for inclusion in the PK subset to substantiate clinical relevance was established by the evaluation of various clinical trial simulation scenarios based upon a prior NOMAC population PK modeling effort (data on file).

9.3 Populations for Analyses

9.3.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as all participants allocated to treatment who took at least one dose of study drug.

The FAS is a supportive population to further characterize the contraceptive efficacy and the vaginal bleeding pattern.

9.3.2 Contraceptive Efficacy Analysis Populations

9.3.2.1 Restricted Full Analysis Set

The restricted FAS (rFAS) is defined as the subset of all participants included in the FAS who have at least one at-risk treatment cycle of NOMAC-E2 COC, or participants with a treatment cycle (at-risk or not) of NOMAC-E2 COC in which a pregnancy has occurred (ie, treatment cycle containing an estimated conception date for a pregnancy).

The rFAS will be used for the primary (contraceptive) efficacy analysis.

9.3.2.2 Per Protocol 1 Population

The PP 1 population is defined as the subset of all participants in the rFAS, with at least one treatment cycle of NOMAC-E2 COC that occurs without specific protocol deviations, as defined in Section 9.3.4.

The PP 1 is used to further characterize the contraceptive efficacy.

9.3.3 Vaginal Bleeding Analysis Populations

The FAS evaluable for the Cycle Control Analysis (FAS CCA evaluable) is the primary analysis population for cycle-based vaginal bleeding analyses and is defined as the subset of all participants included in the FAS who have at least one treatment cycle evaluable for the CCA.

The FAS reference period (RP) evaluable is the primary analysis population for reference period-based vaginal bleeding analysis and is defined as the subset of all participants included in the FAS who have at least one RP evaluable.

Details regarding the definition of evaluable cycles for FAS CCA evaluable analysis and evaluable RPs for FAS RP analysis, along with any PP population that may correspond to either FAS population, will be clarified in the SAP.

9.3.4 Per-Protocol Analysis and Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in an approved protocol.

The final determination of important or non-important protocol deviations, and thereby the composition of important deviations which would exclude participants or time periods from an associated PP population, will be made prior to the final database lock and will be documented in a separate memo. These deviations may include, but are not limited to, the presence of any of the following:

- Treatment cycles in which the participant is non-compliant with study drug will be excluded. Non-compliance to tablet intake during the scheduled active cycle period (Days 1 to 24) is defined as either:
  - 4 or more days with forgotten tablets, or
  - 2 or more consecutive days with forgotten tablets.
- Participant has >75% of treatment cycles in which either the participant was not considered at risk for pregnancy or was non-compliant with study drug or e-Diary completion will exclude the participant from the PP 1 set.
- Treatment cycles from participant having used prohibited medication listed in Table 6. Treatment cycles will be excluded in which the medication was used, including treatment cycles started within 28 days after discontinuation of prohibited medication. The remaining treatment cycles of the participant will be included in the PP analysis unless excluded by other protocol deviations.

  Note: Treatment cycles in which hormonal contraception other than the NOMAC-E2 COC has been used are considered a protocol deviation for the purposes of the CCA or RPA, and to be excluded from the FAS evaluable. Such treatment cycles have already been excluded from the contraceptive efficacy calculation in the rFAS. Treatment cycles in which condoms (or other non-hormonal methods of back-up contraception) are used will be considered in the CCA and RPA, in contrast to the contraceptive efficacy analysis, as such use is not expected to affect the CCA and RPA outcomes.
- Participant is pregnant or has taken study drug without a documented negative pregnancy test, on the day of first study drug intake.
- Participant has undiagnosed (unexplained) abnormal vaginal bleeding or any other abnormal bleeding that meets exclusion criteria at screening as being attributable to underlying pathology

(ie, cervical/endometrial polyp, uterine fibroids, endometriosis, etc.) which has not been treated/resolved.

- Participant is breastfeeding.

9.3.5 Safety Analysis Population

The All-Participants-as-Treated (APaT) population will consist of all participants allocated to treatment who took at least one dose of study treatment.

The APaT population will be used for the analysis of all safety data in this study.

9.3.6 Pharmacokinetic Analysis Population

A subset of approximately 200 participants, representative of the study population in terms of BMI distribution, will be selected for inclusion in the NOMAC PK evaluation.

9.4 Statistical Analyses

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. The SAP document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and will supersede the protocol in case of differences.

Statistical analysis will be performed using SAS® software (version 9.4 or higher) (SAS Institute Inc., Cary, NC, USA).

9.4.1 General Considerations

All data will be listed, and summary tables will be provided. Summary statistics will be presented by treatment group. Continuous variables will be summarized for the measured values and change from baseline values using the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized with counts and percentage for each category. Point estimates will be presented together with 95% CIs as appropriate.

9.4.2 Efficacy Analyses

9.4.2.1 Contraceptive Efficacy Endpoints

9.4.2.1.1 Definitions

An on-treatment pregnancy is defined as a pregnancy with an estimated date of conception from the day of first intake of study drug up to and including 7 days after the last intake of active study drug.

A pre-treatment pregnancy is defined as a pregnancy with an estimated date of conception after signing informed consent, but before the first intake of study drug. Also, all pregnancies in

participants in which all dispensed study drug is returned unused (per Investigator's record) will be considered pre-treatment pregnancies.

A post-treatment pregnancy is defined as a pregnancy with an estimated date of conception more than 7 days after the last intake of active study drug.

See Section 8.2.1.2.1 for confirming reported pregnancies and determining conception date.

A treatment cycle is defined by the period between 2 start dates of a blister, as recorded in the participant's e-Diary. The last treatment cycle ends by the last recorded day of tablet intake.

An at-risk cycle for pregnancy is a treatment cycle in which the participant has used no contraceptives of any type other than the study drug *and* in which the participant has affirmed heterosexual vaginal intercourse.

[redacted]

[redacted] (20).

