Clinical Trial Protocol

A Randomized Double-blind Placebo Controlled Phase 3 Trial to evaluate the Efficacy and Safety of Estetrol for the Treatment of Moderate to Severe Vasomotor Symptoms in Postmenopausal Women (E4Comfort Study II)

Short title: Estetrol for the Treatment of Moderate to Severe Vasomotor Symptoms in Postmenopausal Women

Trial Identification:	MIT-Do001-C302
IND Number:	[redacted]
Investigational medicinal product:	Estetrol (E4)
Indication:	Treatment of moderate to severe vasomotor symptoms associated with menopause
Clinical phase:	Phase 3
Sponsor:	Estetra SRL Rue Saint-Georges 5/7 4000 Liège, Belgium
Protocol version and date:	Final Version 1.1, June 11, 2019 Final Version 2.0, July 18, 2019 (Amendment 1) Final Version 3.0, August 13, 2019 (Amendment 2) Final Version 4.0, October 08, 2019 (Amendment 3) Final Version 5.0, February 03, 2020 (Amendment 4) Final Version 6.0, September 23, 2020 (Amendment 5) Final Version 7.1, July 30, 2021 (Amendment 6.1) Final Version 8.0, June 21, 2022 (Amendment 7)

1. ADMINISTRATIVE INFORMATION

1.1. Serious Adverse Event Reporting

In case of a serious adverse event, including a suspected unexpected serious adverse reaction (SUSAR) the Investigator or clinical trial center personnel will send a report within 24 hours of notification to:

[redacted]

1.2. Contact Information

Sponsor	Estetra SRL Rue Saint-Georges 5/7 4000 Liège, Belgium
Head of Clinical Operations Estetra SRL	[redacted]
Clinical Project Leader Estetra SRL	[redacted]
Medical Advisor Estetra SRL	[redacted]
CRO	ICON Clinical Research Limited [redacted]
Director Project Management CRO	[redacted]
Project Manager CRO	[redacted]
Study Monitoring	ICON Clinical Research Limited [redacted]

Central laboratory	[redacted]
Bioanalytical laboratory for E4 analysis	[redacted]
Laboratory for analysis of hemostasis samples	[redacted]
Laboratory for analysis of endometrial biopsies	[redacted]
Storage facilities for additional analysis	[redacted]

1.3. Sponsor Authorization

The Sponsor, Estetra SRL, agrees to conduct the study as outlined in this clinical trial protocol. Any modification of the clinical trial protocol must be agreed upon by the Sponsor, Contract Research Organization (CRO), and the investigator and must be documented in writing.

Name/position	Date	Signature
Clinical Project Leader [redacted]	----------	----------
Medical Advisor [redacted]	----------	----------
Regulatory Affairs Leader [redacted]	----------	----------
Safety Physician [redacted]	----------	----------
Statistics [redacted]	----------	----------
Medical Writer [redacted]	----------	----------

1.4. Investigator Approval and Signature Page

I have read and understood all pages of this clinical trial protocol and relevant appendices. I agree that they contain all information required to conduct this trial. I agree to conduct the trial as outlined in the protocol and to comply with all terms and conditions set out therein. Any modification of the clinical trial protocol must be agreed upon by the Sponsor and the investigator and must be documented in writing.

I confirm that I will conduct the trial in accordance with the local and applicable regulatory requirements, The International Council for harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) - Good Clinical Practice (GCP) guidelines, the provisions of the Declaration of Helsinki and the Clinical Trials Directive 2001/20/EC. I will also ensure that all relevant members of my staff have access to copies of this protocol and to all information relating to preclinical and prior clinical experience (e.g., Investigator's Brochure), local and applicable regulatory requirements, ICH GCP guidelines, and the Declaration of Helsinki to enable them to work in accordance with the provisions of these documents.

Name/position/institution	Date	Signature
Investigator	----------	----------

1.5. CRO Approval and Signature Page

ICON employees have read and understood all pages of this clinical trial protocol and relevant appendices. They agree that they have received all information required to conduct this trial. They agree to conduct the trial as outlined in the protocol and to comply with all terms and conditions set out therein. Any modification of the clinical trial protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

ICON employees confirm that they will conduct the trial in accordance with the local and applicable regulatory requirements, The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) - Good Clinical Practice (GCP) guidelines, the provisions of the Declaration of Helsinki and the Clinical Trials Directive 2001/20/EC. They will also ensure that Investigator(s) and other relevant members have access to copies of this protocol and to all information relating to preclinical and prior clinical experience (e.g., Investigator's Brochure), local and applicable regulatory requirements, ICH GCP guidelines, and the Declaration of Helsinki to enable them to work in accordance with the provisions of these documents.

Name/position	Date	Signature
Director Project Management, ICON Clinical Research Limited	----------	----------

1.6. List of Changes

Amendment 7, leading to version 8.0 of the protocol, date June 21, 2022

All changes are clearly identified in the track-changes version of the amendment.

Major changes		
Description of changes	**Reason for change**	**Sections affected**
Disordered proliferative endometrium has been re-included as an exclusion criterion.	The FDA doesn't agree with the modification of IC#5 and EC#4 introduced with PA 6.1. Postmenopausal women with a screening endometrial biopsy histological diagnosis of disordered proliferative endometrium must not be enrolled.	2 Study Synopsis 8.2 Inclusion and Exclusion Criteria
Disordered proliferative endometrium has been re-included as a reason for discontinuation.	The FDA doesn't agree with the modification to the stopping criteria for non-hysterectomized women introduced with PA 6.1. Women with a biopsy and histological evidence of disordered proliferative endometrium must not be exposed to continued unopposed estrogen treatment.	2 Study Synopsis 5.4 Risk-benefit Assessment 7.1.1 Trial Design (Figure 1) 8.3. Subject Discontinuation and Replacement Procedures 10.4.1. Treatment Emergent Adverse Events 10.4.8. Endometrial biopsy in non-hysterectomized subjects. 10.4.10. Endometrial safety assessment and stopping rules (non-hysterectomized subjects only)
Minor changes		
Description of changes	**Reason for change**	**Sections affected**
[redacted]	Update of ICON responsible party.	1.2 Contact Information 1.5. CRO Approval and Signature Page

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Minor changes		
Description of changes	**Reason for change**	**Sections affected**
DPE has been re-included as an endometrial event for which administration of P4 200 mg (once a day, for 14 consecutive days) should be considered by the Investigator.	DPE has been re-included as an endometrial event leading to discontinuation (see Major Changes).	2. Study Synopsis 5.4 Risk-benefit Assessment 10.4.1 Treatment Emergent Adverse Events 10.4.8 Endometrial biopsy in non-hysterectomized subjects 10.4.10 Endometrial safety assessment and stopping rules (non-hysterectomized subjects only)
A Clinical Event Committee is created to support the DSMB in the adjudication of the cardiovascular and thrombotic events that arise during the course of the study.	The DSMB has requested the creation of a Clinical Event Committee.	10.5 Data Safety Monitoring Board

Amendment 6.1, leading to version 7.1 of the protocol, date July 30, 2021

All changes are clearly identified in the track-changes version of the amendment.

Note: Amendment 6.0, leading to version 7.0 of the protocol, date May 26, 2021, was never submitted. All changes of Amendment 6.1 have been tracked against Protocol Version 6.0, date September 23, 2020.

Major changes		
Description of changes	**Reason for change**	**Sections affected**
Disordered proliferative endometrium has been removed from the reasons for discontinuation.	To align with regulatory approach and based on the available safety information.	2 Study Synopsis 5.4 Risk-benefit Assessment 7.1.1 Trial Design (Figure 1) 8.3. Subject Discontinuation and Replacement Procedures 10.4.1. Treatment Emergent Adverse Events 10.4.8. Endometrial biopsy in non-hysterectomized subjects. 10.4.10. Endometrial safety assessment and stopping rules
Disordered proliferative endometrium has been removed from the Exclusion Criteria.	To align with regulatory approach and based on the available safety information.	2 Study Synopsis 8.2 Inclusion and Exclusion Criteria
The maximum screening period has been extended to 8 weeks (instead of 6 weeks) in both study parts.	To limit the screen failure rate, which is in part due to the COVID-19 situation because it limits access to the hospital facilities.	2 Study Synopsis 2.1 Schedule of Trial Procedures Efficacy Study Part 2.2 Schedule of Trial Procedures Safety Study part 7.1.1. Trial Design 10.1. Experimental Flow
Text has been added on COVID-19 vaccination during the trial, including a recommendation on the timing of vaccination in relation to study assessments.	To provide guidance on COVID-19 vaccination during the trial.	9.6.3 COVID-19 vaccination
The endometrial biopsies will be read by four pathologists instead of three pathologists. The pathologist performing the initial reading for safety diagnosis, will not be involved in the reading for consensus diagnosis.	According to FDA guidelines 3 independent pathologist have to read slides for Consensus diagnosis. The initial reader will only assess the safety.	10.4.8 Endometrial Biopsy in Non-hysterectomized Subjects

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Major changes		
Description of changes	**Reason for change**	**Sections affected**
The number of days with bleeding and/or spotting and the cumulative rates of amenorrhea have been added as endpoints to the safety objective on vaginal bleeding.	To further define the evaluation of vaginal bleeding during treatment with E4.	2 Study Synopsis 6.1.2 Secondary Objectives and Endpoints (Efficacy Study part) 6.2.2. Secondary Objectives and Endpoints (Safety Study part)
The secondary objective and endpoints for frequency and severity of VMS have been updated.	To further define the evaluation of the secondary efficacy of E4.	2 Study Synopsis 6.1.2 Secondary Objectives and Endpoints (Efficacy Study part)
The secondary objectives 1 and 2 have been added to the timing of the final efficacy analysis.	To clarify that also the final analysis of the secondary efficacy objectives 1 and 2 will be done in parallel with the final analysis of the primary efficacy objective.	2 Study Synopsis 7.4.1 Blinding after analysis of data up to Visit 4 in the Efficacy Study part. 12.9 Timing of analysis.
The interim analysis of safety endpoints in the Efficacy Study part of the study has been deleted.	No interim analysis will be performed on the safety endpoints.	2 Study Synopsis 7.4.1 Blinding after analysis of data up to Visit 4 in the Efficacy Study part. 12.9 Timing of analysis.
Sentence on treatment restart has been added: “If study treatment is interrupted for 4 days and more per week, the Investigator will need approval from the Medical Monitor to restart the patient on study treatment.”	Compliance of treatment intake.	9.2. Timing of Administration
Text on the use of 200 mg P4 in non-hysterectomized subjects has been harmonized throughout the Protocol.	To ensure consistency across protocol sections.	2. Study Synopsis 5.4. Risk-benefit Assessment 7.1.1 Trial Design (Figure 1) 8.3 Subjects Discontinuation and Replacement Procedures. 10.4.8. Endometrial Biopsy in Non-hysterectomized Subjects 10.4.10. Endometrial safety assessment and stopping rules (non-hysterectomized subjects only)
Resolution of endometrial events has been defined.	The definition of the resolution of endometrial events was missing.	2. Study Synopsis 10.4.1. Treatment Emergent Adverse Events 10.4.10. Endometrial Safety Assessment and Stopping Rules
Exclusion criterion # 3 has been updated to specify that high risk oncogene HPV includes subtypes 16 and 18.	To limit the screen failure due to positivity of HPV testing to subtypes of lower significance.	2. Study Synopsis 8.2.2. Criteria for Exclusion

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Major changes		
Description of changes	**Reason for change**	**Sections affected**
Hierarchy of the pathologic diagnoses of endometrial tissue has been updated.	To align with the Statistical Analysis Plan.	10.4.8. Endometrial biopsy in non-hysterectomized subjects.
Minor changes		
Description of changes	**Reason for change**	**Sections affected**
Exclusion criterion # 23 has been updated from "Inadequately treated hyperthyroidism with abnormal TSH and free T4 at screening. Subjects with low TSH are allowed if free T4 at screening is within normal range" to "Inadequately treated hyperthyroidism with abnormal TSH and free T4 at screening. Subjects with low **or high** TSH are allowed if free T4 at screening is within normal range"	To clarify that subjects with TSH outside normal range at screening, including high and low TSH, may be allowed in the study if free T4 is within normal range.	2 Study Synopsis 8.2.2 Criteria for Exclusion 9.6.2. Concomitant Medication/Therapy
Lactate dehydrogenase enzyme and isoenzymes have been specified in the list of parameters for lab analysis.	To better describe the analysed parameters.	10.4.5. Routine Clinical Laboratory Tests
The Endometrial Safety Analysis set has been added.	To clarify the definition of the different statistical populations.	2 Study Synopsis 12.1 Statistical populations
The pathologic diagnosis prompting discontinuation will be reported as an AESI and not as an SAE.	Correction in the protocol. The pathologic diagnosis prompting discontinuation should not be reported as an SAE, unless the AESI fulfils the criteria of an SAE. A clarification letter for this change has been implemented, ahead of this Amendment.	10.4 10 Endometrial safety assessment and stopping rules
A sentence was added to clarify when the study treatment could be restarted.	To ensure treatment compliance.	9.2. Timing of Administration
Start of AESI collection was specified.	To avoid unnecessary retrospective reporting.	10.6. Adverse Events of Special Interest
For the haemostasis parameter APCsr ETP the text "*in a subset of subjects in selected study centers"* has been removed.	The APCsr ETP has been collected in all subjects in all centers.	2. Study synopsis 6.1.2 Secondary Objectives and Endpoints 10.3.3 Laboratory Assessments for Efficacy

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Minor changes		
Description of changes	**Reason for change**	**Sections affected**
The sentence: "The 95% two-sided CI will be computed on the observed frequency of hyperplasia/carcinoma of the endometrium in order to show that the frequency is not superior to 2% (upper bound lower than the 2% threshold)." has been corrected as follows: "The 95% two-sided CI will be computed on the observed frequency of hyperplasia/carcinoma of the endometrium ~~in order to show that the frequency is not superior to 2% (upper bound lower than the 2% threshold)~~."	The quoted frequency is relevant to combined hormone therapy (estrogen plus progestin) not for unopposed estrogen therapy.	2. Study synopsis 12.8 Safety parameters (safety set)
The section below was added to Section 12.9; "The analyses of all other efficacy and safety objectives from the Efficacy and Safety Study parts will be triggered when the overall end of the trial is reached (i.e. when all subjects in the Efficacy Study part have completed Visit 8). The efficacy endpoints and the safety endpoints of the Safety Study will be analyzed separately from those of the Efficacy Study at the end of the Safety Study."	To be consistent with the synopsis section "Timing of analysis".	12.9 Timing of analysis
The words in bold and italics were added: "• P4, 200 mg, oral, once daily for 14 consecutive days (after completion ***or discontinuation*** of E4/placebo treatment)"	For completeness.	2. Study synopsis
Name and contact details of several sponsor study team members haven been changed. Estetra SPRL has been changed to Estetra SRL. Name of the storage facilities for additional analysis has been updated.	To reflect the changes in the study team members, the change in the name of the Sponsor and the change in the name of the storage facilities for additional analysis.	1.2 Contact Information 1.3 Sponsor Authorisation 4.3 List of Abbreviations

Amendment 5, leading to version 6.0 of the protocol, date September 23, 2020

Major changes		
Description of changes	**Reason for change**	**Sections affected**
Changes in trial design and or trial procedures		
A section on Adverse Events of Special Interest (AESI) has been added to the protocol. Reference to the section on AESI has been made in several other safety sections.	A section on AESI was missing in earlier version of the protocol and has now been added.	10.4.1 Treatment Emergent Adverse Events 10.4.8 Endometrial biopsy in non-hysterectomized subjects 10.4.9 Vaginal bleeding events 10.6 Adverse Events of Special Interest
The footnote belonging to inclusion criterion 8 regarding the mammography has been changed from: ".. i.e BI-RADS 0, is not acceptable" ".. i.e BI-RADS 0, is not acceptable and requires further assessment". The text in Section 10.4.6 has been changed accordingly.	To clarify that a BI-RADS 0 is not acceptable, unless further assessment is done, demonstrating no clinically significant findings.	2. Study synopsis 8.2 Inclusion and Exclusion Criteria 10.4.6 Mammography
An additional TVUS assessment has been added to be performed after 9 months of treatment (Week 41, Visit 6 Efficacy Study part and Visit 5 Safety Study part).	The additional TVUS assessment was recommended by the DSMB.	2. Study synopsis 10.1.5.6 Visit 6: 9 month Safety Visit 10.1.6.5 Visit 5: 9 month Safety Visit 10.4.7 Transvaginal Ultrasound in Non-hysterectomized Subjects
Text has been added in Section 10.4.8 regarding follow-up of subjects in case of disordered proliferative endometrium or in case of hyperplasia or worse.	Text was added to provide more details on the follow-up and reporting.	10.4.8 Endometrial Biopsy in Non-hysterectomized Subjects

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Minor changes		
Description of changes	**Reason for change**	**Sections affected**
CSM has been added to the list of contact information.	To provide a complete overview of all facilities.	1.2 Contact Information
The text on the additional statistical analysis of the daily severity score has been moved from **Secondary Efficacy Variables** to **Primary Efficacy Variables**: and now reads as follows: "The daily severity score as defined above will also be recomputed for post baseline weeks as [((2 x number of moderate VMS) + (3 x number of severe VMS)) / (Total number of moderate + severe VMS)] if at least one moderate or severe VMS is recorded during the day."	There are differences between the FDA and EMA regulatory requirements on the assessment of efficacy in the treatment of VMS. The EMA guidance only includes moderate and severe VMS in the primary analysis, while in the FDA guidance also mild VMS are taken into account. Both analyses were included in the previous version of the protocol, although in different subsections. Because results of this study will be used for submission to the FDA as well as to the EMA, both analyses have now been placed in the same section of the protocol (Primary Efficacy Variables), to indicate that they are equally important.	2. Study synopsis (Statistical Methods) 12.4 Primary Efficacy Analysis 12.6 Secondary Efficacy Analysis
Week and treatment by week interaction have been added as fixed factors in the MMRM.	These models factors are necessary to get the estimates of the primary endpoint.	2. Study synopsis (Statistical Methods) 12.5. Analysis of Primary Efficacy Variables
The number of subjects has been made more flexible throughout the protocol.	For operational purposes this multiple centre trial requires some flexibility in the number of patients in each study part and stratum.	Throughout the protocol
Study-specific description of the Safety, ITT and PP analysis sets	To clarify the definition of the different statistical populations	12.1 Statistical Populations
The text on blood sampling for exploratory research has been adapted	Updates have been made for clarification purposes.	10.3.4 Blood Sampling for Exploratory Research
The text on retainment of samples for optional additional analyses in Section 10.4.5 has been reworded and has also been added to section 10.3.5.	Updates have been made for clarification purposes.	10.3.5 Endocrine assessment for inclusion and monitoring of treatment compliance 10.4.5 Routine Clinical Laboratory Tests
The text on repeat of BP measurements in Section 10.4.3 at screening has been made consistent with the footnote in exclusion criteria.	Update have been made to remove inconsistencies.	10.4.3 Vital signs