9.4.2.2 Primary Contraceptive Efficacy Endpoint(s)

PI ***at-risk***

The PI at-risk analyzed in the rFAS population is selected as the primary efficacy endpoint. As specified by the FDA Draft Guidance on Contraceptive Efficacy Trials, the calculation of the PI for the primary efficacy evaluation should include only cycles during which (a) heterosexual vaginal intercourse occurred and (b) no back-up or emergency contraception was used based on

e-Diary data (19). The participants will be asked to record in the e-Diary each time a new medication blister is started whether during the preceding cycle heterosexual vaginal intercourse has taken place and whether any other form of contraception has been used, and if so, which form. For a treatment cycle to be included in the primary efficacy analysis, it must be confirmed that heterosexual vaginal intercourse did occur and that no other forms of contraception were used.

Note: any cycle in which a pregnancy is conceived is included in the PI $_{\text{at-risk}}$ even when back-up contraception has been used and/or heterosexual vaginal intercourse has been claimed to not have occurred. Missing information regarding heterosexual vaginal intercourse or the use of additional contraception will result in exclusion of a cycle from the denominator of the PI calculation, except for a cycle in which a pregnancy has occurred.

9.4.2.3 Secondary Contraceptive Efficacy Endpoint(s)

***PI** perfect use*

The PI $_{\text{perfect use}}$ is selected as a key secondary efficacy endpoint. The PI $_{\text{perfect use}}$ will be analyzed using the PP 1 population. The PP 1 population is a subset of the rFAS population; see Section 9.3.4. For a cycle to be included in this secondary efficacy analysis, it must be confirmed that heterosexual vaginal intercourse did occur, that no other forms of contraception were used and that there were no protocol deviations as defined in Section 9.3.4. This analysis, also known as *method failure* analysis, estimates the contraceptive efficacy of the method when used as directed and is considered to approach the inherent contraceptive properties of the NOMAC-E2 COC most closely.

***PI** typical use*

The PI $_{\text{typical use}}$ analyzed using the FAS is selected as another secondary efficacy endpoint. The FAS contains all participants allocated to treatment who took at least one dose of study drug. All cycles, regardless of heterosexual vaginal intercourse, use of other forms of contraception, and protocol deviations are included in this supportive efficacy analysis. This analysis, also known as *user failure* analysis, estimates the contraceptive efficacy of the method under typical use conditions is considered to approach the real-life contraceptive properties of the NOMAC-E2 COC most closely.

Subgroup Analysis

[redacted]

9.4.2.4 One-year Cumulative Pregnancy Rate

A time-to-pregnancy analysis will be performed using the Kaplan-Meier approach and will be further defined in the SAP. Participants who do not become pregnant will be censored at the last

day of the on-treatment period. The cumulative probabilities of in-treatment pregnancies after thirteen 28-day treatment cycles will be estimated.

9.4.2.5 Vaginal Bleeding Endpoint(s)

Participants will record daily their experience of vaginal bleeding-spotting over the last 24 hours in the e-Diary, defined as follows:

No bleeding: no vaginal discharge containing blood.

Bleeding: vaginal discharge containing blood that requires the use of a sanitary product (ie, pad, panty liner, tampon, or menstrual cup).

Spotting: vaginal discharge containing blood that requires no use of a sanitary product (ie, pad, panty liner, tampon, or menstrual cup).

Note: The routine use of a panty liner or other sanitary protection for other reasons such as vaginal discharge or urinary incontinence will not be counted as a bleeding-spotting day.

Vaginal bleeding-spotting information collected prior to the date of V2 will be used to assess diary compliance and will not contribute to the study analysis.

9.4.2.5.1 Cycle Control Analysis

In conventional contraceptives with a 21/7 regimen the *expected bleeding interval* is the 7-day period during which no active treatment is taken (ie, Day 22 to Day 28 of the cycle). A scheduled, or withdrawal, bleeding is expected to start during this hormone-free interval. No bleeding is expected during the period with active treatment, the *expected non-bleeding interval*.

In this study, participants will be treated with a 24/4 regimen. Therefore, scheduled bleedings will start later and will likely continue into the next cycle. To perform the CCA with this different dosing regimen without introducing an *a priori* increased probability of unscheduled bleeding and an *a priori* decreased probability of scheduled bleeding, the following definitions for the expected non-bleeding and expected bleeding interval will be used:

Expected bleeding interval: 7-day period starting on Day 25 of the cycle and ending on Day 3 of the next cycle.

Expected non-bleeding interval: 21-day period starting on Day 4 of the cycle.

In other words, the cycles will be “shifted” by 3 days in comparison to contraceptives with a traditional 21/7 regimen. To analyze all 13 cycles from this group, the 3 days following the very last tablet intake (scheduled at Day 364) will be included in the analysis of Cycle 13, irrespective of any use of (post-study) contraceptives on one of these days.

The following definitions will be used in the CCA.

- Bleeding-spotting episode: one or more consecutive days during which bleeding or spotting occurred, bounded at each end by bleeding-spotting-free days.
- Bleeding episode: one or more consecutive days during which bleeding occurred, bounded at each end by days on which no bleeding was recorded (with spotting allowed as boundary).
- Bleeding-spotting-free interval: one or more consecutive days with no bleeding, bounded at each end by bleeding or spotting days.
- Unscheduled bleeding-spotting: any bleeding that occurred during the expected non-bleeding interval that was neither an early nor a continued scheduled bleeding-spotting.
- Scheduled bleeding-spotting: any bleeding-spotting that started during or continued into the expected bleeding interval
- Continued scheduled bleeding-spotting: any scheduled bleeding-spotting that continued into the expected non-bleeding interval of the next treatment cycle. For the cycle analysis, continued scheduled bleeding-spotting is counted in the treatment cycle in which it originated and not in the treatment cycle into which it continued.
- Early scheduled bleeding-spotting: any scheduled bleeding-spotting that started before the current expected bleeding interval and continued into the expected bleeding interval.
- Absent scheduled bleeding-spotting: no scheduled bleeding-spotting episode during the expected bleeding interval.
- Absence of any bleeding-spotting: no scheduled or unscheduled bleeding-spotting at all.

The main vaginal bleeding endpoints in the CCA are:

- Proportion of participants who experienced unscheduled bleeding-spotting
- Proportion of participants who experienced absence of scheduled bleeding-spotting
- Proportion of participants who experienced no scheduled or unscheduled bleeding-spotting at all

Point estimates with associated 95% CIs will be estimated for these main vaginal bleeding outcome proportions and presented by treatment cycle.

Additional vaginal bleeding endpoints in the CCA include:

- Number of bleeding days
- Number of spotting days
- Number of bleeding-spotting days
- Mean duration of bleeding-spotting episodes

All CCA will be performed on the FAS evaluable, as the primary efficacy analyses, and on the PP 2 population as supporting analyses.

Frequency tables and/or summary statistics for continuous variables will be calculated for all primary and secondary parameters and presented per cycle. The number and percentage of participants with a bleeding day and the number and percentage of participants with a

bleeding/spotting day will be presented per cycle and within cycle per cycle day, with a denominator based on the number of participants who are considered evaluable for the complete cycle.

Data Handling Conventions

Because of the possible influence of missing data for the bleeding variables, the following additional conventions will be used for the analysis of bleeding events:

- Interpolation rule: In cases, where for one or 2 consecutive days bleeding information is missing, the bleeding information of the day immediately preceding will be imputed for these days. If bleeding information is missing for more than 2 consecutive days, no imputation will be carried out (non-evaluable cycle).
- Irrespective of what was recorded in the e-Diaries, "no bleeding" will be imputed for the first 7 days of Cycle 1 (before "shifting" of cycles for the NOMAC-E2 group). This imputation will be carried out because many women will start during their menstrual period.

9.4.2.6 Reference Period Analysis

Because of the varying treatment cycle lengths allowed within the FAS evaluable (≥22 days and ≤35 days, see Section 9.3.3), an RPA will also be conducted. The RPA is based on occurrence of vaginal bleeding within 91-day long RPs. In this analysis, all bleeding events are counted within consecutive 91-day periods that begin with the first intake of the study drug, regardless of their occurrence in relation to expected bleeding and expected non-bleeding intervals.

The following RPs with a fixed length of 91 days will be defined from the first to the last day of study drug intake and will be defined in more details in the SAP:

- RP 1: from Day 1 to Day 91.
- RP 1.1: from Day 29 to Day 119.
- RP 2: from Day 92 to Day 182.
- RP 3: from Day 183 to Day 273.
- RP 4: from Day 274 to Day 364.
- RP 5: the last 91 days.

The length of the RPs is defined as 91 days (4 × 91 days equal 13 treatment cycles of 28 days) in accordance with the minimum World Health Organization (WHO) requirement of 90 days and is considered to be sufficiently long to allow several bleeding events to occur in an RP.

In some participants the timing of the first tablet intake is aligned with the first day of menstruation, which may result in the beginning of the first RP including days with bleeding events due to menstruation. As this could affect the derived indices of amenorrhea, infrequent, frequent, and prolonged bleeding-spotting, an additional RP designated RP 1.1 starting with treatment Cycle 2 (Day 29), and covering Days 29 to 119, has also been defined.

With respect to the RPA the following definitions will be used:

- Bleeding-spotting-free interval: One or more consecutive bleeding-free days which are bounded at each end by at least one bleeding/spotting day.
- Bleeding-spotting episode: one or more consecutive days during which bleeding or spotting occurred, bounded at each end by bleeding-spotting-free days.
- Bleeding-only episode: one or more consecutive days during which bleeding occurred, bounded at each end by days on which no bleeding was recorded (with spotting allowed as boundary).
- Spotting-only episode: one or more consecutive days during which spotting occurred, bounded at each end by days on which no spotting and no bleeding was recorded.
- Amenorrhea: No bleeding and/or spotting throughout the RP.
- Infrequent bleeding: Less than 3 bleeding/spotting episodes starting within an RP, excluding amenorrhea.
- Frequent bleeding: More than 5 bleeding/spotting episodes, starting within an RP
- Prolonged bleeding (WHO definition): At least one bleeding/spotting episode starting within an RP, with a length of >14 days.
- Prolonged bleeding (FDA definition): At least one bleeding/spotting episode starting within an RP, with a length of >7 days.

The RPA will be conducted on the following endpoints for the FAS evaluable:

- Number of bleeding days, spotting days, and bleeding-spotting days
- Proportion of participants with the following:
  - Amenorrhea;
  - Infrequent, frequent, or normal frequency bleeding-spotting; and
  - Prolonged bleeding-spotting.
- Mean duration of bleeding-spotting episodes defined as abnormal uterine bleeding that occur between periods.

Data Handling Conventions

The same data handling conventions as for the cycle analysis will be used concerning the interpolation rule for missing bleeding information and the imputation of "no bleeding" for the first 7 days of RP1.

Bleeding-spotting episodes and bleeding-spotting-free intervals will be assigned to the RP in which they started and, therefore, counted only once even if they ended in a later RP. Their lengths will not be truncated if they overlapped 2 or more RPs. If for a participant and RP the number of episodes or intervals was zero, the corresponding length variable will be set to missing. If an episode or interval was right- or left-bounded by missing values (after application of the

interpolation rule), the length was excluded from the calculation of the mean length statistics; such bounds may result from the exclusion of non-evaluable RPs. The very last episode or interval in progress on the last day of tablet intake will be counted in the mean length statistics with its truncated (by the last day of tablet intake) length because other treatments may follow after the EOS drug administration.

9.4.3 Safety Analysis

The APaT population will be used for all safety analyses.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values, vital signs, and body weight.

For the analysis of safety data, the following conventions will be used:

- Baseline will be defined as the last measurement before the first study drug intake.
- The on-treatment period will be defined as the period from the day of first tablet intake up to and including the day of last active study drug intake, extended by 14 days. However, any delayed events or diagnoses judged by the Investigator to be related to study drug will also be considered to have occurred on-treatment and will be included in the safety analysis.
- Last measurement is the last value obtained during the on-treatment period.