Amendment 4, leading to version 5.0 of the protocol, date February 03, 2020

Major changes		
Description of changes	**Reason for change**	**Sections affected**
Changes in trial design and or trial procedures		
The Safety Study part will also include non-hysterectomized women. The sample size in the Safety Study part has been changed from "≤ 400 hysterectomized subjects" to "200 hysterectomized subjects and 200 non- hysterectomized subjects".	Inclusion of non-hysterectomized subjects in the safety part of the study is requested by the FDA in order to gain sufficient safety information for the benefit/risk assessment of the product in this population.	2 Study synopsis 6.2 Objective and Endpoints of the Safety Study part 7.1.1 Trial Design 7.1.4 Justification of Study Population 8.1.1 Justification of Sample Size 10.1.6 Visits Safety Study part 10.4 Safety Assessments
Inclusion criterion 4 on bi-layer endometrial thickness on TVUS at screening has been changed from "≤ 5 mm" to "≤ 4 mm".	At the request of the FDA, the endometrial thickness has been updated	2 Study synopsis 8.2.1 Criteria for Inclusion
Exclusion criterion 4e has been updated.	Exclusion criterion 4e has been updated to clarify that it covers any uterine/endometrial abnormality that in the judgment of the investigator contraindicates the use of estrogen and/or progestin therapy.	2 Study synopsis 8.2 Inclusion and Exclusion Criteria
Exclusion criterion 8 has been changed from: "diabetes mellitus with poor glycemic control in the last 6 months assessed by fasting glucose outside the normal ranges and glycated hemoglobin above 7%" to "Laboratory values of fasting glucose above 125 mg/dL and/or glycated hemoglobin above 7%".	Updates have been made to clarify that glucose levels and glycated hemoglobin levels need to be within the set values.	2 Study synopsis 8.2.2 Criteria for Exclusion
Exclusion criterion 9 on dyslipoproteinemia has been changed from "(LDL >190 mg/dL and triglycerides >300 mg/dL)" to "(LDL >190 mg/dL and/**or** triglycerides >300 mg/dL)	Updates have been made for clarification purposes.	2 Study synopsis 8.2.2 Criteria for Exclusion

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Major changes (*continued*)		
Description of changes	**Reason for change**	**Sections affected**
Exclusion criterion 10 on smoking in the Efficacy Study part has been changed from >5 cigarettes per day to >15 cigarettes per day. The number of packs per week has been deleted for both study parts.	Smoking habits in the Efficacy Study part has been made consistent with the smoking habits in the Safety Study part. Number of packs was deleted because number of cigarettes per pack may vary.	2 Study synopsis 8.2.2 Criteria for Exclusion
Exclusion criterion 23 has been changed from "Inadequately treated hyperthyroidism at screening" to "Inadequately treated hyperthyroidism with abnormal TSH and free T4 at screening. Subjects with low TSH are allowed if free T4 at screening is within normal range	Changes were made to further define inadequately treated hyperthyroidism.	2 Study synopsis 8.2.2 Criteria for Exclusion
A footnote about reflex T4 testing was added to exclusion criterion 23.	Footnote was added for clarifying purposes.	2 Study synopsis 8.2.2 Criteria for Exclusion

Minor changes		
Description of changes	**Reason for change**	**Sections affected**
Name and contact details for the Clinical Study Leader of Estetra SPRL were added to the contact information page and sponsor authorisation page.	Addition was made for operational purposes.	1.2 Contact Information 1.3 Sponsor Authorization
The QP for pharmacovigilance has been replaced on the authorisation page.	Change in study personnel	1.3 Sponsor Authorization
The statistician has been replaced on the authorisation page.	Change in study personnel	1.3. Sponsor Authorization
The sample size of the Efficacy Study part has been updated from ± 200 per study arm to 200 per study arm and a sentence has been added that enrollment will stop when the minimum required number of subjects in each study group and study part is enrolled.	To clarify the number of subject in the Efficacy Study part and allow sufficient subjects for the objectives of the study.	2 Study Synopsis 8.1. Source and Number
The definition of the end of trial "the date when the last patient has completed the last study visit" has been added.	Update has been made for clarification purposes.	2 Study Synopsis 7.1.2 Trial Duration

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Minor changes (*continued*)		
Description of changes	**Reason for change**	**Sections affected**
A footnote "u" in Table 2.1 and footnote "s" in Table 2.2 were added to clarify when lipid and glucose parameters need to be assessed at the washout visit or during the screening period.	Updates have been made for clarification purposes.	2.1 Schedule of Trial Procedures Efficacy Study Part 2.2 Schedule of Trial Procedures Safety Study Part
Text has been added in footnotes "d" of Schedule of Trial Procedures Efficacy Study Part and "f" of Schedule of Trial Procedures Safety Study Part, and in Screening Visit section to include that the PAP test may be repeated once in case of inadequate or insufficient sample.	Update has been made allowing a repeat of the PAP test at screening.	2.1 Schedule of Trial Procedures Efficacy Study Part 2.2 Schedule of Trial Procedures Safety Study Part 10.1.3 Screening Visit
Text has been added in footnotes "m" and "v" of Schedule of Trial Procedures Efficacy Study Part and footnotes "a" and "t" of Schedule of Trial Procedures Safety Study Part, and in Screening Visit section to include that the laboratory tests may be repeated once at the discretion of the investigator.	Update has been made and to allow a repeat of the laboratory tests at screening.	2.1 Schedule of Trial Procedures Efficacy Study Part 2.2 Schedule of Trial Procedures Safety Study Part 10.1.3 Screening Visit
A footnote "v" in Schedule of Trial Procedures Efficacy Study Part and footnote "t" in Schedule of Trial Procedures Safety Study Part were added to clarify that FSH assessment is not required for subjects with bilateral oophorectomy.	Updates have been made for clarification purposes.	2.1 Schedule of Trial Procedures Efficacy Study Part 2.2 Schedule of Trial Procedures Safety Study Part
Throughout the protocol the pathologic diagnosis based on the endometrial biopsy results prompting discontinuation from study treatment and the start of progestin treatment has been made consistent to an endometrial biopsy showing disordered proliferative endometrium, hyperplasia or worse.	To ensure consistency throughout the protocol on criteria for discontinuation based on endometrial biopsy results.	2 Study Synopsis 8.3 Subject discontinuation and Replacement Procedures 10.4.8 Endometrial biopsy in non-hysterectomized subjects 10.4.10 Endometrial safety assessment and stopping rules
Wording in section on assignment has been changed to add assignment to study part.	Changes have been made to clarify the assignment to the study part.	7.2. Study and Treatment Assignment

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Minor changes (*continued*)		
Description of changes	**Reason for change**	**Sections affected**
Section and Table 3 (Washout period) on prior medication have been changed to specify use of non-hormonal or OTC prescriptions for the treatment of VMS, and to define criteria for use of thyroid treatment.	Changes have been made to clarify the prior use of VMS medication and thyroid treatments.	9.6.1 Prior Medication/Therapy 9.6.2 Concomitant Medication
A footnote has been added to Table 3 (washout period) for tapering off a medication. n	Footnote has been added to clarify the washout period in case of tapering off medication	9.6.1 Prior Medication/Therapy
A footnote has been added in Table 4 (Visit schedule) to explain flexibility in the Washout period and Screening period.	Updates have been made for clarification purposes.	10.1. Experimental Flow
Text on screening requirements is added in case screening procedures cannot be met within 4 weeks, and the screening period needs to be extended. However, Screening period may not exceed 6 weeks.	Wording was added to clarify the process and requirements in case the screening period needs to be extended.	2 Study Synopsis 2.1 Schedule of Trial Procedures Efficacy Study Part 2.2 Schedule of Trial Procedures Safety Study Part 10.1 Experimental Flow 10.1.3 Screening Visit
For re-screening added that repeat of the PAP is not needed (if a normal written result is available within 18 months before the start of screening)	To avoid unnecessary repeats of PAP tests.	10.1.4. Subject Re-screening
Wording on VMS recording has updated to state this VMS will be done during screening, and during the Efficacy Study part.	Changes made to clarify when VMS will be recorded.	10.3 Efficacy assessments
Wording on hyperthyroidism has been updated to add “inadequately treated” hyperthyroidism.	Change made to be consistent with changes made in the inclusion criteria regarding hyperthyroidism.	10.3.5 Endocrine assessment for inclusion and monitoring of treatment compliance
Wording on follow-up of subjects discontinued due to endometrial biopsy results has been added. Sentence on digital recording has been removed.	Wording was added to define follow-up process in case of discontinuation. Wording on digital recording is provided in the Endometrial Biopsy Charter.	10.4.8 Endometrial Biopsy in Non-hysterectomized Subjects
Correction made in schedule of TVUS assessments: “Visit 1 (Baseline) changed to “screening”.	Change made in Section 10.4.10 to be consistent with schedule of assessments.	10.4.10 Endometrial Safety Assessment and Stopping Rules

Minor changes (*continued*)		
Description of changes	**Reason for change**	**Sections affected**
In the section on endometrial safety wording has been added for SAE reporting. The sentence on stopping enrolment and treatment of non-hysterectomized subjects in the Efficacy Study part due to endometrial safety concerns has been deleted.	Additions have been made to clarify SAE reporting for endometrial safety. The decision to stop (part of) the study and/or enrolment NH of subjects will be the responsibility of the DSMB, based on actual safety data.	10.4.10 Endometrial Safety Assessment and Stopping Rules

Amendment 3, leading to version 4.0 of the protocol, date October 08, 2019

Major changes		
Description of changes	**Reason for change**	**Sections affected**
Changes in trial design and or trial procedures		
An inclusion criterion was added for non-hysterectomized subjects: uterus with bi-layer endometrial thickness ≤ 5mm on TVUS is now also required.	Inclusion criterion was added to ensure an additional safety measure.	2 Study synopsis 8.2 Inclusion and Exclusion Criteria

Minor changes		
Description of changes	**Reason for change**	**Sections affected**
Clarifying Changes		
Footnote in Figure 1 has been clarified by including the corresponding Visits linked to the mentioned follow up times of treatment.	Update was made to ensure ease of reading and consistency throughout the protocol.	2 Study Synopsis 7.1.1 Trial Design
Wording was updated to state “generally up to 8 weeks” instead of “up to 8 weeks”.	Update was made to ensure consistency in wording throughout the protocol.	2 Study Synopsis 7.1.2 Trial Duration
Footnote “c” of Table 2.1 was updated.	Week 9 was added to footnote “c” of Table 2.1 for clarification as it was mistakenly omitted.	2.1 Schedule of Trial Procedures Efficacy Study Part
Footnotes “g” of Table 2.1 “f” of Table 2.2 have been updated to clarify that PAP smear is to be done in women with uterus and/or cervix.	Updates have been made for clarification purposes and to ensure consistency throughout the protocol.	2.1 Schedule of Trial Procedures Efficacy Study Part 2.2 Schedule of Trial Procedures Safety Study Part
Footnotes “a” of Tables 2.1 and 2.2 was updated to clarify that for implantable or injectable androgen therapy or dehydroepiandrosterone (DHEA) containing drugs, a washout period of 6 months is required.	To ensure consistency throughout protocol.	2.1 Schedule of Trial Procedures Efficacy Study Part 2.2 Schedule of Trial Procedures Safety Study Part

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Minor changes (*continued*)		
Description of changes	**Reason for change**	**Sections affected**
Clarifying Changes		
Table and text have been updated to state treatment allocation instead of randomization for the safety study part.	To ensure accuracy of procedures in safety study part.	2.2 Schedule of Trial Procedures Safety Study Part, Section 10.1.6 Visits Safety Study part 8.2 Inclusion and Exclusion Criteria (Inclusion 2) 10.4.5. Routine Clinical Laboratory Tests (pregnancy test)
Reference has been made to Table 3 in Section 9.6.1.	Change was done to improve the flow of the reader and help with cross referencing.	7.1.1 Trial Design
First paragraph was updated to state the following: "Treatment assignment into any of the study parts (i.e. Efficacy and Safety) and subgroups (15 mg, 20 mg and placebo) will be done by the IWRS system. The treatment assignment will take into account the modified MENQOL score, frequency and severity of hot flashes, hysterectomized vs. non-hysterectomized status, and availability of places in each study part/subgroup."	Wording was added for clarification.	7.2 Treatment Assignment
The wording "electronic data capture system" has been replaced by "Interactive Web Response System (IWRS)".	Change was done to improve accuracy of information.	7.3 Randomization
The wording Interactive X Response System (IXRS) has been replaced by Interactive Web Response System (IWRS).	To ensure consistency throughout protocol	4.3 List of Abbreviations 7.2 Treatment Assignment 7.3 Randomization
Footnote has been added for exclusion criterion 8.	Footnote was added to bring clarity to all readers that lab values from past 6 months should be considered to identify a subject with poor glycemic control.	8.2.2 Exclusion Criteria
Footnote has been added for exclusion criterion 1.	Footnote was added to ensure clarity across readers. All malignancies are excluded, except for basal cell carcinoma and squamous cell carcinoma of the skin if these were diagnosed more than a year before screening.	8.2.2 Exclusion Criteria
Last part of the 5th sentence was removed.	Change was done to avoid misinterpretation.	9.4 Packaging and Labelling

Table continued on the next page

Minor changes (*continued*)		
Description of changes	**Reason for change**	**Sections affected**
Clarifying Changes		
Wording on P4 treatment was added	Wording has been added for completeness.	9.4 Packaging and Labelling
Table 1 was updated	Table 1 was updated to include P4 treatment information and ensure completeness.	9.4 Packaging and Labelling
Wording was updated to state Safety Study part instead of Endometrial and General Safety Study Part.	Change was made to ensure consistency in protocol and correct sentence with appropriate wording	9.6.1 Prior Medication/Therapy 10.1.3 Screening Visit
TVUS was deleted from the assessments needed to be done at Baseline visit.	TVUS is performed at screening, it was mistakenly repeated as a procedure at Baseline Visit. Table and specific section have been updated.	2.1 Schedule of Trial Procedures Efficacy Study Part 10.1.5.1 Randomization Visit and Baseline Assessments
It has been clarified that TVUS should be performed not only at screening but also at End of Trial Visit in non-hysterectomized subjects or subjects with ovaries in both the Efficacy and Safety study parts.	Update was made to ensure consistency and clarity throughout the protocol.	2.2 Schedule of Trial Procedures Safety Study Part 10.1.6 6 Visit 6: End of Trial
Reference was added to the Imaging Manual.	Reference was added to cross refer to the appropriate document containing detailed information on the mammography process and guide sites in identifying appropriate source of information.	10.4.6 Mammography
Wording under “Evaluation of endometrial tissue” subtitle has been updated.	Wording was added to clarify the decision process in place and to add reference to the Charter for Endometrial Biopsy Management.	10.4.8 Endometrial Biopsy in Non-hysterectomized Subjects
Section on Country Specific Requirements was added to accommodate requirements from Health Canada.	Health Canada requested a country specific amendment to ensure that Canadian sites are aware that only hysterectomized subjects are to be enrolled in both parts of the study (Efficacy and Safety parts).	16.5 Country Specific Requirements
Administrative changes		
ERT Lab information has been deleted	Since all ECGs have been confirmed will be read locally, there is no need for ERT central reading.	1.2 Contact Information 10.4.4 Electrocardiogram
Total number of pages was added to each footer	For completeness and avoid misinterpretation due to lost pages.	Throughout the document
Typographic corrections	To correct typographical errors.	Throughout the document

Amendment 2, leading to version 3.0 of the protocol, date August 13th 2019

Major changes		
Description of changes	**Reason for change**	**Sections affected**
Changes in trial design and or trial procedures		
Exclusion criterion 4c has been updated	At the request of the Central IRB, the exclusion criterion 4c has been updated to clarify that it also covers undiagnosed abnormal uterine bleeding.	2 Study synopsis 8.2 Inclusion and Exclusion Criteria
Exclusion criterion 14 has been updated	At the request of the Central IRB, the exclusion criterion 14 has been updated to clarify that it also covers the presence or history of severe hepatic disease or liver tumors	2 Study synopsis 8.2 Inclusion and Exclusion Criteria
Minor changes		
Description of changes	**Reason for change**	**Sections affected**
Administrative changes		
[redacted] contact information has been deleted	Since PAP test reading will be done locally, the information on [redacted] central lab has been deleted.	1.2 Contact Information

Amendment 1, leading to version 2.0 of the protocol, dated July 18th 2019

Major changes		
Description of changes	**Reason for change**	**Sections affected**
Changes in trial design and or trial procedures		
Addition of an exclusion criterion for non-hysterectomized subjects regarding peanut allergy.	P4 provided as part of this study contains peanut oil and should never be used by subjects with allergy to peanuts.	2 Study synopsis 8. 2 Inclusion and Exclusion Criteria
Changes in study evaluation		
In the Efficacy Study part the timing of the-efficacy analysis has been changed to be done after all subjects have completed Visit 4. At the same time also an interim analysis of the safety will be performed.	To clarify the original intention of the protocol, which is to analyse the primary efficacy objective when efficacy follow up for primary analysis is completed (i.e. Visit 4 of the Efficacy Study part).	2 Study Synopsis, (Timing of analysis) 12.9 Timing of Analysis
Additional wording has been added on the process to ensure the study blind after analyses in the Efficacy Study part are conducted while the study is still ongoing.	Because the primary analysis on efficacy and an interim analysis on safety will be conducted in the Efficacy Study part before database lock, additional measures are needed to keep the study blind.	Section 7.4.1 Blinding procedures Section 12.9 Timing of analysis

Minor changes		
Description of changes	**Reason for change**	**Sections affected**
Changes in trial design and or trial procedures		
The Run-in period for VMS recording has been incorporated into the Screening period and wording has been added to make clear that the Screening period will always start with a Screening visit.	For operational purposes; one Screening period, starting with a Screening visit, which includes the VMS recording, is considered to be clearer and more efficient.	Throughout the protocol "Run-in" has been deleted. Specific changes in: 2 Study Synopsis (including Schedule of Trial Procedures). 7.1 Study Design and Justification (including Trial Schedule) 10.1.3: Visit 1 Screening Procedures (previous Section 10.1.3 "Run-in period" combined with current Section 10.1.3).
The duration of the Screening period is reduced from 6 weeks to 4 weeks.	By combining the Run-in period with the Screening period, the total duration of the screening procedures is reduced.	2 Study Synopsis (Trial Schedule, Trial Duration and Schedule of Trial Procedures). 7.1.1 Trial Design 7.1.2 Trial Duration