The proportion of participants with prespecified events listed as ECIs described in Section 8.4.5 during the on-treatment period will be provided along with corresponding 95% Clopper-Pearson CIs. All ECIs will be summarized, even if the incidence is zero.

In addition, the broad AE categories consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, an AE, which is both drug-related and serious, and who discontinued study drug due to an AE will be summarized with corresponding 95% Clopper-Pearson CIs (Table 10). On-treatment AEs are those occurring from first intake of study drug to 14 days after intake of the last active tablet of study drug. AEs occurring during the designated pre-treatment (between V1 and first intake of study drug) and post-treatment (>14 days after last tablet intake of study drug) periods will be provided.

Table 10 Analysis Strategy for Safety Parameters

Safety Endpoint[a]	Within Group 95% CI[b]	Descriptive Statistics
Any AE	X	X
Any Serious AE	X	X
Any Drug-Related AE	X	X
Any Serious and Drug-Related AE	X	X
Discontinuation due to AE	X	X
Specific AEs, SOCs, ECIs, and PDLCs (incidence ≥4 participants)		X
Specific AEs, SOCs, ECIs, and PDLCs (incidence <4 participants)		X
Change from Baseline Results (laboratory tests, vital signs)		X

Abbreviations: AE=adverse event; CI=confidence interval; ECI=event of clinical interest; PDLC=Predefined Limit of Change; SOC=System Organ Class; X=results will be provided.

a. AE references refer to both clinical and laboratory AEs.

b. 95% CIs will be calculated using the Clopper-Pearson method.

For continuous measures such as changes from baseline in laboratory tests and vital sign parameters, summary statistics for on-treatment values will be provided in table format at V2 and V7.

For summary statistics of laboratory parameters and vital signs per visit, visit windows as described in Table 11 will be used.

Table 11 Timeframe Used in the Analysis of Vital Signs and Laboratory Parameters

Definition	Visit	Visit window (treatment day)
Baseline	V1 Screening	<1
In-treatment[a]	V3 After Cycle 1	29 ± 28 days
	V4 After Cycle 4	113 ± 28 days
	V5 After Cycle 7	197 ± 28 days
	V6 After Cycle 10	281 ± 28 days
	V7 After Cycle 13	379 ± 28 days
	Last measurement	>1

Abbreviation: V=Visit

a. From Day 1 until ≤28 days after last tablet intake; Day 1 is defined as day of first study drug intake

Values outside these visit windows, or outside the defined in-treatment period for post-baseline assessments, will be excluded from the analysis of that particular visit.

However, these visit windows will only be applied for analyses performed per visit; no values will be excluded from the determination of markedly abnormal laboratory or vital signs values

(unless outside the defined in-treatment period). If more than one observation is available within a specific visit window, the latest value will be used for analysis.

9.4.3.1 Adverse Events

An overview table of the number (percentage) of participants with any AEs, SAE, drug-related AEs, any serious drug-related AEs, any discontinuation due to AE, any discontinuation due to a SAE, any discontinuation due to a drug-related AE, any discontinuation due to serious drug-related AE, and any deaths will be presented for the on-treatment period. Pre-treatment AEs/SAEs starting before the in-treatment period will be excluded from the AE analyses (unless there is an increase in Investigator assessed intensity or causality, or the AE meets SAE criteria post-treatment allocation) and reported in separate frequency tables with the methods described above.

The number (percentage) of participants with at least one AE will be presented in a frequency table of Medical Dictionary for Regulatory Activities (MedDRA) system organ class (according to the primary path) and MedDRA preferred term. The same tables will be presented by relationship to study drug ("Related" and "Not related") by the Investigator; and by severity of the AE ("mild", "moderate", "severe").

All participants who prematurely discontinue from treatment due to an AE will be summarized considering all their AEs for which the action taken on study drug was "drug withdrawn". The summary will be performed by MedDRA system organ class, preferred term, and relationship.

9.4.3.2 Laboratory Parameters

Routine hematology and biochemistry parameters measured at V1 (Screening) and V7 (EOS or ET) will be determined by a central laboratory, unless the central laboratory results are not available in time for either starting study treatment administration and/or response evaluation. The sexually transmitted infections (STI) panel testing will be performed by a local laboratory. The measurements of each laboratory parameter will be converted to Standard International units before the statistical analysis, unless otherwise specified. The conversion factors will be recorded in the database.

For each parameter, normal reference ranges (including the date of effect) and safety ranges will be presented. Safety ranges are defined on the suggestions of the FDA. If safety ranges are not available for specific parameters, in-house criteria will be used and presented.

Summary Statistics

For each laboratory parameter, summary statistics will be calculated by assessment (V1, V7, and last measurement, respectively). In addition, summary statistics will be presented for the change from baseline. Shifts from baseline to V7 and last measurement will be presented based on shift categories to be identified in the SAP. The incidence of post-baseline markedly abnormal values will be presented based on categories to be identified in the SAP.

9.4.3.3 Vital Signs and Body Weight

Blood pressure and body weight measurements will be performed at screening (V1), treatment allocation (V2), and after Cycles 1, 4, 7, and 10 and at the EOS.

Summary Statistics

For each parameter (including calculated BMI), descriptive statistics will be calculated by visit (including last measurement). In addition, the summary statistics will be presented for the change from baseline. The incidence of post-baseline markedly abnormal values will be presented based on categories to be identified in the SAP.

9.4.3.4 Physical, Gynecological, and Breast Examinations

Clinically significant findings of general physical, gynecological, and breast examinations performed at EOS will be recorded as AEs by the Investigator; these findings will be recorded in the AEs eCRF.

9.4.4 Other Analysis

9.4.4.1 Pharmacokinetics

The population PK evaluation will be performed by the assigned Contract Research Organization. The methodology will be detailed in a separate, stand-alone population PK modeling and simulation analysis plan. Results will be reported separately from the clinical study report.