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Minor changes		
Description of changes	**Reason for change**	**Sections affected**
Changes in trial design and or trial procedures		
The duration of the Washout period is reduced from 10 weeks to 8 weeks.	Usual washout period for most subjects is expected to be 8 weeks instead of 10 weeks.	2 Study Synopsis (Trial Schedule, Trial Duration and Schedule of Trial Procedures). 7.1.1 Trial Design 7.1.2 Trial Duration
Addition of pregnancy test at Visit 1 at the discretion of the Investigator.	Because of the time interval of 4 weeks between the screening Visit and Visit 1 the pregnancy test may be repeated at Visit 1.	2 Study Synopsis (Schedule of Trial Procedures) 10.1.5.1 Randomization Visit (Efficacy Study part) 10.1.6.1 Randomization visit (Safety Study part) 10.4.5 Routine Clinical Laboratory Tests
Collection of data on Medical and Gynecological History and Demographic characteristics has been moved from Screening Visit to Washout Visit.	Because adverse events are collected as of signature of Informed Consent occurring during Washout Visit, collection of Medical and Gynecological History and Demographic Characteristics should be aligned to the same time point.	2 Study Synopsis (Schedule of Trial Procedures) 10.1.2 Washout Visit (Experimental Flow) 10.1.3 Screening Visit 10.2 Demographics and Subject Characteristics
Changes in study evaluation		
Safety endpoints; for physical and gynaecological examination, vital signs, electrocardiogram (ECG), mammography, and breast examination and for routine clinical laboratory tests: the "frequency of change in results" in these parameters will be evaluated instead of the "frequency of clinically relevant results".	The frequency of clinically relevant results in these safety parameters are already evaluated as part of the AEs. The frequency of changes in results these parameters will provide additional safety information.	2 Study Synopsis (Objectives and Endpoints) 6.1.2 Secondary Objectives (for Efficacy Study part) 6.2.1 Primary Objectives (for Safety Study part)
Statistical method section; the text on the secondary efficacy variables in is reworded.	To remove inconsistencies and clarify the secondary evaluation	2. Study Synopsis (Secondary Efficacy variables 12.6 Secondary Efficacy Variables
Clarifying changes		
Changed "Efficacy Study" and "Safety Study" in "Efficacy Study part" and "Safety Study part"	To clarify that this is one trial with two study parts.	Throughout the protocol
Addition of "in the last 7 consecutive days during the Screening period" for the assessments of VMS symptoms during the Screening period.	For clarity and ensure consistency with the in- and exclusion criteria.	Section 2: Study Synopsis (Trial Schedule, Trial Duration and Schedule of Trial Procedures). 7.1.1 Trial Design 7.1.2 Trial Duration

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Minor changes		
Description of changes	**Reason for change**	**Sections affected**
Specified that question number 1 of the modified MENQOL should be used to assess bothersome VMS.	To provide clarity on the definition of bothersome VMS.	2 Study Synopsis (Trial Design and Schedule of Trial Procedures) 7.1.1. Trial Design 8. 2 Inclusion and Exclusion Criteria 10.1.3: Visit 1 Screening procedures
Editorial changes to safety endpoints 6.2, 7.1 and 7.2 of the efficacy study	Clarification of the text to avoid misunderstanding.	2 Study Synopsis 6 Objectives and Endpoints
Editorial changes in the inclusion criteria 2, 6 and 9 and in the exclusion criterion 1, and in the in- and exclusion criteria footnotes	Clarification of the text to avoid misunderstanding.	2 Study Synopsis 8.2 Inclusion and Exclusion Criteria
Wording added for contacting subjects in case of discontinuation.	To provide instructions on the attempts to contact a subject in case of discontinuation, before considering lost to follow up.	8.3 Subject Discontinuation and Replacement Procedures
Addition of a table with the visit schedule.	To provide additional guidance on the visit schedule and permitted time window for each visit.	10.1 Experimental Flow
An additional section is added on the blood sampling for exploratory research.	To provide explanation on the purpose of the optional additional samples.	10.3.4. Blood Sampling for Exploratory Research
QTcFrid has been added as the method to be used when reporting QT intervals.	To provide clarification and guidance.	10.4.4 Electrocardiogram
Administrative changes		
Name of the Medical Director of Sponsor has been changed.	Change in Medical Director.	Section 1.2 Contact information Section 1.3 Sponsor Authorisation
Names of Senior Director Project Management CRO and Program Manager CRO have been changed.	Change in Project Members.	Section 1.2 Contact Information
Names of study personal has been added to the Sponsor authorisation page.	For completion.	Section 1.3 Sponsor Authorisation
Typographic corrections and corrections of inconsistencies.	To correct typographical errors and inconsistencies.	Throughout the protocol

2. STUDY SYNOPSIS

Sponsor:	**Active Ingredient:**
Estetra SRL	Estetrol

Study Title:
A Randomized Double-blind Placebo Controlled Phase 3 Study to evaluate the Efficacy and Safety of Estetrol for the Treatment of Moderate to Severe Vasomotor Symptoms in Postmenopausal Women (E4Comfort Study II).

Study Location: Multiple centers in the USA and Canada	**Study Phase**: 3

Study Design:
The trial has two parts; an Efficacy Study part (Arms 1-3) and a Safety Study part (Arm 4).

The Efficacy Study part has a randomized, double-blinded placebo-controlled design and evaluates the primary efficacy (frequency and severity of vasomotor symptoms [VMS]), secondary efficacy (effect on hemostasis, lipid and glucose metabolism, bone turnover, health-related quality of life [HRQoL] and treatment satisfaction [TS]), and safety of estetrol (E4) in both hysterectomized and non-hysterectomized postmenopausal women, as well as the effect of E4 on the endometrium in non-hysterectomized postmenopausal women.
Subjects will be randomly allocated (1:1:1) to one of the 3 Arms and will receive E4 15 mg (Arm 1), E4 20 mg (Arm 2), or Placebo (Arm 3). During the first 12 weeks of the Efficacy Study part, the effect of E4 on VMS will be evaluated. Thereafter, treatment will proceed for a total duration of up to 53 weeks, to continue the evaluation of secondary efficacy, safety and the effect on the endometrium. For endometrial protection, all non-hysterectomized subjects will receive treatment with 200 mg progesterone (P4) once daily for 14 consecutive days, after completion of the E4/placebo treatment.

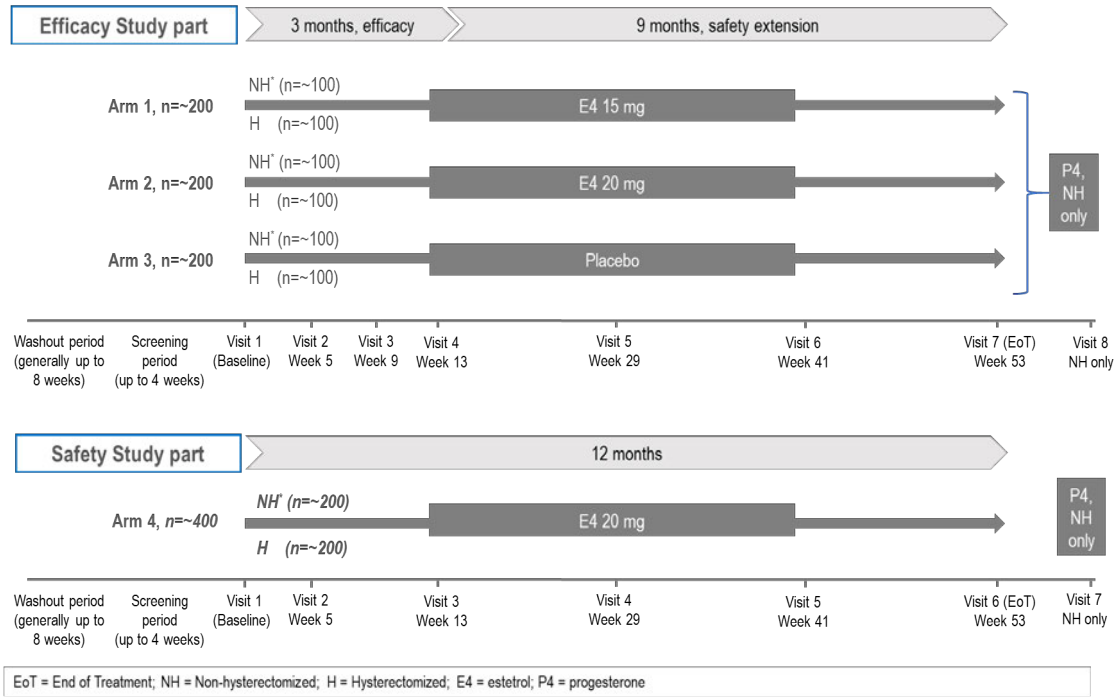
The Safety Study part is conducted in hysterectomized and non-hysterectomized postmenopausal women and has an open label design. The Safety Study part evaluates the general safety, secondary efficacy (lipid and glucose metabolism, HRQoL and TS) of up to 53 weeks treatment with E4 20 mg (Arm 4).

The trial schedule is summarized in Figure 1.

Participants in the Efficacy Study part need to have at least 7 moderate to severe bothersome menopausal related VMS per day or at least 50 moderate to severe bothersome VMS per week in the last 7 consecutive days during the Screening period. Bothersome is defined as a score of 4 to 6 on question 1 of the modified Menopause-specific quality of life (MENQOL) questionnaire at screening. The timing and number of VMS and modified MENQOL score needed for allocation to the Efficacy Study part will not be disclosed to the study subjects to avoid bias in the recording during the Screening process. Participants in the Safety Study part should seek treatment for the relief of VMS associated with menopause, with at least 1 moderate to severe menopausal related VMS per week. Subjects who do not fulfill the VMS requirements for participation in the Efficacy Study part, may participate in the Safety Study part providing that they meet all in- and exclusion criteria for participation in the Safety Study part.

Hysterectomized and non-hysterectomized healthy women will be included in the Efficacy Study part and Safety Study part (approximately 50% of the subjects are anticipated to have a history of hysterectomy).
The target enrollment number of subjects in each of the three arms of the Efficacy Study part is ~200. The target number of subjects to be included in the Safety Study part is ~400.

Figure 1: Trial Schedule



* For non-hysterectomized (NH) subjects, endometrial thickness will be measured after 3, 6, 9 and 12 months of treatment (Visits 4, 5, 6 and 7 of the Efficacy Study part and Visits 3, 4, 5 and 6 of the Safety Study part respectively) by transvaginal ultrasound (TVUS) and subjects will record daily the vaginal bleeding events. If at any time after the first 4 weeks of treatment a subject presents with persistent and/or recurrent bleeding, confirmed by the investigator or presents with a bi-layer endometrial thickness >10 mm as assessed by TVUS, an endometrial biopsy will be performed. If the biopsy shows disordered proliferative endometrium, hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. If the endometrial event has not resolved, treatment with a progestin will be started according to local practice/guidelines. All NH subjects will receive treatment with 200 mg P4 for two weeks after completion of E4/placebo treatment.

Blinding:
Efficacy study part: double-blinded
Safety Study part: open-label

Trial Duration:
Individual subject participation in this trial may be up to 15 months. This includes a washout period of generally up to 8 weeks (usual washout period for most subjects), a screening period of generally up to 4 weeks, and a treatment period with E4 or placebo of up to 53 weeks. For non-hysterectomized subjects there will be an additional follow-up period of approximately 3 weeks.
For subjects requiring a longer washout (up to 6 months) participation period may be extended. For subjects who do not require a washout, the total participation period will be reduced by approximately 8 weeks.

The end of trial is defined as the date when the last patient has completed the last study visit.

Trial Population:
A total of ~1000 subjects will be enrolled in the study. Eligible subjects will be postmenopausal women, ≥ 40 up to ≤ 65 years of age, seeking treatment for relief of moderate to severe VMS associated with menopause.

Efficacy Study part: A total of ~600 subjects will be enrolled. Subjects (~300 hysterectomized and ~300 non-hysterectomized) need to have at least 7 moderate to severe bothersome VMS per day or at least 50 moderate to severe bothersome VMS a week in the last 7 consecutive days during the screening.

Safety Study part: A total of ~400 subjects will be enrolled. Subjects (~200 hysterectomized and ~200 non-hysterectomized should seek treatment for the relief of VMS (condition clinically indicated by the investigator) associated with menopause and have at least 1 moderate to severe menopausal related VMS per week.

Investigational Medicinal Product (dose, and mode of administration):
E4 15 mg (Arm 1) or E4 20 mg (Arm 2 and Arm 4), oral, once daily

Reference therapy (dose, and mode of administration):
Placebo, oral, once daily (Arm 3)

Other trial medication (dose, and mode of administration):
For non-hysterectomized subjects only:
- P4, 200 mg, oral, once daily for 14 consecutive days (after completion or discontinuation of E4/placebo treatment)
- Ad hoc treatment with a progestin according to local practice/guidelines if endometrial biopsy shows disordered proliferative endometrium, hyperplasia or worse

Conduct of the Trial:
For the Efficacy Study part at least 9 visits are planned: a Washout visit followed by a Screening period which will start with a Screening visit, a Baseline visit (Visit 1), and 6 On-treatment visits (Visits 2 to 7). The last treatment visit (Visit 7) is also the end of treatment (EoT) Visit, which will also occur in case of early discontinuation. For non-hysterectomized women an additional endometrial safety follow-up visit (Visit 8) is planned approximately 10 days after completion of the 14 days of P4 treatment, which will also occur in case of early discontinuation.
For the Safety Study part at least 8 visits are planned: a Washout visit followed by a Screening Period which will start a screening visit, a Baseline visit (Visit 1), and 5 On-treatment visits (Visits 2 to 6). The last treatment visit (Visit 6) is also the end of treatment (EoT) Visit, which will also occur in case of early discontinuation. For non-hysterectomized women an additional endometrial safety follow-up visit (Visit 7) is planned approximately 10 days after completion of the 14 days of P4 treatment, which will also occur in case of early discontinuation.

The screening period requires at least one visit, to occur as per protocol, at the beginning of the period, but some assessments (e.g., mammography, biopsy, transvaginal ultrasound [TVUS], electrocardiogram [ECG] and Papanicolaou [PAP] test) may require additional visits in case these assessments cannot be done during the same visit.
Additional unscheduled visits may also be required during the treatment period for ad hoc safety assessments (e.g., TVUS for non-hysterectomized subjects).

Washout and Screening procedures for the Efficacy Study part and Safety Study part
At the Washout visit, after signing the informed consent, the inclusion and exclusion criteria will be checked as well as the prior medication list. If a subject uses prohibited co-medication, then this subject will be asked to stop this medication. After a variable washout period (depending on type of prior medication) the subject will return to start the screening procedures. For subjects who do not use medication that needs to be stopped and washed out, the Washout and Screening visit may occur at the same time. Screening includes a PAP test and mammography for all subjects, a TVUS for subjects with ovaries and/or uterus, and an endometrial biopsy for non-hysterectomized subjects. The length of the Screening period is generally up to 4 weeks, but can be extended (with prior Medical Monitor approval) without exceeding 8 weeks. During this period, and in addition to the screening procedures, the subject will record VMS in a paper diary. VMS data recorded during the last 7 consecutive days of the Screening period will be used to determine eligibility of subjects. If based on VMS symptoms of her current medical history a subject is only eligible for the Safety Study part, this subject may be enrolled directly into the Safety Study part without the VMS count in the Screening period, providing that all the screening assessments have been completed. Subjects who do not fulfill the VMS requirements for participation in the Efficacy Study

part, may participate in the Safety Study part, providing that they meet all other in- and exclusion criteria.

Treatment period Efficacy Study part
During the first 12 weeks of treatment, primary efficacy assessments (the number and severity of VMS) will be recorded on a daily basis in a paper diary. Subjects will also record vaginal bleeding events (non-hysterectomized subjects only) and daily study drug intake in the diary. After completion of the 12 weeks of treatment (Visit 4), only non-hysterectomized subjects will keep the diary to record daily vaginal bleeding events and daily study drug intake. At baseline (Visit 1) secondary efficacy assessments (hemostasis, lipid and glucose metabolism, and bone turnover) will be performed, the MENQOL questionnaire will be completed, and for non-hysterectomized subjects endometrial thickness will be assessed. Subjects will visit the trial center after 4 and 8 weeks of treatment (Visit 2 and Visit 3) for general safety assessments, for review of the diaries, and for completion of the Clinical Global Impression (CGI) questionnaire (Visit 2 only). After 12 weeks of treatment, subjects will visit the trial center for the final primary efficacy assessment (Visit 4). During this visit also secondary efficacy assessments and general safety assessments will be performed and the MENQOL and CGI questionnaires will be completed. For non-hysterectomized subjects endometrial thickness will be assessed. Subjects will visit the trial center again after 6 months of treatment (Visit 5) for general safety assessments and endometrial thickness assessment (non-hysterectomized subjects only) and after 9 months of treatment (Visit 6) for general safety assessments and endometrial thickness assessment (non-hysterectomized subjects only). After 12 months of treatment, subjects will visit the trial center for the EoT visit (Visit 7) during which secondary efficacy assessments and general safety assessments will be performed, the HRQoL and TS questionnaires will be completed and a mammography will be made. For non-hysterectomized subjects endometrial thickness will be assessed and, if they have completed at least 12 weeks of E4/placebo treatment, an endometrial biopsy will be performed. At Visits 1, 2, 3 and 4 blood samples will be taken to monitor estradiol (E2) levels and at Visits 2, 3 and 4 also to monitor E4 levels.
After the EoT procedures, all non-hysterectomized subjects will receive treatment with 200 mg P4 for 14 days. Approximately 10 days after completion of the progestin treatment, endometrial thickness will be measured (Visit 8).

Treatment period Safety Study part
At Baseline (Visit 1) secondary efficacy assessments (lipid and glucose metabolism) will be performed and the MENQOL questionnaire will be completed. Subjects will visit the trial center after 4 weeks (Visit 2), 12 weeks (Visit 3), 6 months (Visit 4) and 9 months (Visit 5) of treatment for safety assessments, and for completion of the CGI questionnaire (Visit 2 only). Visit 3 secondary efficacy assessments will also be performed and the MENQOL and CGI questionnaires will be completed. For non-hysterectomized subjects endometrial thickness will be assessed on visits 3, 4 and 5. During treatment non-hysterectomized subjects will record daily study drug intake and vaginal bleeding events in a paper diary. After 12 months of treatment subjects will visit the trial center for the EoT visit (Visit 6) during which secondary efficacy assessments and safety assessments will be performed, questionnaires will be completed and a mammography will be made. For non-hysterectomized subjects endometrial thickness will be assessed and, if they have completed at least 12 weeks of E4, an endometrial biopsy will be performed.
After the EoT procedures, all non-hysterectomized subjects will receive treatment with 200 mg P4 for 14 days. Approximately 10 days after completion of the progestin treatment, endometrial thickness will be measured (Visit 7).

Endometrial Safety Assessment and Stopping Rules (non-hysterectomized subjects only):
A baseline endometrial biopsy will be obtained for all non-hysterectomized subjects during the Screening period. An end of treatment endometrial biopsy is planned at the EoT Visit (Visit 7 Efficacy Study part, Visit 6 Safety Study part) providing that the subject has been treated with E4/placebo for at least 12 weeks. All non-hysterectomized subjects will receive treatment with 200 mg P4 for two weeks after completion or early termination of the E4/placebo treatment.
Endometrial thickness will be measured after 3, 6, 9 and 12 months (Visits 4, 5, 6 and 7 in the Efficacy Study part and Visits 3, 4, 5 and 6 in the Safety Study part) of treatment by TVUS and subjects will record daily vaginal bleeding events. If at any time after the first 4 weeks of treatment, a subject presents with persistent and/or recurrent bleeding, confirmed by the Investigator or presents with a bi-layer endometrial thickness >10 mm as assessed by

TVUS, an endometrial biopsy will be performed. If the biopsy shows disordered proliferative endometrium, hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. At approximately 10-14 days after completion of the progestin treatment, a new TVUS will be performed to measure endometrial thickness and a biopsy will be carried out, if deemed necessary by the Investigator, to demonstrate the resolution. If the endometrial event is not resolved, the subject will be further treated according to local practice/guidelines and she will be followed up until resolution.
Endometrial safety will be monitored during the trial by an independent Data Safety Monitoring Board (DSMB).

Objectives and Endpoints of the Efficacy Study part (Arms 1-3):

Primary Objective and Endpoints:

1. To measure the effect of treatment with E4 15 mg or E4 20 mg compared to placebo on the frequency and severity of moderate to severe VMS in postmenopausal women at 4 and 12 weeks

   Co-primary efficacy endpoints for primary objective #1

   1.1. Mean change in weekly frequency of moderate to severe VMS from baseline to week 4
   1.2. Mean change in weekly frequency of moderate to severe VMS from baseline to week 12
   1.3. Mean change in severity of moderate to severe VMS from baseline to week 4
   1.4. Mean change in severity of moderate to severe VMS from baseline to week 12

Secondary Objectives and Endpoints:

1. To measure the effect of treatment with E4 15 mg or E4 20 mg compared to placebo on the frequency and severity of mild, moderate and severe VMS in postmenopausal women weekly up to 12 weeks

   Efficacy endpoints for secondary objective #1

   1.1. Change from baseline to week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 in the weekly frequency and severity of moderate to severe VMS
   1.2. Change from baseline to weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 in the weekly frequency and severity of mild, moderate, and severe VMS
   1.3. Percentage of subjects with 50% and 75% reduction from baseline in the weekly frequency of moderate to severe VMS at weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12
   1.4. Percentage of subjects with 50% and 75% reduction from baseline in the weekly frequency of mild, moderate and severe VMS at weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12

2. To measure the clinical meaningfulness of E4 15 mg or E4 20 mg compared to placebo on the reduction of VMS at weeks 4 and 12

   Efficacy endpoint for secondary objective #2

   2.1. Percentage of subjects with a clinically important difference (CID) compared to baseline in the weekly frequency of moderate to severe VMS after weeks 4 and 12 using the CGI questionnaire

3. To evaluate the effect of treatment with E4 15 mg or E4 20 mg compared to placebo on hemostasis, lipid and glucose metabolism, and bone turnover

   Efficacy endpoint for secondary objective #3

   3.1. Change from baseline to week 12 and week 52 in prothrombin fragment 1 + 2, endogenous thrombin potential (ETP)-based activated Protein C sensitivity ratio (APCsr ETP), activated partial thromboplastin time (aPTT) based activated Protein C resistance (APCr), anti-thrombin III, Protein-C, free Protein-S, Factor VIII, angiotensinogen, and Sex Hormone Binding Globulin (SHBG)
   3.2. Change from baseline to week 12 and week 52 in triglycerides, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, total cholesterol, lipoprotein(a), total cholesterol/HDL-cholesterol ratio, fasting glycemia, insulin, glycated hemoglobin and homeostasis model assessment-estimated insulin resistance (HOMA-IR)

3.3. Change from baseline to week 12 and week 52 in procollagen I N-propeptide (PINP), C-terminal telopeptide type 1 (CTX-1), calcium, and vitamin D

4. To evaluate the effect of treatment with E4 15 mg or E4 20 mg compared to placebo on HRQoL and TS

Efficacy endpoints for secondary objective #4

4.1. Change from baseline to week 12 and week 52 in HRQoL using the MENQOL questionnaire
4.2. Total score in TS after 4, 12, and 52 weeks of treatment using the CGI questionnaire

5. To evaluate the general safety of treatment with E4 15 mg or E4 20 mg compared to placebo

Safety endpoints for secondary objective #5

5.1. Frequency of treatment emergent adverse events (TEAEs) (including treatment emergent serious adverse events [SAEs])
5.2. Frequency of changes in results in physical and, gynecological examination, vital signs, ECG, mammography, and breast examination at each measured time point
5.3. Frequency of changes in routine clinical laboratory tests results (hematology and chemistry) at each measured time point

6. To evaluate the effect of treatment with E4 15 mg or E4 20 mg on the endometrium in non-hysterectomized subjects compared to placebo

Safety endpoints for secondary objective #6

6.1. Change from baseline to each measured time point in endometrial thickness measured by ultrasound
6.2. Frequency of subjects in the different endometrial categories according to the Blaustein's pathology (see Appendix 16.3)

7. To evaluate the effect of treatment with E4 15 mg or E4 20 mg on vaginal bleeding in non-hysterectomized subjects compared to placebo

Safety endpoints for secondary objective #7

7.1. Frequency of women with vaginal bleeding and/or spotting during each 28-day cycle of treatment with E4 based on recording in the patient diary
7.2. Number of days with bleeding and/or spotting during each 28-day cycle of treatment based on recording in the patient diary
7.3. Frequency of women with amenorrhea (absence of any bleeding or spotting) during each 28-day cycle of treatment with E4 based on recording in the patient diary
7.4. Cumulative rates of amenorrhea defined as the percentage of women who reported consecutive cycles of amenorrhea for a given cycle of time

Exploratory Objectives and Endpoints of the Efficacy Study part:

1. To evaluate the effect of treatment with E4 15 mg or E4 20 mg compared to placebo on breast density

Safety endpoint for exploratory objective #1

1.1. Change in breast density from digitized mammography readings from baseline to EoT in subjects who had a paired digitalized mammography

2. To evaluate the influence of E4 on the changes in the hemostasis parameters compared to placebo in women with inherited thrombophilia and women without this genetic disorder

Efficacy endpoint for exploratory objective #2

2.1. Change in hemostasis parameters in women with and without inherited thrombophilia (Factor V Leiden mutation and prothrombin G20210A mutations).

Objectives and Endpoints of the Safety Study part (Arm 4):

Primary Objective and Endpoints:

1. To evaluate the general safety of treatment with E4 20 mg

   Safety endpoints for primary objective #1
   - 1.1. Frequency of TEAE (including SAEs)
   - 1.2. Frequency of changes in results in physical and gynecological examination, vital signs, ECG, mammography, and breast examination at each measured time point
   - 1.3. Frequency of changes in routine clinical laboratory tests results (hematology and chemistry) at each measured time point

Secondary Objectives and Endpoints:

1. To evaluate the effect of treatment with E4 20 mg on lipid and glucose metabolism

   Efficacy endpoints for secondary objective #1
   - 1.1. Change from baseline to week 12 and week 52 in triglycerides, HDL-cholesterol, LDL-cholesterol, total cholesterol, lipoprotein(a), total cholesterol/HDL-cholesterol ratio, fasting glycemia, insulin, glycated hemoglobin, and HOMA-IR

2. To evaluate the effect of treatment with E4 20 mg on HRQoL and TS

   Efficacy endpoints for secondary objective #2
   - 2.1. Change from baseline to week 12 and week 52 in HRQoL using the MENQOL questionnaire
   - 2.2. Total score in TS after 4, 12, and 52 weeks of treatment using the CGI

3. To evaluate the effect of treatment with E4 20 mg on the endometrium in non-hysterectomized subjects

   Safety endpoints for secondary objective #3
   - 3.1 Change from baseline to each measured time point in endometrial thickness measured by ultrasound
   - 3.2 Frequency of subjects in the different endometrial categories according to the Blaustein's pathology (see Appendix 16.3)

4. To evaluate the effect of treatment with E4 20 mg on vaginal bleeding in non-hysterectomized subjects

   Safety endpoints for secondary objective #4
   - 4.1 Frequency of women with vaginal bleeding and/or spotting during each 28-day cycle of treatment with E4 based on recording in the patient diary
   - 4.2 Number of days with bleeding and/or spotting during each 28-day cycle of treatment based on recording in the patient diary
   - 4.3 Frequency of women with amenorrhea (absence of any bleeding or spotting) during each 28-day cycle of treatment with E4 based on recording in the patient diary
   - 4.4 Cumulative rates of amenorrhea defined as the percentage of women who reported consecutive cycles of amenorrhea for a given cycle of time

Inclusion Criteria:

Subjects will be allocated to treatment if they meet all of the following inclusion criteria:

1. Signed and dated written informed consent form and any required privacy authorization prior to the initiation of any trial procedure, after the nature of the trial has been explained according to local regulatory requirements;
2. Females, ≥40 up to ≤65 years of age at randomization/treatment allocation;
3. For hysterectomized subjects: documented hysterectomy must have occurred at least 6 weeks prior to the start of screening. Hysterectomy can be total or subtotal (i.e., cervix was not removed);
4. For non-hysterectomized subjects: uterus with bi-layer endometrial thickness ≤ 4 mm on TVUS;

5. For non-hysterectomized subjects: Endometrial biopsy taken during screening that reveals no abnormal results, i.e., presence of hyperplasia (simple or complex, with or without atypia), presence of carcinoma, and presence of disordered proliferative endometrium findings. The screening biopsy should have sufficient endometrial tissue for diagnosis. Biopsies without tissue or with insufficient tissue may be repeated once;
6. Seeking treatment for relief of VMS associated with menopause;
   a. For the Efficacy Study part: at least 7 moderate to severe bothersome VMS per day or at least 50 moderate to severe bothersome VMS per week in the last 7 consecutive days during the Screening period[1];
   b. For the Safety Study part: at least 1 moderate to severe VMS per week;
7. Body mass index ≥18.0 kg/m² up to ≤38.0 kg/m²;
8. A mammogram that shows no sign of significant disease performed during screening or within 9 months prior to the start of screening[2];
9. Postmenopausal status defined as any of the following:
   a) For non-hysterectomized subjects:
      - at least 12 months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) >40 mIU/ml (value obtained after washout of estrogen/progestin containing drugs, see exclusion criteria 18 and 20);
      - or at least 6 months of spontaneous amenorrhea with serum FSH >40 mIU /mL and E2 <20 pg/mL (value obtained after washout of estrogen/progestin containing drugs, see exclusion criteria 18 and 20);
      - or at least 6 weeks postsurgical bilateral oophorectomy[3];
   b) For hysterectomized subjects:
      - serum FSH >40 mIU/mL and E2 <20 pg/mL (values obtained after washout of estrogen/progestin containing drug see exclusion criteria 18 and 20);
      - or at least 6 weeks postsurgical bilateral oophorectomy[3];
10. Good physical and mental health, in the judgement of the Investigator as based on medical history, physical and gynecological examination, and clinical assessments performed prior to Visit 1;
11. Able to understand and comply with the protocol requirements, instructions, and protocol-stated restrictions;
12. Able and willing to complete trial daily diaries (if applicable, see Section 10.1.7) and questionnaires.

Exclusion Criteria:

Subjects will not be allocated to treatment if they meet one of the following exclusion criteria:

1. History of malignancy with the exception of basal cell or squamous cell carcinoma of the skin if diagnosed more than one year prior to the Screening visit[4];
2. Any clinically significant findings found by the Investigator at the breast examination and/or on mammography suspicious of breast malignancy that would require additional clinical testing to rule out breast cancer (however, simple cysts confirmed by ultrasound are allowed);
3. PAP test with atypical squamous cells undetermined significance (ASC-US) or higher (low-grade squamous intraepithelial lesion [LSIL], atypical squamous cells- cannot exclude high-grade squamous intraepithelial lesion [HSIL] [ASC-H], HSIL dysplastic or malignant cells) in sub-totally hysterectomized and non-

[1] Bothersome is defined as a score of 4 to 6 on question 1 of the modified MENQOL questionnaire at screening. The timing and number of VMS and modified MENQOL score needed for allocation to the Efficacy Study part will not be disclosed to the study subjects to avoid bias in the recording during the Screening process.

[2] Subjects must have a Breast Imaging-Reporting And Data System (BI-RADS) score of 1 or 2 to enroll in the study. An incomplete mammogram result, i.e., BI-RADS 0, is not acceptable and requires further assessment. The site must obtain a copy of the official report for the subject's study file. A digitalized imaging should be obtained if mammography is done as part of this study.

[3] A report or a statement on letterhead from the subject's physician documenting both ovaries were removed is needed.

[4] The exception is only for basal cell carcinoma or squamous cell carcinoma of the skin if either of them were diagnosed more than one year prior to the screening of the subject.

Footnote continued on next page

hysterectomized subjects[5]. Note: ASC-US is allowed if a reflex human papilloma virus (HPV) testing is performed and is negative for high risk oncogene HPV subtypes 16 and 18;

4. For non-hysterectomized subjects:
   a) History or presence of uterine cancer, endometrial hyperplasia, or disordered proliferative endometrium;
   b) Presence of endometrial polyp;
   c) Undiagnosed vaginal bleeding or undiagnosed abnormal uterine bleeding;
   d) Endometrial ablation;
   e) Any uterine/endometrial abnormality that in the judgment of the investigator contraindicates the use of estrogen and/or progestin therapy. This includes presence or history of adenomyosis or significant myoma;
5. Systolic blood pressure (BP) higher than 130 mmHg, diastolic BP higher than 80 mmHg[6] during screening;
6. History of venous or arterial thromboembolic disease (e.g., superficial or deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, angina pectoris, etc.), or first-degree family history of VTE;
7. History of known acquired of congenital coagulopathy or abnormal coagulation factors, including known thrombophilia's;
8. Laboratory values of fasting glucose above 125 mg/dL and/or glycated hemoglobin above 7% [7];
9. Dyslipoproteinaemia (LDL >190 mg/dL and/or triglycerides >300 mg/dL)[8];
10. Subjects smoking >15 cigarettes per day;
11. Presence or history of gallbladder disease, unless cholecystectomy has been performed;
12. Systemic lupus erythematosus;
13. Any malabsorption disorders including gastric by-pass surgery;
14. History of acute liver disease in the preceding 12 months before the start of screening or presence or history of chronic or severe liver disease [alanine transaminase (ALT) or aspartate transaminase (AST) >2x upper limit of normal (ULN), bilirubin >1.5 ULN], or liver tumors;
15. Chronic or current acute renal impairment (estimated glomerular filtration rate <60 ml/min);
16. Porphyria;
17. Diagnosis or treatment of major psychiatric disorder (e.g., schizophrenia, bipolar disorder, etc.) in the judgement of the Investigator
18. Use of estrogen/progestin containing drug(s) up to:
   a) 1 week before screening start for vaginal non-systemic hormonal products (rings, creams, gels);
   b) 4 weeks before screening start for vaginal or transdermal estrogen or estrogen/progestin products;
   c) 8 weeks before screening start for oral estrogen and/or progestin products and/or selective estrogen receptor modulator therapy;
   d) 8 weeks before screening start for intrauterine progestin therapy;
   e) 3 months before screening start for progestin implants or estrogen alone injectable drug therapy;
   f) 6 months before screening start for estrogen pellet therapy or progestin injectable drug therapy;
19. Use of androgen/DHEA containing drugs:
   a) 8 weeks before screening start for oral, topical, vaginal or transdermal androgen;
   b) 6 months before screening start for implantable or injectable androgen therapy;
20. Use of phytoestrogens or black cohosh for treatment of VMS up to 2 weeks before the start of screening;
21. For the women participating in the Efficacy Study part: use of prescription or over-the-counter products used for the treatment of VMS, e.g., anti-depressants: paroxetine, escitalopram, methyldopa, opioid and clonidine

[5] As indicated by written documentation of a prior test performed within 18 months prior screening or by a test performed at screening.

[6] BP measurements at screening may be repeated if values are outside the inclusion criteria after sitting for an additional 5 to 10 minutes. The last reading will be used for eligibility. Subjects with mild to moderate hypertension who are controlled on a stable antihypertension regimen may be enrolled if they meet all inclusion/exclusion criteria. Subjects using methyldopa or clonidine containing antihypertensive medication will not be included in the Efficacy Study part.

[7] Laboratory values of fasting glucose outside the normal ranges and glycated hemoglobin assessed during the last 6 months, and during washout and screening should be considered.

[8] Subjects using lipid-lowering therapy should be on a stable dose for at least 1 month before screening.

Footnote continued on next page

up to 4 weeks before the start of screening, and venlafaxine and desvenlafaxine up to 3 months before the start of screening[9], and not willing to stop these during their participation in the trial;
22. Not willing to stop any hormonal products as described in exclusion criteria 18, 19 and 20 during their participation in the trial;
23. Inadequately treated hyperthyroidism with abnormal TSH and free T4 at screening. Subjects with low or high TSH are allowed if free T4 at screening is within normal range[10];
24. History or presence of allergy/intolerance to the investigational product or drugs of this class or any component of it, or history of drug or other allergy that, in the opinion of the Investigator contraindicates subject participation;
25. For non-hysterectomized subjects: history or presence of allergy to peanuts[11];
26. History of alcohol or substance abuse (including marijuana, even if legally allowed) or dependence in the previous 12 months before the start of screening as determined by the Investigator, based on reported observations;
27. Sponsor or CRO employees or employees under the direct supervision of the Investigator and/or involved directly in the trial;
28. Subjects with known or suspected history of a clinically significant systemic disease, unstable medical disorders, life-threatening disease or current malignancies that would pose a risk to the subject in the opinion of the Investigator;
29. Participation in another investigational drug clinical trial within 1 month (30 days) or having received an investigational drug within the last month (30 days) before the start of screening;
30. Is judged by the Investigator to be unsuitable for any reason.

Number of Subjects:

Efficacy Study part: based on the results observed for the E4 15 mg dose in the Phase 2 study, a sample size of ~200 subjects per arm provides a power of at least 80% to simultaneously achieve a superiority (upper bound of a 95% 2-sided confidence interval [CI] lower than zero) over placebo for the four co-primary endpoints together. This sample size accounts for a dropout rate during the first 12 weeks of the trial of 35% and 20% for non-hysterectomized and hysterectomized women, respectively.

It is planned to enroll approximately 100 hysterectomized and 100 non-hysterectomized subjects per treatment arm.

Safety Study part: the target number of ~400 subjects has been selected to fulfill the requirement stated in ICH E1 guideline (CPMP/ICH/375/95) regarding number of subjects exposed to the drug for safety assessments.

Enrollment will stop when the minimum required number of subjects in each study group and study part is enrolled.

Statistical populations:
Analyses will be based on the Enrolled Set, the Safety Analysis Set, the Intent-to-treat (ITT) Set, the Endometrial Safety Analysis Set, the Per-protocol (PP) Set and the modified Intent-to-treat (mITT) Set. The definitions of the analysis sets, with the exception of the mITT, follow those given in the ICH E9 guideline (CMP/ICH/363/96). The mITT Set is defined as the ITT set without subjects presenting at least one of the following features:
- At least one post baseline E4 concentration level below the lower limit of quantification
- At least one post screening E2 concentration level is superior to 40 pg/mL

Statistical Methods:

Baseline Values

[9] If not used for the treatment of VMS, this medication is allowed if on a stable dose for 3 months prior to the Screening visit and no change in the dose regimen is foreseen during the conduct of the trial.
[10] Reflex T4 test to be performed at screening only if TSH at screening is outside normal range
[11] P4 provided as part of this study contains peanut oil and should never be used by subjects with allergy to peanuts

Unless otherwise noted, baseline is defined as the last non-missing value recorded prior to the first dose of trial drug. Unscheduled visits will be used in the determination of baseline values, when applicable. This also applies to the primary efficacy variables derived from the VMS data collected in the subject diary, but on a weekly basis as described in the definition of the primary efficacy variables.