9.4.4.2 Demographics, Baseline Characteristics, and Disposition

Demographics and baseline characteristics include age, race, ethnicity (Hispanic or Latin origin), body weight, height, BMI (kg/m^2), general medical history, gynecological history, and previous use of contraceptives. To further characterize former contraceptive use, “starters” are defined as those who have not taken any hormonal contraceptive within 2 months before the start of treatment and “switchers” are defined as participants who have used any type of hormonal contraceptive within 2 months before the start of treatment (inclusive).

All variables will be summarized by descriptive statistics. Demographics and baseline characteristics will be summarized for the ApaT, the rFAS, and the FAS evaluable populations. No statistical hypothesis tests will be performed on the demographics and baseline characteristics.

The number and percentage (as applicable) of participants screened and allocated to study treatment, the primary reason for screening failure, and the primary reason for discontinuation from study treatment will be displayed. In addition, the primary reason why participants were allocated to study treatment but discontinued prior to study treatment (non-treated participants) will be presented in a table.

The number of participants who were treated and who completed the clinical study will also be tabulated. A disposition graph of participants will be provided.

The number of participants with protocol deviations will be tabulated by deviation for the FAS. In addition, all deviations will be listed by participant.

A cumulative discontinuation rate will be calculated using the Kaplan-Meier method for all reasons combined. The tables and analyses for premature discontinuations will be performed for the ApaT population.

9.4.4.3 Prior and Concomitant Medication

All medications, as documented by the Investigator, will be coded using the latest version of the WHO Drug Dictionary. Prior medications are defined as any medications reported up to the first study drug intake. Concomitant medications are defined as any medications from the first study drug intake day onwards up to the day of last study drug intake, extended by 7 days.

For the ApaT population, the number of participants taking prior medications and the number of participants taking concomitant medications will be summarized using frequency tables.

9.4.5 Interim Analysis

No interim analysis is planned.

9.4.6 Sensitivity Analysis

Additional sensitivity analyses to be used for handling missing data will be described in the SAP.

9.4.7 Missing Data

Data from participants who withdraw from the study, including Aes and any follow-up, will be included in the analyses of primary and secondary outcomes. Further details regarding missing data will be provided in the SAP.

9.4.7.1 Strategies to Minimize Missing Data

In order to minimize missing data, strategies to minimize participant premature discontinuation/withdrawal will be employed as outlined in Section 7.1. Additionally, participant compliance with e-Diary completion, study drug intake, and at-risk cycles will be monitored closely as outlined in Section 8.2.3.

9.4.7.2 How to Handle Missing Data

Conventions for handling missing e-Diary data are described in Section 9.4.2.

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
β-hCG	β-human chorionic gonadotropin
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ApaT	All-Participants-as-Treated
ASCUS	Atypical squamous cells of undetermined significance
AST	Aspartate Aminotransferase (SGOT)
ATE	Arterial thrombotic or thromboembolic events
BMI	Body mass index
CCA	Cycle Control Analysis
CFR	Code of Federal Regulations
CHC	Combined hormonal contraceptives
CI	Confidence interval
COC	Combined oral contraceptive
COVID-19	Coronavirus Disease 2019
DRSP	drospirenone
E2	17β-estradiol
ECI	Event of clinical interest
eCRF	Electronic case report form
e-Diary	Electronic diary
EE	Ethinylestradiol
EOS	End of Study
ET	Early Termination
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation

Abbreviation	Definition
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV(W)RS	Interactive voice (web) response system
LNG	Levonorgestrel
MALV	Markedly abnormal laboratory value
NOMAC	Nomegestrol acetate
PI	Pearl Index
PK	Pharmacokinetic/s
POP	Progestogen-only pill
PP	Per-Protocol
QTL	Quality tolerance limit
rFAS	Restricted Full Analysis Set
RP	Reference Period
RPA	Reference Period Analysis
SAE	Serious adverse event
SAP	Statistical analysis plan
SoA	Schedule of Activities
ULN	Upper limit of normal
UK	United Kingdom
US	United States
V	Visit
VTE	Venous thromboembolism
WHO	World Health Organization
WY	Woman-years

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

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 Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, 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 and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently 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 study site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 7). The study will not start at any study site at which the Investigator has not signed the protocol.

Financial Disclosure

Investigators, sub-Investigators, and any personnel listed on a Form FDA 1572 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.

Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

Informed Consent and Assent Process

The Investigator or his/her representative will explain the nature of the study to the participant (or her legally acceptable representative, if applicable) and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants (or their legally acceptable representative, if applicable) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

The Investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent, and assent if applicable, from each potential participant (or her legally acceptable representative, if applicable) prior to participating in this clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the Investigator or medically qualified designee must ensure the appropriate documented informed consent (and assent, if applicable) is in place.

General Informed Consent and Assent

Informed consent (and assent, if applicable) given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or her legally acceptable representative, if applicable) and of the person conducting the consent discussion. When a participant's assent is obtained because the participant is a minor, consent must be obtained from a parent or legally acceptable representative.

A copy of the signed and dated informed consent (and assent, if applicable) form should be given to the participant (or her legally acceptable representative if applicable) before participation in the study.

The initial informed consent (and assent, if applicable) form, any subsequent revised informed consent (and assent, if applicable) form, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant (or her

legally acceptable representative if applicable) should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent (and assent, if applicable) form or addendum to the original consent (and assent, if applicable) form that captures the participant's (or if applicable, participant's legally acceptable representative's) dated signature.

Specifics about the study and the study population are to be included in the study informed consent (and assent, if applicable) form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The assent, as applicable will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date. A participant who is <18 years of age at the time of screening who turns 18 years of age during study participation must provide another informed consent documenting consent to continue study participation.

Data Protection

Participants will be assigned a unique identifier by the Sponsor. 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.

The participant must be informed that her 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.

The participant must be informed that his/her 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.

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the EU database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

All participant data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the data entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Quality tolerance limits (QTLs) will be pre-defined in the Monitoring Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance 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 (eg, Contract Research Organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer 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.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

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 study site.

Data reported on the CRF or 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.

The Investigator must maintain accurate documentation (source data) that supports the data entered in the eCRF.