Primary Efficacy Variables:
The weekly frequency of moderate to severe VMS at baseline, week 4 and week 12, respectively, is defined as the total number (sum) of all recorded moderate to severe VMS experienced during the last 7 consecutive days during the Screening period (baseline), days 22 to 28 (week 4) and days 78 to 84 (week 12), respectively.
The mean severity score of VMS is defined as the arithmetic mean of the daily severity score values of VMS (moderate or severe) observed from days -7 to -1 at baseline and the arithmetic mean of the daily severity score values of VMS (mild, moderate or severe) observed during the days 22 to 28 and days 78 to 84 for week 4 and week 12 respectively.
At baseline, the daily severity score is computed as [((2 x number of moderate VMS) + (3 x number of severe VMS))/ (total number of moderate + severe VMS)] if at least one moderate to severe VMS was recorded during the day. In case of documented absence of moderate to severe VMS during the day, the daily severity will be set to zero.
Post-baseline (days 22 to 28 [Week 4] and days 78 to 84 [Week 12]), the daily severity score is computed as [((1 x number of mild VMS) + (2 x number of moderate VMS) + (3 x number of severe VMS))/ (total number of mild + moderate + severe VMS)] if at least one mild to severe VMS was recorded during the day. In case of documented absence of VMS during the day, the daily severity will be set to zero.
The primary efficacy variables will be expressed as the changes from baseline computed as the differences between the estimated values at week 4 or 12 and the baseline values.
The daily severity score as defined above will also be recomputed for post baseline weeks as [((2 x number of moderate VMS) + (3 x number of severe VMS)) / (Total number of moderate + severe VMS)] if at least one moderate or severe VMS is recorded during the day.

The analysis including the mild VMS will be used for submission to the FDA, the analysis without the mild VMS will be used for submission to the EMA.

Analysis of Primary Efficacy Variables:

All statistical tests will be supported by presenting estimates and 95% CIs for the respective treatment effects (difference to placebo). These estimates and CIs will be based on the respective statistical models used for the analysis. Since all analyses of the efficacy variables are not exploratory in nature, adjustment for multiplicity will be performed (Dunnet adjustment for the comparison of each active dose versus placebo).
The primary efficacy comparison will test the following hypotheses for each treatment arm:

- H0: The average change from baseline in the primary efficacy endpoint in the treatment arm is greater (less pronounced) or equal to the average change from baseline in the placebo arm
- H1: The average change from baseline in the primary efficacy endpoint in the treatment arm is lower (more pronounced) to the average change from baseline in the placebo arm

The two dose groups of E4 will be compared to placebo regarding the four co-primary efficacy endpoints.

A comparison between treatment arms of the change from baseline at week 1 to week 12 in the weekly frequency of moderate to severe VMS and of the change from baseline in the weekly mean severity of moderate to severe VMS will be made by using Mixed-effect Models for Repeated Measures (MMRM). The MMRM models will include treatment, week, treatment by week interaction, and pooled trial centers as fixed effects and baseline as a covariate. If the pooled center effect included in the model is significant, a treatment by center interaction will be included in the model. Treatment effects will be assessed at Week 4 and 12 using two separate MMRM models (one on weekly frequency and another on weekly mean severity).

The primary analysis will use the data from the ITT population. Since an MMRM model is used, missing data imputation is not necessary. Additional sensitivity analyses will be implemented in order to assess the robustness of the results. These may include sensitivity with respect to:

- An imputation of missing data (last observation carried forward [LOCF] or other)
- The modeling strategy [analysis of covariance (ANCOVA) instead of MMRM]
- Confounders (for example ethnicity, hysterectomized status)
- Populations studied (mITT, PP)
- Any combination of the above

In addition, all primary efficacy variables will be tabulated at baseline and at each post-baseline time point.

Secondary Efficacy Variables:
In addition to all the secondary efficacy endpoints previously described, all the variables described above for the assessment of the primary objectives are also considered as secondary efficacy variables when evaluated at other time points than Week 4 and Week 12.
In addition, three VMS weekly weighted scores, taking into account both the frequency and the severity of VMS, will be computed based on the diary data as:

- [(2 x number of moderate VMS) + (3 x number of severe VMS)] for baseline and post baseline visits if at least one moderate to severe VMS was recorded and zero otherwise.
- [(1 x number of mild VMS) + (2 x number of moderate VMS) + (3 x number of severe VMS)] for baseline and post baseline visits if at least one mild to severe VMS was recorded and zero otherwise.
- [(2 x number of moderate VMS) + (3 x number of severe VMS)] if at least one moderate to severe VMS was recorded for baseline visits and [(1 x number of mild VMS) + (2 x number of moderate VMS) + (3 x number of severe VMS)] for post baseline visits if at least one mild to severe VMS was recorded and zero otherwise.

Furthermore, the severity score will also be recomputed as [((1 x number mild VMS) + (2 x number of moderate VMS) + (3 x number of severe VMS)) / (total number of mild + moderate + severe VMS)] if at least one mild to severe VMS is recorded during the day for baseline and post baseline visits.

In case of documented absence of VMS during the day, the daily severity score will be set to zero. These additional efficacy variables will be derived for every week between baseline and week 12 based on the respective 7-day periods. All VMS related secondary efficacy variables will be expressed as changes from baseline computed as the differences of the estimated values at week 1 to 12 and the baseline values.

The percentage of subjects with a CID in the weekly frequency of moderate to severe VMS at weeks 4 and 12 will be assessed according to Gerlinger et. al. (Gerlinger C. et. al. Menopause. 2012 Jul; 19(7):799-803).

Analysis of Secondary Efficacy Variables:
All VMS related secondary efficacy variables will be analyzed using the same methodology as for the primary efficacy variables and will be based on the data from the ITT population.
All other secondary continuous efficacy variables will be analyzed using either an ANCOVA or a MMRM model depending on the type of endpoint considered. These models will be evaluated using data from the ITT, PP and mITT populations without imputation of data. Appropriate covariates may be included in the analyses.
The other categorical efficacy variables (scores, responder analysis) will be analyzed using appropriate statistical methods for the comparison of each treatment arm to the placebo arm.

In addition, all secondary efficacy variables will be tabulated by baseline and by each post-baseline time point.

Handling of Dropouts or Missing Data:
For days with missing VMS diary information, the number and intensity of VMS will be imputed with the mean values of the remaining days of the respective 7-day period, but only if at least 4 days with VMS data in this 7 day period are available. Otherwise, no calculation of the primary and related secondary efficacy variables will be done for this period.
No method of imputation is planned for the primary efficacy variable analysis since a MMRM model is used. As previously stated, sensitivity analyses of the primary efficacy variables may resort to imputation of missing data in order to assess the robustness of the MMRM results.

Safety parameters (safety set):
All safety parameters will be summarized using data from the Safety Analysis Set if not indicated otherwise. No formal statistical test will be performed to determine statistical significance between treatment groups. Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, maximum), categorical variables will be presented in frequency tables using counts and percentages. The frequency of endometrial events will be computed on the evaluable biopsies of the endometrium. The incidence of spotting/bleeding will be analyzed by a 28-day period. The incidence rate of endometrial events will be computed on the evaluable endometrium. The 95% two-sided CI will be computed on the observed frequency of hyperplasia/carcinoma of the endometrium.

Timing of analysis
The final analysis of the primary efficacy objective and the secondary efficacy objectives 1 and 2 of the Efficacy Study part will be triggered when all subjects in the Efficacy Study part have completed Visit 4. The analyses of all other efficacy and safety objectives from the Efficacy and Safety Study parts (including a final analysis of the safety objectives of the Efficacy Study part) will be triggered when the overall end of the trial is reached (i.e. when all subjects in the Efficacy Study part have completed Visit 8). The efficacy endpoints and the safety endpoints of the Safety Study will be analyzed separately from those of the Efficacy Study at the end of the Safety Study.

Synopsis Final Version 8.0, June 21, 2022

2.1. Schedule of Trial Procedures Efficacy Study Part

Procedures and assessments	Washout period [a]	Screening period	Baseline (random allocation to treatment)	Treatment visits					EoT /early discontinuation visit [b]	Follow up Visit NH subjects
	Washout visit	Screening visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Generally within 8 weeks before screening	Within 4 weeks before baseline [w]	Day 1	Week 5 [c]	Week 9 [c]	Week 13 [c]	Week 29 [c]	Week 41 [c]	Week 53 [c]	Week 55/56 [d]
Informed consent	X									
I/E criteria	X [e]	X [e]	X							
Start washout [a]	X									
Med. & gyn. history	X									
Demographic data	X									
Physical examination		X							X	
Gyn. examination		X							X	
Breast examination		X					X		X	
Vital signs [f]		X	X	X	X	X	X	X	X	
ECG		X							X	
PAP test [g]		X								
Endometrial biopsy [h]		X							X [i]	
TVUS [h, j]		X				X	X	X	X	X
Mammography		X [k]							X [l]	
Modified MENQOL questionnaire		X								
MENQOL questionnaire			X			X			X	
CGI questionnaire				X		X			X	
Fasted blood sampling for: [m]										
Hematol./chem.		X [v]	X						X	
Lipid/glucose parameters for inclusion	X [u, v]	(X) [v]								
Lipid metabolism			X			X			X	
Glucose metabolism			X			X			X	

Table continued on the next page

2.1 Schedule of Trial Procedures Efficacy Study Part (*continued*)

	Washout period [a]	Screening period	Baseline (random allocation to treatment)	Treatment visits					EoT/early discontinuation visit [b]	Follow up visit NH subjects
	Washout visit	Screening visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Generally within 8 weeks before screening	Within 4 weeks before baseline [w]	Day 1	Week 5 [c]	Week 9 [c]	Week 13 [c]	Week 29 [c]	Week 41 [c]	Week 53 [c]	Week 55/56 [d]
Fasting blood sampling for: [m]										
Hemostasis			X			X			X	
Bone turnover			X			X			X	
Optional additional analysis [n]			X						X	
Blood sampling for										
FSH, E2 and TSH for inclusion [v]		X								
E2			X	X	X	X				
E4				X	X	X				
Urinary pregnancy test [o]		X	X							
Daily completion of diaries by subjects for VMS [p]		←	←	—	—	→				
for medication intake all subjects			←	—	—	→				
for medication intake [h]						←	—	—	—	→
for bleeding events [h]			←	—	—	—	—	—	—	→
Weekly reminder [q]		←	—	—	→					
Dispense paper diary [r]		X	X							
Return of paper diary			X	X	X	X	X [h]	X [h]	X [h]	X [h]
Review of paper diary [s]			X	X	X	X	X [h]	X [h]	X [h]	X [h]
Randomization			X							
Dispense trial medication			X	X	X	X	X	X	X [t]	
Daily intake of trial medication			←	—	—	—	—	—	→	
Return trial medication				X	X	X	X	X	X	X [h]
Drug accountability				X	X	X	X	X	X	X [h]
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X [h]
Adverse Events (AEs)	X	X	X	X	X	X	X	X	X	X [h]

Abbreviations and footnotes are on the next page

2.1 Schedule of Trial Procedures Efficacy Study Part (*continued*)

CGI=Clinical Global Impression; discont=discontinuation; E2=estradiol; E4=estetrol; ECG=electrocardiogram; EoT=end of treatment; FSH= follicle stimulating hormone; gyn=gynecological; Hematol/chem=hematology/chemistry; I/E= in and exclusion criteria; med=medical; MENQOL=Menopause-specific Quality of Life; PAP= Papanicolaou; TSH= Thyroid stimulating hormone; TVUS=transvaginal ultrasound; VMS= vasomotor symptoms

a) In case the subject uses medication that is not allowed during the duration of the trial, she is asked to stop this medication. The subject will return for the screening after a variable washout period that depends on the type of prior medication. Subjects not using medication that needs to be stopped and washed out can continue with the screening procedures.
Washout periods are: 1 week for vaginal hormonal products (rings, creams, gels); 4 weeks for transdermal estrogen or estrogen/progestin products; 8 weeks for oral estrogen and/or progestin and/or selective estrogen receptor modulator therapy; 8 weeks for intrauterine progestin therapy; 3 months for progestin implants or estrogen alone injectable drug therapy; 6 months for estrogen pellet therapy or progestin injectable drug therapy; 8 weeks for oral, topical, vaginal, patch of androgen/DHEA; 6 months for implantable or injectable androgen therapy; 2 weeks for phytoestrogens or black cohosh, 3 months for venlafaxine and desvenlafaxine if used for the treatment of VMS and 4 weeks all other non-hormonal prescription or over-the-counter treatments used for VMS.
b) Every effort needs to be made to perform the procedures of the end of trial visit for those subjects that discontinue their participation.
c) Visits will be scheduled in one of the seven days of week 5, week 9, week 13, week 29, week 41 and week 53, thus allowing a visit window of 7 days. Unscheduled visits may be needed during the treatment period for additional ultrasounds, biopsies or any other unforeseen safety assessments.
d) Visit 8 for non-hysterectomized subjects only at approximately 10 days after completion of the progestin treatment.
e) At washout visit and during the Screening Period only available I/E criteria at that time point will be checked.
f) Blood pressure, heart rate, body height (during screening only) and body weight (during screening and EoT only).
g) To be performed in subjects with uterus and/or cervix, unless a written normal result is available within 18 months before screening start. The PAP test may be repeated once in case of inadequate or insufficient sample.
h) Non-hysterectomized subjects only.
i) If the subject was treated for at least 12 weeks
j) TVUS at screening and EoT will be taken for all subjects who still have a uterus and/or ovaries. At all other time points a TVUS will be performed to monitor the endometrium thickness only for subjects who still have a uterus.
k) Unless a written normal result is available within 9 months before screening start.
l) Mammography at EoT visit may only be performed if the subject was treated for at least 12 weeks and the last mammography was taken at least 9 months earlier)
m) If the subject is not fasting, a new appointment needs to be made as soon as possible. Laboratory tests may be repeated once during the screening period, at the discretion of the investigator.
n) Additional blood samples including one DNA sample at Visit 1 only, will be collected for optional additional analysis of in the context of this program or any further research on E4.
o) A pregnancy test may be performed at the discretion of the Investigator.
p) VMS will be recorded daily in the paper diary during the Screening period and during the treatment period up to Visit 4.
q) During VMS recording subjects will be reminded weekly (phone, e-mail, SMS etc.) to complete the diary. The first reminder will be sent 5 ± 2 days after start of VMS recording.
r) Subjects are instructed during screening on how to fill in the diary and if needed can be reinstructed.
s) At each visit the diary will be checked. Completed pages will be collected and will remain at the study site.
t) Progestin treatment for non-hysterectomized subjects only.
u) If lipid and/or glucose parameters could be a reason of concern in the judgement of the Investigator, fasted blood sampling for lipid and glucose parameters assessment may be done during the Washout Visit. Otherwise, this assessment will be done during the screening period.
v) Laboratory tests may be repeated once during the screening period, at the discretion of the investigator. FSH measurement is not required for subjects with bilateral oophorectomy.
w) In the event screening requirements cannot be met within 4 weeks, the screening period may be extended with prior Medical Monitor approval, but screening period may not exceed 8 weeks.

2.2. Schedule of Trial Procedures Safety Study Part

Procedures and assessments	Washout period [a]	Screening period	Baseline (allocation to treatment)		Treatment visits			EoT/early discontinuation visit [b]	Follow up visit NH subjects
	Washout visit	Screening visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Generally within 8 weeks before screening	Within 4 weeks before baseline [u]	Day 1	Week 5 [c]	Week 13 [c]	Week 29 [c]	Week 41 [c]	Week 53 [c]	Week 55/56 [m]
Informed consent	X								
I/E criteria	X [d]	X [d]	X						
Start washout [a]	X								
Med. & gyn. history	X								
Demographic data	X								
Physical examination		X						X	
Gyn. examination		X						X	
Vital signs [e]		X	X	X	X	X	X	X	
ECG		X						X	
PAP test [f]		X							
Endometrial biopsy [n]		X						X [o]	
TVUS [l]		X			X	X	X	X	X
Breast examination		X				X		X	
Mammography		X [g]						X [h]	
Modified MENQOL questionnaire		X							
MENQOL questionnaire			X		X			X	
CGI questionnaire				X	X			X	
Fasted blood sampling for: [i]									
Hematol./chem.		X [t]	X					X	
Lipid/glucose parameters (for inclusion)	X [s, t]	(X) [t]							
Lipid metabolism			X		X			X	
Glucose metabolism			X		X			X	
Optional additional analysis [j]			X					X	

Table continued on the next page

2.2 Schedule of Trial Procedures Safety Study Part (*continued*)

	Washout period [a]	Screening period	Baseline (allocation to treatment)	Treatment visits				EoT/early discontinuation visit [b]	Follow up visit NH subjects
	Washout visit	Screening visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Generally within 8 weeks before screening	Within 4 weeks before baseline [u]	Day 1	Week 5 [c]	Week 13 [c]	Week 29 [c]	Week 41 [c]	Week 53 [c]	Week 55/56 [m]
Blood sampling for:									
FSH, E2 and TSH for inclusion [t]		X							
Urinary pregnancy test [k]		X	X						
Daily completion of diaries by subjects [n]									
for medication intake			◄	—	—	—	—	—	►
for bleeding events			◄	—	—	—	—	—	►
Dispense paper diary [n,p]		X	X						
Return of paper diary [n]			X	X	X	X	X	X	X
Review of paper diary [n,q]			X	X	X	X	X	X	X
Allocation to Treatment			X						
Dispense trial medication			X	X	X	X	X	X [r]	
Daily intake of trial medication			◄	—	—	—	—	►	
Return trial medication				X	X	X	X	X	X
Drug accountability				X	X	X	X	X	X
Prior/concomitant medication	X	X	X	X	X	X	X	X	X
Adverse Events (AEs)	X	X	X	X	X	X	X	X	X

CGI= Clinical Global Impression; discont=discontinuation; E2=estradiol; E4=estetrol; ECG=electrocardiogram; EoT=end of treatment; FSH= follicle stimulating hormone; gyn=gynecological; Hematol/chem=hematology/chemistry; I/E= in and exclusion criteria; med=medical; MENQOL=Menopause-specific Quality of Life; PAP= Papanicolaou; TSH= Thyroid stimulating hormone; TVUS=transvaginal ultrasound; VMS= vasomotor symptoms

a) In case the subject uses medication that is not allowed during the duration of the trial, she is asked to stop this medication. The subject will return to complete the screening after a variable washout period that depends on the type of prior medication. Subjects not using medication that needs to be stopped and washed out can continue with the screening procedures.
Washout periods are: 1 week for vaginal hormonal products (rings, creams, gels); 4 weeks for transdermal estrogen or estrogen/progestin products; 8 weeks for oral estrogen and/or progestin and/or selective estrogen receptor modulator therapy; 8 weeks for intrauterine progestin therapy; 3 months for progestin implants or estrogen alone injectable drug therapy; 6 months for estrogen pellet therapy or progestin injectable drug therapy; 8 weeks for oral, topical, vaginal, patch of androgen/DHEA; 6 months for implantable or injectable androgen therapy; 2 weeks for phytoestrogens or black cohosh, 3 months for venlafaxine and desvenlafaxine if used for the treatment of VMS and 4 weeks all other non-hormonal prescription or over-the-counter treatments used for VMS.
b) Every effort needs to be made to perform the procedures of the end of trial visit for those subjects that discontinue their participation.
c) Visits will be scheduled in one of the seven days of week 5, week 13, week 29, week 41, and week 53 thus allowing a visit window of 7 days. Unscheduled visits may be needed during the treatment period for additional unforeseen safety assessments.
d) At Washout visit and Screening visit only available I/E criteria at that time point will be checked.
e) Blood pressure, heart rate, body height (during screening only) and body weight (during screening and EoT only).
f) To be performed in subjects with uterus and/or cervix, unless a written normal result is available within 18 months before screening start. The PAP test may be repeated once in case of inadequate or insufficient sample.
g) Unless a written normal result, including digital imaging, is available within 9 months before screening start.
h) Mammography at EoT visit may only be performed if the subject was treated for at least 12 weeks and the last mammography was taken at least 9 months earlier
i) If the subject is not fasting, a new appointment needs to be made as soon as possible. Laboratory tests may be repeated once during the screening period, at the discretion of the investigator.
j) Additional blood samples, including one DNA sample at Visit 1 only, will be collected for optional additional analysis of in the context of this program or any further research on E4.
k) A pregnancy test may be performed at the discretion of the Investigator.
l) TVUS at screening and EoT will be taken for all subjects who still have a uterus and/or ovaries. At all other time points a TVUS will be performed to monitor the endometrium thickness only for subjects who still have a uterus.
m) Visit 7 for non-hysterectomized subjects only at approximately 10 days after completion of the progestin treatment.
n) Non-hysterectomized subjects only.
o) If the subject was treated for at least 12 weeks.
p) Subjects are instructed during screening on how to fill in the diary and if needed can be reinstructed.
q) At each visit the diary will be checked. Completed pages will be collected and will remain at the study site.
r) Progestin treatment for non-hysterectomized subjects only.
s) If lipid and/or glucose parameters could be a reason of concern in the judgement of the Investigator, fasted blood sampling for lipid and glucose parameters assessment may be done during the Washout Visit. Otherwise, this assessment will be done during the Screening Period
t) Laboratory tests may be repeated once during the screening period, at the discretion of the investigator. FSH measurement is not required for subjects with bilateral oophorectomy.
u) In the event screening requirements cannot be met within 4 weeks, the screening period may be extended with prior Medical Monitor approval, but screening period may not exceed 8 weeks.

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4. REFERENCE INFORMATION

4.1. Trial-Related Responsibilities

The Sponsor is responsible for this trial but may transfer any or all trial related activities to a CRO. However, the ultimate responsibility for the quality and integrity of the trial data always resides with the Sponsor. Any trial-related duties and functions that are transferred to and assumed by a CRO will be specified in writing in a separate document.

4.2. Principal Investigator

The Sponsor may select a Signatory Principal Investigator(s) (PI) from the investigators who participate in the trial, according to national law. Selection criteria for this investigator will include significant knowledge of the trial protocol, the investigational product, their expertise in the therapeutic area and the conduct of clinical research as well as trial participation. The Signatory PI(s) will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the trial.

4.3. List of Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ASC-US	Atypical squamous cells of undetermined significance
AST	Aspartate transaminase
BI-RADS	Breast imaging-reporting and data system
BMI	Body mass index
BP	Blood pressure
CEE	Conjugated equine estrogens
CGI	Clinical global impression
CI	Confidence interval
CID	Clinically important difference
CRO	Contract research organization
CSR	Clinical study report
CTX-1	C-terminal telopeptide type 1
DHEA	Dehydroepiandrosterone
DSMB	Data Safety Monitoring Board
E2	Estradiol
E4	Estetrol
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European medicines agency
EoT	End of treatment
ETP	Endogenous thrombin potential
FDA	Food and drug administration
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GMP	Good manufacturing practice
GSM	Genitourinary syndrome of menopause

HDL	High-density lipoprotein
HF	Hot flash(es)
HOMA-IR	Homeostasis model assessment-estimated insulin resistance
HPV	Human papilloma virus
HRQoL	Health related quality of life
IB	Investigator's brochure
IC	Informed consent
ICF	Informed consent form
ICH	International council for harmonization of technical requirements for pharmaceuticals for human use
IEC	Independent ethics committee
IRB	Institutional review board
ITT	Intention to treat
IWRS	Interactive Web Response System
kg	Kilogram
LH	Luteinizing hormone
LOCF	Last observation carried forward
LDL	Low-density lipoprotein
MED	Minimum effective dose
MENQOL	Menopause-specific quality of life
mg	Milligram
MHT	Menopausal hormone therapy
mITT	Modified intention to treat
mL	Milliliter
MMRM	Mixed-effect model for repeated measures
MPA	Medroxyprogesterone acetate
MRS	Menopause rating scale
NAMS	North American Menopause Society
ng	Nanogram
PI	Principle Investigator
PINP	procollagen I N-propeptide
PP	Per protocol

SAE	Serious adverse event
SHBG	Sex hormone binding globulin
SOP	Standard operation procedure
SRL	Société à responsabilité limitée
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TS	Treatment satisfaction
TSH	Thyroid stimulating hormone
TVUS	Transvaginal ultrasound
ULN	Upper limit of normal
VMS	Vasomotor symptoms
VTE	Venous thromboembolism
VVA	Vulvovaginal atrophy
WHI	World health initiative

5. INTRODUCTION

Detailed background information on estetrol (E4), including previous clinical experience can be found in the Investigator's Brochure (IB).[1] A summary is provided in the sections below.

5.1. Background

Menopausal hormone therapy (MHT) is the broad term used to describe unopposed estrogen use (for women who have undergone hysterectomy) or combined estrogen-progestin therapy (for women with an intact uterus). The goal of MHT is to relieve menopausal symptoms, most importantly vasomotor symptoms (VMS) such as hot flashes (HF). Other symptoms associated with perimenopause and menopause that respond to estrogen therapy include vulvovaginal atrophy (VVA), sleep disturbances (when related to VMS), etc.

Vasomotor symptoms occur most often in the late menopausal transition and the early post menopause and they are the most common menopausal complaints. Estimates suggest that about 75% of women who are more than 50 years of age will suffer from VMS.[2] Most experience VMS for about two to five years, although at least 10% suffer for more than 10 years.[3] VMS can contribute towards physical and psycho-social impairment, with a consequent reduction in health related quality of life (HRQoL), and are one of the main reasons why women may seek medical care for the menopause.[4] Although there are alternative therapies for VMS, none are as effective as estrogen.

The epithelial linings of the vagina and urethra are very sensitive to estrogen, and estrogen deficiency leads to thinning both epithelia. This results in VVA and urinary complaints, causing symptoms of vaginal dryness, itching, dyspareunia, dysuria, urinary frequency and an increased risk of recurrent urinary infections. In early 2014, the International Society for the Study of Women's Sexual Health (ISSWSH) and the North American Menopause Society (NAMS) endorsed the new terminology "genitourinary syndrome of menopause (GSM)" to replace the VVA terminology. The rationale for using this new terminology was that VVA term was considered to be too restrictive whereas GSM is a more comprehensive term that includes symptomatic VVA as well as lower urinary tract symptoms related to low estrogen levels.[5] Note that because the GSM terminology has not been adopted in guidances for industry issued by Food and Drug Administration (FDA) and European Medicines Agency (EMA), the VVA terminology will be used throughout this document.

With current MHT, women with an intact uterus need a progestin in addition to estrogen to prevent endometrial changes, which can occur after as little as 6 months of estrogen therapy.[6] Women who have undergone hysterectomy do not require addition of a progestin when prescribed estrogen therapy.

Along with the endometrial safety issue, MHT has been seriously questioned or even abandoned by many women and physicians following publication of data from the Women's Health Initiative (WHI) study in 2002. The results of the WHI studies with either conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) or CEE alone [7-9] showed increased rates of venous thromboembolism (VTE), breast cancer (CEE+MPA only), gallbladder disease, coronary heart disease (CEE+MPA only), in the first year of use, or stroke.

Therefore, FDA and EMA guidances encourage pharmaceutical companies to develop the lowest doses and exposures for MHT, even though specific relationships between dose, exposure, and risk of adverse events (AEs) may not be known.

Safety concerns that were attributed in the past to MHT are being re-considered following recent publications derived from long-term follow-up of the WHI trials. Estrogen alone therapy for postmenopausal women who underwent hysterectomy (the target population for the present study) showed that:

1. Treatment with CEE alone for a median of 7.2 years was not associated with an increased risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.[10]
2. No differences were observed in the time to the first occurrence of coronary heart disease, breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, or death between oral CEE versus oral or transdermal estradiol-containing regimen.[11]
3. The risk of cardiovascular disease and cancer was not increased among postmenopausal women using vaginal estrogens compared with non-users.[12]

E4 is a natural estrogen produced by the fetal liver. In humans, it is only produced during pregnancy and reaches the maternal circulation through the placenta. The fetal liver, which contains 15 alpha-hydroxylase and 16 alpha-hydroxylase, is the exclusive site of E4 production.[13] E4 is not produced by other species tested so far (mice, rat, and rabbit) except in Cynomolgus monkey (unpublished data). Human maternal plasma levels increase during pregnancy to high concentrations towards the end of gestation (≥1 ng/mL).[13,14] Fetal plasma levels have been reported to be nearly 20 times higher than maternal plasma levels at parturition.[15]

Since early 2000, E4 has been extensively studied in several women's health care therapeutic indications such as contraception, VMS and VVA related to menopause and breast cancer. Both preclinical and clinical data obtained to date indicate that E4 may be promising for use in women.[16] In particular, from Phase 1/2 clinical results, it appears that E4 alone or in combination with a progestin minimally impacts the synthesis of liver proteins, and only slightly increases triglyceride levels, potentially minimizing the risk of VTE and cardiovascular disease.[17]

Data from a recently completed Phase 2 study [18] have also shown that E4 15 mg, administered to postmenopausal women for 12 consecutive weeks showed proof of concept on the two main symptoms associated with the menopause, namely VMS and VVA. In this context, the present study in postmenopausal women is planned.

5.2. Prior Clinical Experience in Postmenopausal Women

When administered orally, E4 is absorbed rapidly (median T_{max} of about 0.25 to 0.50 hour) and C_{max} are dose-dependent. E4 does not bind to sex hormone binding globulin (SHBG) and is principally metabolized to glucuronide and sulphate conjugates and eliminated by the kidney. Steady-state is reached between 6 to 8 days. The mean $T_{1/2}$ of E4 following single ascending dose administration (from 0.1 mg to 100 mg) in postmenopausal women is about 28 hours.[14,16,19,20]

Previous clinical studies with E4 alone have shown that it is well tolerated and safe up to 100 mg given as a single dose and up to 40 mg given once daily for 28 days.[20,21] Moreover, data from postmenopausal women showed that E4 inhibited secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) in a dose-dependent manner denoting the central inhibiting potency of the compound. Endometrial thickness and proliferation were directly related to the dose of E4 administered. The daily oral intake of ascending E4 doses (from 2 mg to 20 mg) for 28 days also allowed demonstrating a beneficial effect of E4 for the treatment of VMS and for the vaginal epithelium in a possible dose-dependent fashion.[21]

Based on this first proof of concept of E4 as MHT, a randomized, placebo-controlled, double-blinded, dose-finding study was conducted, with the primary objective to establish the oral Minimum Effective Dose (MED) of E4 for the treatment of VMS in postmenopausal women (hysterectomized and non-hysterectomized).[18] E4 doses tested included 2.5 mg, 5 mg, 10 mg, and 15 mg for the reduction of VMS at week 4 and week 12 with the greatest improvement observed in the E4 15 mg group. Between 47 and 55 subjects were randomized in each treatment arm. Statistically significant effects versus placebo were observed for the percentage of change in the weekly frequency of VMS and the absolute decrease of the severity of VMS. Absolute changes versus placebo in VMS frequency and percentage of change on the severity of VMS were borderline significant. In all the other E4 groups, the changes in the VMS endpoints were numerically lower than in the E4 15 mg group and did not reach statistical significance versus placebo. The greatest response with E4 15 mg was supported with the evaluation of menopause-related complaints (assessed by the menopause rating scale [MRS]) which resulted in a reduction of MRS reported severity of HFs and sweating when compared to placebo.

All 4 doses of E4 had a positive effect on the vaginal epithelium, as indicated by a substantial increase in the percentage of superficial cells at week 12. The incidence and severity of VVA symptoms improved from baseline to week 12 in all groups with the greatest reduction in the E4 15 mg group compared to placebo.

Other estrogen responsive endpoints demonstrated potential benefits of E4. All E4 doses (in particular 10 mg and E4 15 mg) reduced the level of two bone markers, C-terminal telopeptide type 1 (CTX-1) and osteocalcin. Changes in hemostatic, lipid and glucose metabolism markers were within normal ranges. E4 did not affect coagulation markers, except for a small but statistically significant decrease in free protein S concentration which was observed in the E4 15 mg group at week 12 while the absolute concentration remained within the normal range. A statistically significant increase in SHBG plasma concentrations was observed in the 10 mg and E4 15 mg groups, showing only small absolute changes at 12 weeks. Small and potential beneficial changes in increased high-density lipoprotein (HDL) cholesterol and decreases HbA1c values were observed in the 10 mg E4 and E4 15 mg groups. In non-hysterectomized women, vaginal hemorrhage and endometrial thickening, was seen in more subjects from the E4 10 and 15 mg groups than from the other groups. Endometrium thickness increased with increasing dose of E4 and returned to pretreatment levels at the end of study, i.e., after 2-weeks of treatment with Didrogesterone 10 mg once daily for 14 days. None of the biopsies performed revealed endometrial hyperplasia or carcinoma. In conclusion vaginal hemorrhage and endometrial thickening, in particular, were seen in more subjects from the E4 10 and 15 mg groups than from the other groups. Endometrial thickness increased with increasing dose during treatment with E4 and returned towards pretreatment levels after 2-week intake of progestin.

None of the biopsies performed revealed hyperplasia or other abnormalities that would have required treatment.

5.3. Rationale for the Present Study

In the last 2 decades, the fetal estrogen E4 has attracted renewed attention because of its distinct pharmacological profile.[13,16,22-24] Currently it is in development for several indications. In previous trials, E4 has been shown to be effective in reducing VMS in postmenopausal women (Refer to Section 5.2). There were no safety concerns arising from these trials. Overall, E4 appears to be a new treatment that could bring added value to the already existing hormonal treatment options. The main purpose of this phase 3 trial is to further evaluate the clinical efficacy and safety of E4 in postmenopausal women.

The trial has two parts: an Efficacy Study part (Arms 1 to 3) and a Safety Study part (Arm 4).

The Efficacy Study part is conducted in hysterectomized and non-hysterectomized postmenopausal subjects and evaluates the primary efficacy (frequency and severity of VMS), secondary efficacy (effect on hemostasis, lipid and glucose metabolism, bone turnover, HRQoL and treatment satisfaction [TS]), and safety of E4. All subjects will be treated with E4 15 mg, E4 20 mg or placebo for a total treatment duration of 12 months. After completion of the E4/placebo treatment, all non-hysterectomized subjects will receive treatment with 200 mg progesterone (P4) for 14 days for endometrial protection.

The Safety Study part of this trial evaluates the general safety and secondary efficacy (effect on lipid and glucose metabolism, HRQoL and TS) in hysterectomized and non-hysterectomized postmenopausal subjects. All subjects will be treated with E4 20 mg for a total treatment duration of 12 months.

The design of this study allows for the assessment of the efficacy of E4 in terms of the relief of moderate to severe VMS and for the assessment of the long-term safety of E4 in both hysterectomized and non-hysterectomized postmenopausal women.

The design of the study is consistent with the recommendations given by the FDA and the EMA in their respective guidance:

- "Guidance for Industry. Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms - Recommendations for Clinical Evaluation" (draft guidance, January 2003),
- "Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women" (EMEA/CHMP/021/97 Rev. 1, 2005).
- The design is also consistent with the meeting minutes of the End-of-Phase 2 meeting held with the FDA ([redacted]).

The results of this study will be part of the planned dossier for submission to regulatory agencies to gain approval for E4 for the relief of moderate to severe VMS in postmenopausal women.

5.4. Risk-benefit Assessment

Benefits of MHT are that it is a highly effective therapy for relief of VMS as well as for vaginal dryness and atrophic changes linked to menopause. Additionally, it has dose-related benefit for bone health and for prevention of osteoporosis. MHT also has been shown to enhance libido and QoL. Lastly, MHT can be administered via multiple routes (oral, transdermal, injection, intra-uterine, vaginal) and can thus be provided in a preferred form to meet the needs of most women who require this treatment.[25,26]

Risks of MHT include estrogen-dependent endometrial neoplasia in women with an intact uterus. Both hysterectomized as well as non-hysterectomized postmenopausal women will be included in this study. An endometrial biopsy is part of the screening procedures in non-hysterectomized women and any findings indicating polyps, disordered proliferative endometrium, endometrial hyperplasia or cancer will result in exclusion from enrollment. To monitor the effect of E4 on the endometrium, transvaginal ultrasounds (TVUS) will be performed at multiple time points during E4 treatment to measure the endometrial thickness and subjects will record daily the vaginal bleeding pattern. If, after the first 4 weeks of treatment, a non-hysterectomized subject presents with a bi-layer endometrial thickness > 10 mm as assessed by TVUS or presents with persistent and/or recurrent bleeding, confirmed by the investigator, an endometrial biopsy will be performed. If the biopsy shows disordered proliferative endometrium, hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. If the endometrial event has not resolved, treatment with a progestin will be started according to local practice/guidelines. Subjects will be followed up until resolution.

Non-hysterectomized subjects in the trial will receive treatment with 200 mg P4 for 2 weeks after completion of the E4/placebo treatment.

With MHT use, there is a known risk for thromboembolic disease; and this risk increases with age and other risk factors (e.g., cardiovascular disease, obesity, fracture, immobilization, surgery, cancer, congenital and acquired thrombophilic disorders, smoking). Induction or exacerbation of hypertension has also been found in women using MHT, although MHT is typically associated with a reduction in blood pressure. Women with cardiovascular disease should not initiate or continue MHT for secondary prevention of coronary artery disease. Currently, data from controlled trials, as well as observational studies, indicate that when initiated before 60 years of age, MHT, used even for long periods of time in postmenopausal women, induces lower rates of mortality and coronary heart disease than in comparable women who do not use MHT, [10,27,28] although there may be an increased risk of stroke with MHT use.[29]

Other minor risks include vaginal bleeding secondary to endometrial stimulation (in women with a uterus) which may be mitigated with progestin therapy; nausea or vomiting also has been noted in a small percentage of women.

Contraindications include undiagnosed abnormal genital bleeding; known, suspected, or history of estrogen-dependent neoplasm; presence or history of deep vein thrombosis or pulmonary embolism; presence or history of arterial thromboembolic disease (stroke or myocardial infarction); liver dysfunction or disease; known or suspected pregnancy; and women who may have hypersensitivity to MHT preparations.

6. OBJECTIVES AND ENDPOINTS

This trial has two parts; an Efficacy Study part (Arms 1-3) and Safety Study part (Arm 4). The design of the trial is described in more detail in Section 7.1. The objectives and endpoints for the two parts of the trial are described in separate sections below.