Study monitors will perform ongoing source data verification 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.

Study and Study Site Closure

The Sponsor 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 the Sponsor. 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 drug 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 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 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.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study site will be set forth in the Clinical Trial Agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center studies only in their entirety and not as individual study site data. In this case, a Coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 Clinical Laboratory Tests

The tests detailed in Table 12 will be performed by the central laboratory, with the exception of STI panel testing, which will be performed by a local laboratory. Otherwise, local laboratory results are only required in the event that the central laboratory results are not available in time for either starting study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.0 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.

All study-required laboratory assessments will be performed by a central laboratory, with the exception of STI panel testing which will be performed by a local laboratory, and of urine pregnancy tests which will be performed on-site or at the participant's home.

Investigators must document their review of each laboratory safety report.

Table 12 Protocol-required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count WBC (total and differential)	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Calcium Chloride Creatinine (for determination of eGFR) Glucose (nonfasting) Phosphorus Potassium Sodium Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN) Total protein Blood urea nitrogen	Blood Glucose Protein Specific gravity pH Leukocyte esterase Nitrate Microscopic examination if abnormal results noted on urinalysis	Cervical cytology Serum β-hCG STI panel (local laboratory)

Abbreviations: β-hCG=beta human chorionic gonadotropin; eGFR=estimated glomerular filtration rate; ULN=upper limit of normal; WBC=white blood cell.

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

Definition of AE

AE Definition
• Any untoward medical occurrence in a patient or participant (clinical investigation participant) administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. • 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 medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, 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 conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of study treatment. Overdose per se will not be considered as an AE/SAE but should be reported on the AE Form as an overdose without adverse effect.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (eg, 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). • An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE. • 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.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
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 detained (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 AEs. 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 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the screening number, will be redacted on the copies of the medical records before submission to the Sponsor.
- 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.

Assessment of Severity

The severity of an AE is an estimate of the relative severity of the event made by the Investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as unrelated, unlikely to be related, possibly related, probably related, or unknown (unable to judge).
  - "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
  - "Possibly related" suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions.
  - "Unlikely to be related" suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
  - "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
  - All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, eg, because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

- The Investigator will also consult the IB, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Sponsor. 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 Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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 Sponsor 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 completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to Sponsor via an Electronic Data Collection System

- The primary mechanism for reporting an SAE to the Sponsor or designee will be the electronic data collection system. The study site will enter the event into the electronic data collection system within 24 hours of the Investigator's awareness of the event.
- If the electronic system is unavailable, then the study site will use the paper SAE report form (see next section) to report the event and will enter the event into the electronic data collection system as soon as the system becomes available.
- After the study is completed at a given study site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a study site receives a report of a new SAE from a participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study site can report this information on a paper SAE form (see next section) or to the Medical Monitor/SAE coordinator.
- Contacts for SAE reporting can be found in the study manual, Investigator Study File Binder, or equivalent.

SAE Reporting to the Sponsor or Designee via Paper SAE Report Form

- Email transmission of the SAE form should be done in case there are technical issues with the electronic data capture system and SAE cannot be reported within 24 hours of awareness per the ICH guidelines via electronic data capture. The SAE/Pregnancy paper forms should be emailed to the [redacted] safety project mailbox detailed in the form.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in study manual, Investigator Study File Binder, or equivalent.

Appendix 5 Collection of Pregnancy Information

Pregnancy Testing:

Participants should only be included after a confirmed negative serum pregnancy test at Screening (V1) and a negative urine pregnancy test at treatment allocation (V2). In addition to the negative Visit 2 serum β-hCG test result, it is required to have a negative urine home pregnancy test result on the day of the intended first tablet intake, just prior to the actual first tablet intake.

Additional urine pregnancy testing will be performed by participants at home at prior to starting each blister, whenever a pregnancy is suspected, and within 48 hours after the last tablet from the last blister. Results are to be recorded in the e-Diary. A positive urine pregnancy test must be reported to the site immediately and must be confirmed by a serum test within 24 hours. The earliest positive pregnancy test should be entered into the e-Diary and into the database (even if performed at home) after confirming the results.

Note, serum pregnancy testing may be performed in a local laboratory to confirm the results of a positive urine pregnancy test. Otherwise, all serum pregnancy testing will be performed and assayed in the central laboratory (see Laboratory Manual for more information).

Urine pregnancy testing is to be performed using the test kit provided by the Sponsor and in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Female Participants Who Become Pregnant

The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. For pregnancies potentially exposed to NOMAC-E2, ie, pre-treatment pregnancies diagnosed after the onset of treatment and pregnancies with a conception date between first tablet intake and 7 days after the last active tablet intake, the Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Follow-up will be required until delivery/termination of pregnancy (unless the participant withdraws consent or assent, if applicable). Any information on termination of pregnancy will be collected, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

A first trimester ultrasound must be performed to determine the gestational age of the pregnancy.

While pregnancy itself is the primary study efficacy endpoint, and is therefore not treated as an AE, any pregnancy complication will be reported as an AE or SAE, and pregnancy outcomes such as spontaneous abortion, missed abortion, benign or malignant hydatidiform mole, fetal death,

intrauterine death, ectopic pregnancy, and stillbirth must be reported as serious events (important medical events).

Any female participant who becomes pregnant while participating in the study will discontinue study treatment and be withdrawn from the study.

Appendix 6 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment (Amendment 2) is located directly before the table of contents.