6.1. Objectives and Endpoints of the Efficacy Study Part (Arms 1-3)

6.1.1. Primary Objective and Endpoints

1. To measure the effect of treatment with E4 15 mg or E4 20 mg E4 compared to placebo on the frequency and severity of moderate to severe VMS in postmenopausal women at 4 and 12 weeks

   Co-primary efficacy endpoints for primary objective #1

   1.1. Mean change in weekly frequency of moderate to severe VMS from baseline to week 4
   1.2. Mean change in weekly frequency of moderate to severe VMS from baseline to week 12
   1.3. Mean change in severity of moderate to severe VMS from baseline to week 4
   1.4. Mean change in severity of moderate to severe VMS from baseline to week 12

6.1.2. Secondary Objectives and Endpoints

1. To measure the effect of treatment with E4 15 mg or E4 20 mg compared to placebo on the frequency and severity of mild, moderate and severe VMS in postmenopausal women weekly up to 12 weeks

   Efficacy endpoints for secondary objective #1

   1.1. Change from baseline to week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 in the weekly frequency of and severity of moderate to severe VMS
   1.2. Change from baseline to weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and12 in the weekly frequency and severity of mild, moderate, and severe VMS
   1.3. Percentage of subjects with 50% and 75% reduction from baseline in the weekly frequency of moderate to severe VMS at weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12
   1.4. Percentage of subjects with 50% and 75% reduction from baseline in the weekly frequency of mild, moderate and severe VMS at weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12

2. To measure the clinical meaningfulness of E4 15 mg or E4 20 mg compared to placebo on the reduction of VMS at weeks 4 and 12

   Efficacy endpoint for secondary objective #2

   2.1. Percentage of subjects with a clinically important difference (CID) compared to baseline in the weekly frequency of moderate to severe VMS after weeks 4 and 12 using the Clinical Global Impression (CGI) questionnaire

3. To evaluate the effect of treatment with E4 15 mg or E4 20 mg compared to placebo on hemostasis, lipid and glucose metabolism, and bone turnover

   Efficacy endpoint for secondary objective #3

   3.1. Change from baseline to week 12 and week 52 in prothrombin fragment 1 + 2, endogenous thrombin potential (ETP)-based activated Protein C sensitivity ratio (APCsr ETP), activated partial thromboplastin time (aPTT) based activated Protein C resistance (APCr), anti-thrombin III, Protein-C, free Protein-S, Factor VIII, angiotensinogen, and SHBG
   3.2. Change from baseline to week 12 and week 52 in triglycerides, HDL-cholesterol, low-density lipoprotein (LDL)-cholesterol, total cholesterol, lipoprotein(a), total cholesterol/HDL-cholesterol ratio, fasting glycemia, insulin, glycated hemoglobin and homeostasis model assessment-estimated insulin resistance (HOMA-IR)
   3.3. Change from baseline to week 12 and week 52 in procollagen I N-propeptide (PINP), CTX-1, calcium, and vitamin D

4. To evaluate the effect of treatment with E4 15 mg or E4 20 mg compared to placebo on HRQoL and TS

   Efficacy endpoints for secondary objective #4

   4.1. Change from baseline to week 12 and week 52 in HRQoL using the Menopause-specific Quality of Life (MENQOL) questionnaire
   4.2. Total score in TS after 4, 12, and 52 weeks of treatment using the CGI questionnaire

5. To evaluate the general safety of treatment with E4 15 mg or E4 20 mg compared to placebo

   Safety endpoints for secondary objective #5

   5.1. Frequency of treatment emergent adverse events (TEAEs) (including treatment-emergent serious adverse events [SAEs])
   5.2. Frequency of changes in results in physical and gynecological examination, vital signs, electrocardiogram (ECG), mammography, and breast examination at each measured time point
   5.3. Frequency of changes in routine clinical laboratory tests results (hematology and chemistry) at each measured time point

6. To evaluate the effect of treatment with E4 15 mg or E4 20 mg on the endometrium in non-hysterectomized subjects compared to placebo

   Safety endpoints for secondary objective #6

   6.1. Change from baseline to each measured time point in endometrial thickness measured by ultrasound
   6.2. Frequency of subjects in the different endometrial categories according to the Blaustein's pathology (see Appendix 16.3)

7. To evaluate the effect of treatment with E4 15 mg or E4 20 mg on vaginal bleeding in non-hysterectomized subjects compared to placebo

   Safety endpoints for secondary objective #7

7.1. Frequency of women with vaginal bleeding and/or spotting during each 28-day cycle of treatment with E4 based on data in the patient diary
7.2. Number of days with bleeding and/or spotting during each 28-day cycle of treatment based on data in the patient diary
7.3. Frequency of women with amenorrhea (absence of any bleeding or spotting) during each 28-day cycle of treatment with E4 based on data in the patient diary
7.4. Cumulative rates of amenorrhea defined as the percentage of women who reported consecutive cycles of amenorrhea for a given cycle of time

6.1.3. Exploratory Objectives and Endpoints

1. To evaluate the effect of treatment with E4 15 mg or E4 20 mg compared to placebo on breast density

   Safety endpoint for exploratory objective #1

   1.1. Change in breast density from digitized mammography readings from baseline to EoT in subjects who had a paired digitalized mammography

2. To evaluate the influence of E4 on the changes in the hemostasis parameters compared to placebo in women with inherited thrombophilia and women without this genetic disorder

   Efficacy endpoint for exploratory objective #2

   2.1. Change in hemostasis parameters in women with and without inherited thrombophilia (Factor V Leiden mutation and prothrombin G20210A mutations).

6.2. Objectives and Endpoints of the Safety Study Part (Arm 4)

6.2.1. Primary Objective and Endpoints

1. To evaluate the general safety of treatment with E4 20 mg

   Safety endpoints for primary objective #1

   1.1. Frequency of TEAE (including SAEs)
   1.2. Frequency of changes in results in physical and gynecological examination, vital signs, ECG, mammography, and breast examination at each measured time point
   1.3. Frequency of changes in routine clinical laboratory tests results (hematology and chemistry) at each measured time point

6.2.2. Secondary Objectives and Endpoints

1. To evaluate the effect of treatment with E4 20 mg on lipid and glucose metabolism

   Efficacy endpoints for secondary objective #1

   1.1. Change from baseline to week 12 and week 52 in triglycerides, HDL-cholesterol, LDL-cholesterol, total cholesterol, lipoprotein(a), total cholesterol/HDL-cholesterol ratio, fasting glycemia, insulin, glycated hemoglobin, and HOMA-IR

2. To evaluate the effect of treatment with E4 20 mg on HRQoL and TS

   Efficacy endpoints for secondary objective #2

   2.1. Change from baseline to week 12 and week 52 in HRQoL using the MENQOL questionnaire
   2.2. Total score in TS after 4 weeks, 12 weeks, and 52 weeks of treatment using the CGI questionnaire

3. To evaluate the effect of treatment with E4 20 mg on the endometrium in non-hysterectomized subjects

   Safety endpoints for secondary objective #3

   3.1 Change from baseline to each measured time point in endometrial thickness measured by ultrasound
   3.2 Frequency of subjects in the different endometrial categories according to the Blaustein's pathology (see Appendix 16.3)

4. To evaluate the effect of treatment with E4 20 mg on vaginal bleeding in non-hysterectomized subjects

   Safety endpoints for secondary objective #4

   4.1 Frequency of women with vaginal bleeding and/or spotting during each 28-day cycle of treatment with E4 based on data in the patient diary
   4.2 Number of days with bleeding and/or spotting during each 28-day cycle of treatment based on data in the patient diary
   4.3 Frequency of women with amenorrhea (absence of any bleeding or spotting) during each 28-day cycle of treatment with E4 based on data in the patient diary
   4.4 Cumulative rates of amenorrhea defined as the percentage of women who reported consecutive cycles of amenorrhea for a given cycle of time

7. CLINICAL TRIAL PLAN

7.1. Clinical Trial Design and Justification

7.1.1. Trial Design

The trial has two parts; an Efficacy Study part and a Safety Study part.

The Efficacy Study part has a randomized, double-blinded placebo-controlled design and evaluates the primary efficacy (frequency and severity of VMS), secondary efficacy (effect on hemostasis, lipid and glucose metabolism, bone turnover, HRQoL and TS), and safety of (E4) in both hysterectomized and non-hysterectomized women, as well as the effect of E4 on endometrium in non-hysterectomized women.

A total of ~600 subjects will be randomly allocated (1:1:1) to one of the 3 Arms and will receive E4 15 mg (Arm 1), E4 20 mg (Arm 2), or Placebo (Arm 3). During the first 12 weeks of the Efficacy Study part the effect of E4 on VMS will be evaluated. Thereafter treatment will proceed for a total duration of 12 months (52 weeks), to continue evaluation of secondary efficacy, safety and effect on the endometrium. For endometrial protection, all non-hysterectomized subjects will receive treatment with 200 mg progesterone (P4) once daily for 14 consecutive days, after completion of the E4/placebo treatment.

The Safety Study part of this trial is conducted in ~200 hysterectomized and ~200 non-hysterectomized women and has an open label design. All subjects will receive treatment with E4 20 mg for 12 months (Arm 4). The Safety Study part evaluates the general safety, secondary efficacy (lipid and glucose metabolism, HRQoL and TS) of E4 during treatment for 52 weeks. For endometrial protection, all non-hysterectomized subjects will receive treatment with 200 mg progesterone (P4) once daily for 14 consecutive days, after completion of the E4 treatment.

The trial schedule is provided in Figure 1.

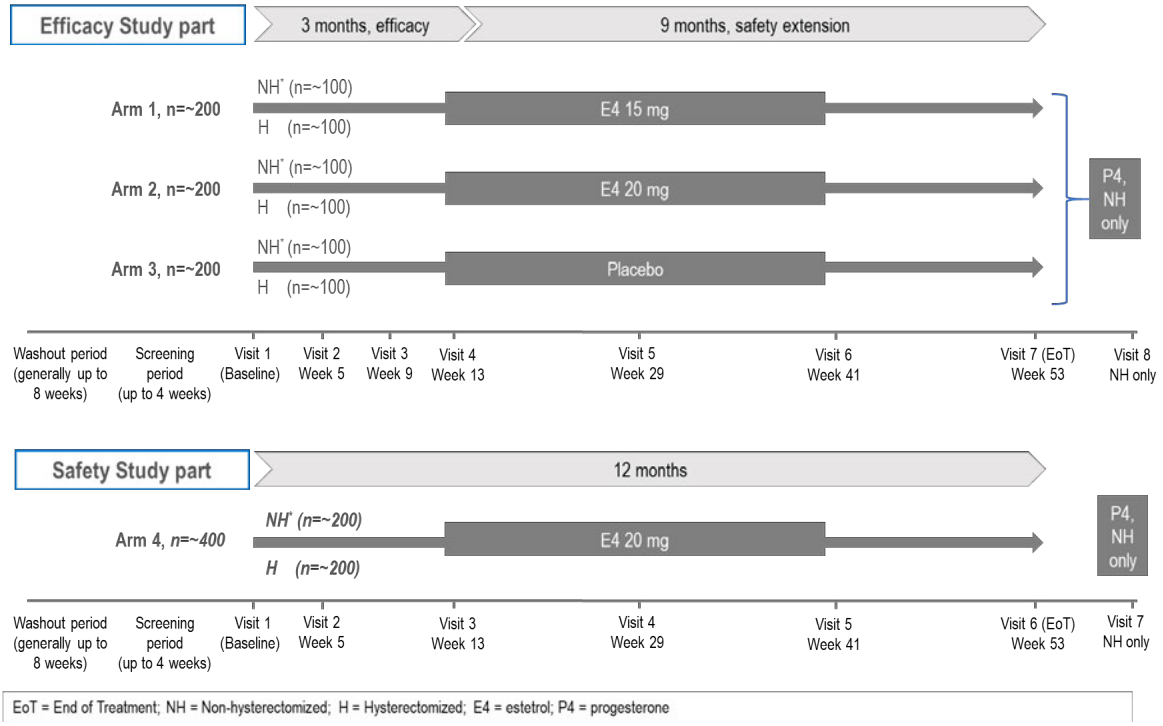
Participants in the Efficacy Study part need to have at least 7 moderate to severe bothersome menopausal related vasomotor symptoms (VMS) per day or at least 50 moderate to severe bothersome VMS per week in the last 7 consecutive days during the Screening period. Bothersome is defined as a score of 4 to 6 on question 1 of the modified MENQOL questionnaire at screening. The number of VMS and modified MENQOL score needed for allocation to the Efficacy Study part will not be disclosed to the study subjects to avoid bias in the recording during the Screening process.

Participants in the Safety Study part should seek treatment for the relief of VMS associated with menopause, with at least 1 moderate to severe menopausal related VMS per week. Subjects who do not fulfill the VMS requirements for participation in the Efficacy Study part, may participate in the Safety Study part providing that they meet all in- and exclusion criteria for participation the Safety study part.

Hysterectomized and non-hysterectomized healthy women will be included in the Efficacy Study part and in the Safety Study part (approximately 50% of the subjects are anticipated to have a history of hysterectomy).

The target enrollment number of subjects in each of the three arms of the Efficacy Study part is ~200. The target number of subjects to be included in the Safety Study part is ~400.

Figure 1: Trial Schedule



* For non-hysterectomized (NH) subjects endometrial thickness will be measured after 3, 6, 9 and 12 months (Visits 4, 5, 6 and 7 of the Efficacy Study part and Visits 3, 4, 5 and 6 of the Safety Study part respectively) of treatment by TVUS and subjects will record daily the vaginal bleeding events. If after the first 4 weeks of treatment a subject presents with a bi-layer endometrial thickness >10 mm as assessed by TVUS or presents with persistent and/or recurrent bleeding, confirmed by the investigator, an endometrial biopsy will be performed. If the biopsy shows disordered proliferative endometrium, hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. If the endometrial event has not resolved, treatment with a progestin will be started according to local practice/guidelines. All NH subjects will receive treatment with 200 mg P4 for two weeks after completion of E4 treatment.

Study flow

For the Efficacy Study part at least 9 visits are planned: a Washout visit followed by a Screening period, which will start with a Screening visit, a baseline visit (Visit 1), and 6 On-treatment visits (Visits 2, 3, 4, 5, 6 and 7). The last treatment visit (Visit 7) is also the end of treatment (EoT) Visit, which will also occur in case of early discontinuation. For non-hysterectomized women an additional endometrial safety follow-up visit (Visit 8) is planned after completion of the 14 days of P4 treatment, which will also occur in case of early discontinuation.

For the Safety Study part at least 8 visits are planned: a Washout visit followed by a Screening period, which will start with a Screening visit, a baseline visit (Visit 1), and 5 On-treatment visits (Visits 2, 3, 4, 5 and 6). The last treatment visit (Visit 6) is also the end of treatment (EoT) Visit, which will also occur in case of early discontinuation. For non-hysterectomized women an additional endometrial safety follow-up visit (Visit 7) is planned approximately 10 days after completion of the 14 days of P4 treatment, which will also occur in case of early discontinuation.

The screening period requires at least one visit, to occur as per protocol, at the beginning of the period, but some assessments (e.g., mammography, biopsy, transvaginal ultrasound [TVUS],

electrocardiogram [ECG] and Papanicolaou [PAP] test) may require additional visits in case these assessments cannot be done during the same visit.

Additional unscheduled visits may also be required for ad hoc safety assessments (e.g., TVUS for non-hysterectomized subjects) during the treatment period.

Washout screening procedures for the Efficacy Study part and Safety Study part

At the Washout visit, after signing the informed consent, the inclusion and exclusion criteria will be checked as well as the prior medication list. If a subject uses prohibited co-medication, then this subject will be asked to stop this medication. After a variable washout period (depending on type of prior medication, Table 3, Section 9.6.1) the subject will return to start the screening. For subjects who do not use medication that needs to be stopped and washed out, the Washout visit and screening Visit may occur at the same time. Screening procedures include a PAP test and mammography for all subjects, a TVUS for subjects with ovaries and/or uterus, and an endometrial biopsy for non-hysterectomized subjects. The length of the Screening period is generally up to 4 weeks, but can be extended (with prior Medical Monitor approval) without exceeding 8 weeks. During this period, and in addition to screening procedures, the subject will record VMS in a paper diary. VMS data recorded during the last 7 consecutive days of the Screening period will be used to determine eligibility of subjects. If based on VMS symptoms of her current medical history a subject is only eligible for the Safety Study part, this subject may be enrolled directly into the Safety Study part without the VMS count in the Screening period, providing that all the screening assessments have been completed. Subjects who do not fulfill the VMS requirements for participation in the Efficacy Study part, may participate in the Safety Study part, providing that they meet all other in- and exclusion criteria.

Treatment period Efficacy Study part

During the first 12 weeks of treatment, primary efficacy assessments (the number and severity of VMS) will be recorded on a daily basis in a paper diary. Subjects will also record vaginal bleeding events (non-hysterectomized subjects only) and daily study drug intake in the diary. After completion of the 12 weeks of treatment (Visit 4), only non-hysterectomized subjects will keep the diary to record daily vaginal bleeding events and daily study drug intake. At baseline (Visit 1) secondary efficacy assessments (hemostasis, lipid and glucose metabolism, and bone turnover) will be performed, the MENQOL questionnaire will be completed, and for non-hysterectomized subjects endometrial thickness will be assessed. Subjects will visit the trial center after 4 and 8 weeks of treatment (Visit 2 and Visit 3) for general safety assessments, for review of the diaries, and for completion of the CGI questionnaire (Visit 2 only). After 12 weeks of treatment, subjects will visit the trial center for the final primary efficacy assessment (Visit 4). During this visit also secondary efficacy assessments and general safety assessments will be performed and the MENQOL and CGI questionnaires will be completed. For non-hysterectomized subjects endometrial thickness will be assessed. Subjects will visit the trial center again after 6 months of treatment (Visit 5) for general safety assessments and endometrial thickness assessment (non-hysterectomized subjects only) and after 9 months of treatment (Visit 6) for general safety assessments and endometrial thickness assessment (non-hysterectomized subjects only). After 12 months of treatment, subjects will visit the trial center for the EoT visit (Visit 7) during which secondary efficacy assessments and general safety assessments will be performed, the HRQoL and TS questionnaires will be completed, and a mammography will be made. For non-hysterectomized subjects endometrial thickness will be

assessed and, if they have completed at least 12 weeks of E4/placebo treatment, an endometrial biopsy will be performed. At Visits 1, 2, 3 and 4 blood samples will be taken to monitor estradiol (E2) levels and at Visits 2, 3 and 4 also to monitor E4 levels.

After the EoT procedures, all non-hysterectomized subjects will receive treatment with 200 mg P4 for 14 days. Approximately 10 days after completion of the progestin treatment, endometrial thickness will be measured (Visit 8).

Treatment period Safety Study part

At baseline (Visit 1) secondary efficacy assessments (lipid and glucose metabolism) will be performed and the MENQOL questionnaire will be completed. Subjects will visit the trial center after 4 weeks (Visit 2), 12 weeks (Visit 3), 6 months (Visit 4) and 9 months (Visit 5) of treatment for safety assessments, and for completion of the CGI questionnaire (Visit 2 only). At Visit 3 secondary efficacy assessments will also be performed and the MENQOL and CGI questionnaires will be completed. For non-hysterectomized subjects endometrial thickness will be assessed on visits 3, 4 and 5. During treatment non-hysterectomized subjects will record vaginal bleeding events in a paper diary. After 12 months of treatment subjects will visit the trial center for the EoT visit (Visit 6) during which secondary efficacy assessments and safety assessments will be performed, questionnaires will be completed and a mammography will be made. For non-hysterectomized subjects endometrial thickness will be assessed and, if they have completed at least 12 weeks of E4, an endometrial biopsy will be performed.

After the EoT procedures, all non-hysterectomized subjects will receive treatment with 200 mg P4 for 14 days. Approximately 10 days after completion of the progestin treatment, endometrial thickness will be measured (Visit 7).