Amendment 1 (01 December 2021)

Overall Rationale for the Amendment: [redacted]

Table 13 Description of Changes in Amendment 1

Section # and Name	Description of Change	Brief Rationale
Title Page (Protocol Title) 1.1 Synopsis (Protocol Title, Overall Design, Key Inclusion/Exclusion Criteria, Number of Participants, Statistical Methods) 3.0 Objectives and Endpoints 4.1 Overall Design 4.2 Scientific Rationale for Study Design 5.1 Inclusion Criteria 9.2.1 Main Analysis	Inclusion criteria #1, and corresponding protocol text, revised to specify lower age limit (14 years) for inclusion in study	For alignment with the current Investigator's Brochure, as per Central IRB request
1.1 Synopsis (Overall Design) 1.3 Table 3 Schedule of Activities 2.3 Benefit/Risk Assessment 4.1 Overall Design Appendix 3, Table 12 Protocol-specified Safety Laboratory Assessment	STI panel revised to include mandatory testing for gonorrhea and chlamydia at V1 and V6, and if abnormal discharge is present, trichomonas and bacterial vaginosis at V1, and as needed throughout the study	To mitigate the possibility of participants contracting a sexually transmitted disease, as per Central IRB request
1.1 Synopsis (Objectives and Endpoints, Overall Design) 3.0 Table 4 Study Objectives and Endpoints 4.1 Overall Design 8.0 Table 7 Blood Volume 8.6 Pharmacokinetics and Pharmacodynamics 9.2.2 Pharmacokinetic Analysis 9.3.6 Pharmacokinetic Analysis Population 9.4.4.1 Pharmacokinetics	Study design (including objectives, assessments, procedures, and statistical considerations) amended to include collection of sparse PK samples for development of a population PK model for NOMAC	[redacted]
1.1 Synopsis (Overall Design) 1.3 Table 3 Schedule of Activities 4.1 Overall Design 8.2.1.1.1 Home Urine Pregnancy Test	Study procedures for urine home pregnancy tests revised to include the following: • Urine home pregnancy test must be performed within 48 hours after the last tablet from the last blister of study drug has been taken • If a positive urine home pregnancy result is obtained, a confirmatory serum β-hCG must be performed within 24 hours	Clarification to ensure participants are not pregnant at the time they completed the last blister of study drug

Section # and Name	Description of Change	Brief Rationale
	(can be completed by local laboratory, if required) • Negative urine home pregnancy tests to be documented in the e-Diary	
1.1 Synopsis (Overall Design) 1.3 Table 3 Schedule of Activities 4.1 Overall Design 8.2.3.1 Participant e-Diary 8.2.3.1.3 Monitoring e-Diary Compliance 9.2.1 Main Analysis 9.4.2.1.1 Definitions 9.4.2.2 Primary Contraceptive Efficacy Endpoint(s) 9.4.2.3 Secondary Contraceptive Efficacy Endpoint(s)	Overall design text revised to specify that participants must engage in heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile or infertile All references to "vaginal intercourse" or "sexual intercourse" throughout document revised to "heterosexual vaginal intercourse"	Clarification
1.1 Synopsis (Objectives and Endpoints, Overall Design) 3.0 Table 4 Study Objectives and Endpoints 4.1 Overall Design 9.4.2.3 Secondary Contraceptive Efficacy Endpoints(s)	Description of endpoints associated with the secondary objective assessing contraceptive efficacy of NOMAC-E2 COC by BMI subgroup was revised (text updated to state "efficacy endpoints" and "potential" removed from description of PI evaluation)	Clarification
1.1 Synopsis (Objectives and Endpoints, Bleeding Profile) 3.0 Table 4 Study Objectives and Endpoints 9.4.2.5.1 Cycle Control Analysis	Bleeding definitions for Cycle Control Analysis revised to replace "amenorrhea" with "no scheduled or unscheduled bleeding-spotting at all". Corresponding secondary bleeding endpoint updated accordingly.	Clarification of terminology to reflect different definitions for "amenorrhea" used in the Cycle Control Analysis compared with the Reference Period Analysis
1.1 Synopsis (Objectives and Endpoints) 3.0 Objectives and Endpoints	Reference Period length changed from "90 days" to "91 days"	Clarification to align with information presented in other protocol sections
1.1 Synopsis (Overall Design) 4.1 Overall Design	Text describing Screening Visit and V1 assessments revised to specify that pregnancy will be evaluated as part of blood sampling	To align with Schedule of Activities

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis (Overall Design) 4.1 Overall Design 8.2.3.1 Participant e-Diary 8.2.3.1.1 Daily e-Diary Questions 8.2.3.1.2 Monthly e-Diary Questions (before Starting a New Blister)	Procedures for e-Diary use revised to include the following: • Clarified duration of monitoring for estimating e-Diary compliance prior to treatment allocation (revised to "at least 7 days") • Statement added to specify that only participants provided with a device are expected to return it on completion of the required e-Diary entries • Description of data to be collected in the e-Diary revised to specify information to be collected on a daily basis versus a monthly basis • Every day from V2 onwards, participants should record their intake of study drug during the past 24 hours • Menstrual cup use to be recorded in daily e-Diary entries • Daily e-Diary questions to be completed every day until V7 • Monthly e-Diary questions to be completed before starting a new blister • Timeframe (4 days) for completion of monthly e-Diary questions added	To clarify expectations of device ownership and return of devices provided, as well as procedures for e-Diary data collection
1.1 Synopsis (Objectives and Endpoints, Statistical Methods) 3.0 Table 4 Objectives and Endpoints 9.2.1 Main Analysis 9.4.2.1.1 Definitions	Calculation of Pearl Index revised to specify that it is calculated from total exposure expressed in 28-day cycles "at-risk" for conception	Clarification
1.2 Figure 1 Study Schema	Figure revised to include visit windows in days	Clarification
5.1 Inclusion Criteria	Inclusion criteria #3 revised to specify that withdrawal method is considered a form of contraception	To clarify forms of contraception which should not be used by participant
5.2 Exclusion Criteria	New exclusion criteria added (#20) excluding participants with a history or presence of meningioma	To reflect new information released by the Periodic Risk Assessment Committee of the European Medicines Agency, and upon

Section # and Name	Description of Change	Brief Rationale
		recommendation by Organon's Risk Management Safety Team and endorsement by Organon's Safety Review Committee
5.2 Exclusion Criteria	Exclusion criteria #26 revised to exclude individuals with history or current evidence of a circumstance that affects their well-being	Clarification, as per Central IRB request
5.4 Screen Failures	Description of AE and SAE reporting for screen failures revised to clarify that events are defined as "pre-treatment"	To align with clarifications to the definition of AEs and SAEs in Section 8.4.1
6.2 Preparation/ Handling/ Storage/ Accountability	Text added to refer to the Pharmacy Manual for reporting of quality issues with blister	Clarification
6.4.1 Timing of the First Dose	Text added to note that participants using a non-hormone medicated intrauterine device should have the device removed prior to starting study drug	To clarify the timing of removing non-hormone medicated intrauterine devices in relation to starting study drug
6.6.1 Prohibited Medications	Text revised to state that contraceptive use can begin the day after the last tablet intake of study drug from the last blister (last cycle) Table 6 updated to list Contraceptive Vaginal Ring, Contraceptive Patch (last allowable use clarified as Cycle 1 Day 1), and oral contraceptives (other than study drug) as prohibited medications, supplements, and other substances	To clarify the timing for initiation of contraception after completion of participation in the study
7.2 Discontinuation of Study Treatment	The criteria for discontinuing a participant from study drug due to the participant not being at risk for pregnancy revised to specify participant must be persistently not a risk of pregnancy	For alignment with compliance guidance in Section 8.2.3.3
8.2.1 Assessment of On-treatment Pregnancy 9.4.2.1.1 Definitions	Definitions of on-treatment pregnancy and post-treatment pregnancy revised to specify timing relates to last intake of "active" study drug	For clarity of assessment of on-treatment pregnancy
8.2.1.1 Pregnancy Testing 8.2.1.2 Pregnancy	Text updated to specify that a urine pregnancy test performed either at home or during a study visit can be used for a rapid result if pregnancy	Clarification

Section # and Name	Description of Change	Brief Rationale
	is suspected (result should be confirmed by serum β-hCG within 24 hours). Text updated to specify that participants with a confirmed pregnancy during the study will be discontinued from study drug and from the study	
8.2.1.2 Pregnancy	Follow-up and outcomes procedures clarified	Clarification
8.2.2 Vaginal Bleeding Event 8.2.3.1 Participant e-Diary 9.4.2.5 Vaginal Bleeding Endpoint(s)	Procedures for recording sanitary product use and definition for "no bleeding" clarified	Clarification
8.2.3.2 Study Treatment Compliance	Section restructured and procedures for measuring compliance clarified (accountability-specific information moved to Section 6.2)	To clarify procedures for assessing treatment compliance
8.3.4 Clinical Safety Laboratory Assessment	Definition of clinically significant abnormal laboratory findings removed	Statement is part of standard template text and is not applicable to the study
8.4.1 Time Period and Frequency for Collecting AE and SAE Information	Definition of AEs and SAEs revised Table 8 revised to clarify procedures for reporting events, to change "cancer" event type to "tumor" event type, and to remove overdose events	To clarify the distinction between events reported after provision of consent but before treatment initiation and events reported after treatment initiation, and to clarify the procedures for event reporting
8.4.1, Table 8 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events 8.4.5 Events of Clinical Interest Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Description of events of clinical interest revised to remove overdose events and procedures for regulatory reporting of overdose events Adverse event definitions revised to state that while overdose events will not be considered as an AE/SAE, overdose will be reported on the AE form	To align with FDA guidance which indicates that overdose without an associated AE or (suspected unexpected) SAE does not require regulatory reporting within 24 hours
8.9 Changes to Study Procedures Due to COVID-19 Pandemic	Statement regarding rescreening revised to remove "or run-in period"	Statement is part of standard template text and is not applicable to the study
9.4.2.6 Reference Period Analysis	Bleeding definitions revised; bleeding episode revised to "Bleeding-only episode" and definition added for spotting-only	Clarification of bleeding definitions for Reference Period Analysis

Section # and Name	Description of Change	Brief Rationale
	episodes	
9.4.3 Safety Analysis	Definitions of on-treatment period and on-treatment AEs revised to specify period includes the day of last "active" study drug intake	Clarification
Appendix 2 Regulatory, Ethical, and Study Oversight Considerations	Personnel responsible for providing financial information revised to include "any personnel listed on a Form FDA 1572"	Clarification
Appendix 3, Table 12 Protocol-required Safety Laboratory Assessments	Assessment of "highly sensitive serum β-hCG" replaced with "serum β-hCG"	Clarification for consistency with revised pregnancy procedures in study
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Definition of AE and procedures for assessment of causality and for reporting SAEs via paper CRF updated	To reflect an update to the ICH-GCP guidelines for definition of an AE, and to accurately reflect the procedures to be undertaken in this study
Appendix 5 Collection of Pregnancy Information	Section revised for alignment with revised pregnancy procedures in study	Appendix contains standard template text and was revised for consistency with the study design and procedures
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Abbreviations: AE=adverse event; β-hCG=β-human chorionic gonadotropin; BMI=body mass index; COC=combined oral contraceptive; COVID-19=Coronavirus Disease 2019; E-diary = electronic diary; FDA=Food and Drug Administration; GCP=Good Clinical Practice; ICH= International Council for Harmonisation; IRB= Institutional Review Board; NOMAC-E2=nomegestrol acetate + 17β-estradiol; PI=Pearl Index; PK=pharmacokinetic/s; SAE=serious adverse event; STI=sexually transmitted infections; V=visit.

Appendix 7 Signature of Investigator

PROTOCOL TITLE: A Phase 3, Open-label, Multi-center, Single-arm Study to Assess Contraceptive Efficacy and Safety of the Nomegestrol Acetate + 17β-estradiol Combined Oral Contraceptive (OG-8175A) in Premenopausal Females Aged 14 to 35 Years (Inclusive)

PROTOCOL NO: OG-8175A-023

VERSION: Amendment 2

This protocol is a confidential communication of Organon LLC. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to Organon LLC.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

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DOCUMENT ID: 0FFKJS

FILE NAME: OG-8175A-023 Protocol Amendment 2

ELECTRONIC SIGNATURES	
Signed By:	**Meaning of Signature** **Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)**
[redacted]	Proxy Responsible Medical Officer 25-Oct-2022 13:28:43 GMT+0000