Details on assessments in each visit in the Efficacy Study part and in the Safety Study part are provided in Section 10.1.

7.1.2. Trial Duration

Individual subject participation in this trial may be up to 15 months. This includes a washout period of generally up to 8 weeks (usual washout period for most subjects), a screening period of up to 4 weeks, and a treatment period with E4 of up to 53 weeks. For non-hysterectomized subjects the trial duration will be 3 weeks longer due to an additional endometrium safety follow-up period of approximately 3 weeks.

For subjects requiring a longer washout (up to 6 months) participation period may be extended to allow this washout length. For subjects who do not require a washout, the participation period will be reduced by approximately 8 weeks.

The end of trial is defined as the date when the last patient has completed the last study visit.

7.1.3. Justification of Design, Dose and Endpoints

7.1.3.1. Justification of the Design and Primary Efficacy Endpoints

The design of the trial is consistent with the recommendation given by the FDA and the EMA in the respective guidance:

- "Guidance for Industry. Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms - Recommendations for Clinical Evaluation" (draft guidance, January 2003),
- "Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1, 2005).

The design is also consistent with the meeting minutes of the End-of-Phase 2 meeting held with the FDA ([redacted]).

The agencies recommend performing a randomized, placebo-controlled, double-blinded trial to evaluate the efficacy and safety of estrogen treatment. For the treatment of moderate to severe VMS, the recommended endpoints are the mean change and frequency of moderate to severe VMS from baseline to Week 4 and to Week 12.

The length of the trial is based on the requirements of regulatory bodies in the United States (FDA) and the European Union (EMA) and is sufficient to assess the efficacy, general safety of treatment with E4 in individual subjects with VMS. A period of 12 weeks is required to determine the effect of E4 treatment on the frequency and severity of moderate to severe VMS, which is the primary objective in the Efficacy Study part. In addition, the total treatment duration of 12 months in the Efficacy and Safety Study parts is required to evaluate the long-term safety of E4 in menopausal subjects.

7.1.3.2. Justification of Other Endpoints

This study will also evaluate other symptoms associated with menopause such as quality of life and treatment satisfaction through questionnaires. The parameters will be used to further delineate the optimal dose for the treatment of moderate to severe VMS.

The use of estrogens in the treatment of menopausal complaints has been associated with an increased risk for thromboembolic disease, through changes in blood coagulation and fibrinolysis. This risk is particularly high for women who are carriers of inherited thrombophilia. During the study blood samples will be taken to measure the effect of E4 treatment on hemostasis parameters. Post-hoc pharmacogenomics studies in a subset of E4 users will investigate the relationship between genetic variants and changes in hemostasis parameters levels elicited by E4 with the objective to understand any correlation and predictive factors.

Estrogen treatment may also affect lipid and glucose metabolism and bone turnover, which will be monitored during the study.

In this study a mammogram will be performed at screening (if not performed within 9 months prior to screening start) to exclude subjects with any signs of significant symptoms in breast tissue. At the end of the study a mammogram will be made for subjects who were treated for at least 12 weeks and for whom the last mammography was taken at least 9 months earlier, to monitor any effects on breast tissue. Change from baseline to EoT in breast density will also be evaluated in subjects who have a paired digitalized mammography. Breast density being considered as a risk factor for breast cancer.

In women with an intact uterus the treatment with unopposed estrogen increases the risk of estrogen-dependent endometrial hyperplastic changes that may ultimately result in

premalignant lesions and then carcinomas. The effect of E4 on the endometrium in non-hysterectomized subjects will be monitored by TVUS, bleeding events and endometrial biopsy (see Section 7.1.4).

As some of these efficacy and safety effects may only appear after prolonged exposure, the treatment duration in this trial is extended beyond the 3 months to evaluate the effect of E4 treatment on these endpoints. In order to collect long-term safety data the treatment will continue up to 12 months.

7.1.3.3. Justification of E4 Dose

The objective of the Phase 2 trial with E4 was to assess the minimum effective dose of E4 for the relief of VMS. The results of this trial showed that E4 is safe and well tolerated when administered daily up to 15 mg in postmenopausal women over a period of 3 months. The effect on VMS was the most pronounced with the highest dose tested, i.e., E4 15 mg. Although this dose was associated with a significant reduction in VMS severity compared to placebo, the reduction in VMS frequency failed to reach statistical significance. The advantage over placebo was nevertheless estimated as clinically relevant given the marked placebo effect observed in this trial (65% of VMS reduction compared to baseline for the placebo group versus 84% for the E4 15 mg group). The current trial will continue to study the E4 15 mg doses as well as evaluate a higher dose (E4 20 mg) in order to further delineate the optimal E4 dose for the treatment of moderate to severe VMS.

7.1.3.4. Justification of Placebo

The Efficacy Study part of the current trial is designed to evaluate and compare the effect on VMS reduction of E4 15 mg and E4 20 mg versus placebo. The use of a placebo to compare the effect of E4 on VMS is consistent with the recommendation given by the FDA and the EMA in the guidance referenced in Section 7.1.3.1. The use of placebo is considered necessary to demonstrate efficacy on VMS relief of an estrogenic product.

7.1.4. Justification of Study Population

The trial will be performed in postmenopausal women, which is the intended target population of E4 for the treatment of moderate to severe VMS.

Both hysterectomized and non-hysterectomized postmenopausal women will be included in the trial to determine the efficacy and safety of E4 in the total postmenopausal population.

To further evaluate the safety of 20 mg E4, hysterectomized and non-hysterectomized subjects will be included in the Safety Study part.

7.2. Study and Treatment Assignment

Assignment into any of the study parts (i.e. Efficacy and Safety) and treatment subgroups (15 mg, 20 mg and placebo) will be done by the Interactive Web Response System (IWRS) system (i.e cannot be done by site staff). This assignment will take into account the modified MENQOL score, frequency and severity of hot flashes, hysterectomized vs. non-hysterectomized status, and availability of places in each study part/subgroup.

Efficacy Study part

Subjects eligible for participation in the Efficacy Study part will be randomly allocated to one of the three treatment arms [E4 15 mg (Arm 1), E4 20 mg (Arm 2) or placebo (Arm 3)] in a 1:1:1 ratio using a computer-generated randomization schedule.

Safety Study part

Subjects eligible for participation in the Safety Study part will all be allocated to treatment with E4 20 mg (Arm 4).

7.3. Randomization

A randomization schedule will be generated within the Biometrics Department of the designated CRO by a statistician not involved in the trial. The randomization schedule will be generated by means of the PLAN procedure of SAS®. The computer program uses the method of randomly permuted blocks. The block size will not be revealed before unblinding.

An Interactive Web Response System (IWRS) will be used for the randomization procedure. A subject ready for randomization will be entered in the IWRS. The respective next subject eligible for randomization will receive the lowest available randomization number at the trial center. A randomization confirmation including treatment assignment (i.e., kit number), date and time will be sent to the center, to the designated project managers or designee of the CRO and to the Sponsor's project manager.

The randomization schedule and the complete generation procedure will be filed at a secure place by the designated CRO until the trial database is unblinded. A copy of the list will be sent to the Pharmaceutical Supply for the purpose of assigning the kits to the subjects.

7.4. Blinding Procedures

The Efficacy Study part will have a double-blind placebo-controlled design. Subjects will receive one of the two dosages of E4 or placebo in a blinded manner. Neither trial center personnel, nor the subjects, nor the CRO or Sponsor will know who is receiving E4 15 mg, E4 20 mg or placebo. Active trial treatments will be supplied as tablets indistinguishable from placebo. The Safety Study part will have an open label design; all these subjects will receive E4 20 mg.

The Investigator, trial center personnel, CRO or Sponsor must maintain the blind through database lock and must not break the blind via IWRS or code break envelopes without a valid reason (e.g., in case of emergency). Emergency unblinding is to be done only when knowing the study drug is absolutely necessary for the management of an individual subject and where stopping the blinded medication is not sufficient in the judgment of the Investigator. The Medical Monitor is to be notified by the Investigator when unblinding of a subject's treatment is being considered or has already occurred. The Investigator has the final decision whether the unblinding of a subject's treatment is in the best interest of the subject.

The Safety Study part will have an open label design and blinding is not applicable for this part of the trial.

7.4.1. Blinding after analysis of data up to Visit 4 in the Efficacy Study part

The final analysis of the primary and secondary efficacy objectives 1 and 2 of the Efficacy Study part are to be triggered when all subjects in the Efficacy Study part have completed Visit 4 and will be conducted by an independent statistician. A firewall group, composed of Estetra SRL representatives independent of the E4 project will be appointed. This group will have access to the unblinded data of final and interim analyses of the Efficacy Study part. Further details regarding the composition and role of the firewall group will be provided in a charter. The clinical team, the subjects and the site and sponsor personnel involved in the clinical evaluation of the subjects will remain blinded of the treatment assignment in the Efficacy Study part until the end of the study.

The analyses to be done after completion of Visit 4 will be performed by an independent statistician. Only the overall outcome of the results will be provided to the clinical team. The clinical team, the subjects and the site and sponsor personnel involved in the clinical evaluation of the subjects will remain blinded of the treatment assignment until the end of the study. Blinding for the data at subject and treatment group levels will be kept through a firewall process that will be put in place. No individual listings with the subject numbers' information or tables per treatment group will be disseminated at the time of final or interim triggered analysis of the Efficacy Study part.

No changes in the study conduct will be undertaken regardless of the primary efficacy analysis results. The study will continue until its completion in order to contribute to the safety profile of the study medication.

8. SUBJECT SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

8.1. Source and Number

This will be a multicenter trial performed in multiple study sites in the United States of America and Canada. Subjects will be recruited by the investigator from his/her patients or will be recruited by recruitment campaigns. Subjects must seek treatment for the relief of menopausal symptoms, or subject may already be treated for menopausal symptoms and willing to discontinue their current treatment.

All investigators must keep a record of subjects who were considered for enrollment and were consented, but were never enrolled e.g., subject screening log to address concerns over selection bias.

This trial will enroll a total of approximately 1,000 subjects; ~600 subjects ~200 per treatment arm) in the Efficacy Study part and ~400 subjects in the Safety Study part of the trial. Enrollment will stop when the minimum required number of subjects in each study group and study part is enrolled.

The number of completers after three months of treatment in the Efficacy Study part is anticipated to be around 435, anticipating a drop-out rate of 35% and 20% for non-hysterectomized and hysterectomized women, respectively. The number of completers after 12 months of treatment is anticipated to be ~300, anticipating a drop-out rate of 50% after one year of treatment.

The number of completers in Safety Study part after 12 months of treatment is expected to be ~200, anticipating a drop-out rate of 50%.

8.1.1. Justification of Sample Size

Efficacy Study part: based on results observed for the E4 15 mg dose in the Phase 2 study, a sample size of ~200 subjects per arm provides a power of at least 80% to simultaneously achieve a superiority (upper bound of a 95% 2-sided confidence interval [CI] lower than zero) over placebo for the four co-primary endpoints together. This sample size accounts for a dropout rate during the first 12 weeks of the study of 35% and 20% for non-hysterectomized and hysterectomized women, respectively.

It is planned to enroll approximately 100 hysterectomized and 100 non-hysterectomized subjects per treatment arm.

Safety Study part: the target number of ~400 subjects has been selected to fulfill the requirement stated in International council for harmonization of technical requirements for pharmaceuticals for human use (ICH) E1 guideline (CPMP/ICH/375/95) regarding number of subjects exposed to the drug for safety assessments.

8.2. Inclusion and Exclusion Criteria

8.2.1. Criteria for Inclusion

Subjects will be allocated to treatment if they meet all of the following inclusion criteria:

1. Signed and dated written informed consent form and any required privacy authorization prior to the initiation of any trial procedure, after the nature of the trial has been explained according to local regulatory requirements;
2. Females, ≥40 up to ≤65 years of age at randomization/treatment allocation;
3. For hysterectomized subjects: documented hysterectomy must have occurred at least 6 weeks prior to the start of screening. Hysterectomy can be total or subtotal (i.e., cervix was not removed);
4. For non-hysterectomized subjects: uterus with bi-layer endometrial thickness ≤ 4 mm on TVUS;
5. For non-hysterectomized subjects: endometrial biopsy taken during screening that reveals no abnormal result, i.e., presence of hyperplasia (simple or complex, with or without atypia), presence of carcinoma, and presence of disordered proliferative endometrium findings. The screening biopsy should have sufficient endometrial tissue for diagnosis. Biopsies without tissue or with insufficient tissue may be repeated once;
6. Seeking treatment for relief of VMS associated with menopause;
   a. For the Efficacy Study part: at least 7 moderate to severe bothersome VMS per day or at least 50 moderate to severe bothersome VMS per week in the last 7 consecutive days during the Screening period[12];
   b. For the Safety Study part: at least 1 moderate to severe VMS per week;
7. Body mass index ≥18.0 kg/m² up to ≤38.0 kg/m²;
8. A mammogram that shows no sign of significant disease performed during screening or within 9 months prior to the start of screening[13];
9. Postmenopausal status defined as any of the following:
   a. For non-hysterectomized subjects:
      - At least 12 months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) >40 mIU/mL (value obtained after washout of estrogen/progestin containing drugs, see exclusion criteria 18 and 20);
      - or at least 6 months of spontaneous amenorrhea with serum FSH >40 mIU /mL and E2 <20 pg/mL (value obtained after washout of estrogen/progestin containing drugs, see exclusion criteria 18 and 20);
      - or at least 6 weeks postsurgical bilateral oophorectomy[3];

[12] Bothersome is defined as a score of 4 to 6 on question 1 of the modified MENQOL questionnaire at screening. The timing and number of VMS and modified MENQOL score needed for allocation to the Efficacy Study part will not be disclosed to the study subjects to avoid bias in the recording during the screening process.

[13] Subjects must have a Breast Imaging-Reporting And Data System (BI-RADS) score of 1 or 2 to enroll in the study. An incomplete mammogram result, i.e., BI-RADS 0, is not acceptable and requires further assessment. The site must obtain a copy of the official report for the subject's study file. A digitalized imaging should be obtained if mammography is done as part of this study.

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b. For hysterectomized subjects:
   - serum FSH >40 mIU/mL and E2 <20 pg/mL (values obtained after washout of estrogen/progestin containing drug, see exclusion criteria 18 and 20);
   - or at least 6 weeks postsurgical bilateral oophorectomy[14];

10. Good physical and mental health, in the judgement of the Investigator as based on medical history, physical and gynecological examination, and clinical assessments performed prior to Visit 1;
11. Able to understand and comply with the protocol requirements, instructions, and protocol-stated restrictions;
12. Able and willing to complete trial daily diaries (if applicable, see Section 10.1.7) and questionnaires.

8.2.2. Criteria for Exclusion

Subjects will not be allocated to treatment if they meet one of the following exclusion criteria:

1. History of malignancy, with the exception of basal cell or squamous cell carcinoma of the skin if diagnosed more than 1 year prior to the Screening visit[15];
2. Any clinically significant findings found by the Investigator at the breast examination and/or on mammography suspicious of breast malignancy that would require additional clinical testing to rule out breast cancer (however, simple cysts confirmed by ultrasound are allowed);
3. PAP test with atypical squamous cells undetermined significance (ASC-US) or higher (low-grade squamous intraepithelial lesion [LSIL], atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion [HSIL] [ASC-H], HSIL dysplastic or malignant cells) in sub-totally hysterectomized and non-hysterectomized subjects[16]. Note: ASC-US is allowed if a reflex human papilloma virus (HPV) testing is performed and is negative for high risk oncogene HPV subtypes 16 and 18;
4. For non-hysterectomized subjects:
   a. History or presence of uterine cancer, endometrial hyperplasia, or disordered proliferative endometrium;
   b. Presence of endometrial polyp;
   c. Undiagnosed vaginal bleeding or undiagnosed abnormal uterine bleeding;
   d. Endometrial ablation;

[14] A report or a statement on letterhead from the subject's physician documenting both ovaries were removed is needed.
[15] The exception is only for basal cell carcinoma or squamous cell carcinoma of the skin if either of them were diagnosed more than one year prior to the screening of the subject.
[16] As indicated by written documentation of a prior test performed within 18 months prior screening or by a test performed at screening.

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e. Any uterine/endometrial abnormality that in the judgment of the investigator contraindicates the use of estrogen and/or progestin therapy. This includes presence or history of adenomyosis or significant myoma;

5. Systolic blood pressure (BP) higher than 130 mmHg, diastolic BP higher than 80 mmHg[17] during screening;
6. History of venous or arterial thromboembolic disease (e.g., superficial or deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, angina pectoris, etc.), or first-degree family history of VTE;
7. History of known acquired of congenital coagulopathy or abnormal coagulation factors, including known thrombophilia's;
8. Laboratory values of fasting glucose above 125 mg/dL and/or glycated hemoglobin above 7%[18];
9. Dyslipoproteinemia (LDL >190 mg/dL and/or triglycerides >300 mg/dL)[19];
10. Subjects smoking >15 cigarettes per day;
11. Presence or history of gallbladder disease, unless cholecystectomy has been performed;
12. Systemic lupus erythematosus;
13. Any malabsorption disorders including gastric bypass surgery;
14. History of acute liver disease in the preceding 12 months before the start of screening or presence or history of chronic or severe liver disease [alanine transaminase (ALT) or aspartate transaminase (AST) >2x upper limit of normal (ULN), bilirubin >1.5 ULN], or liver tumors;
15. Chronic or current acute renal impairment (estimated glomerular filtration rate <60 ml/min);
16. Porphyria;
17. Diagnosis or treatment of major psychiatric disorder (e.g., schizophrenia, bipolar disorder, etc.) in the judgement of the Investigator;
18. Use of estrogen/progestin containing drug(s) up to:
    a. 1 week before screening start for vaginal non-systemic hormonal products (rings, creams, gels);
    b. 4 weeks before screening start for vaginal or transdermal estrogen or estrogen/progestin products;
    c. 8 weeks before screening start for oral estrogen and/or progestin products and/or selective estrogen receptor modulator therapy;

[17] BP measurements at screening may be repeated if values are outside the inclusion criteria after sitting for an additional 5 to 10 minutes. The last reading will be used for eligibility. Subjects with mild to moderate hypertension who are controlled on a stable antihypertension regimen may be enrolled if they meet all inclusion/exclusion criteria. Subjects using methyldopa or clonidine containing antihypertensive medication will not be included in the Efficacy Study part.

[18] Laboratory values of fasting glucose and glycated hemoglobin assessed during the last 6 months, and during washout and screening should be considered.

[19] Subjects using lipid-lowering therapy should be on a stable dose for at least 1 month before screening.

d. 8 weeks before screening start for intrauterine progestin therapy;

e. 3 months before screening start for progestin implants or estrogen alone injectable drug therapy;

f. 6 months before screening start for estrogen pellet therapy or progestin injectable drug therapy;

19. Use of androgen/DHEA containing drugs:

a. 8 weeks before screening start for oral, topical, vaginal or transdermal androgen;

b. 6 months before screening start for implantable or injectable androgen therapy;

20. Use of phytoestrogens or black cohosh for treatment of VMS up to 2 weeks before the start of screening;

21. For the women participating in the Efficacy Study part: use of prescription or over-the-counter products used for the treatment of VMS, e.g., anti-depressants: paroxetine, escitalopram, methyldopa, opioid and clonidine up to 4 weeks before the start of screening, and venlafaxine and desvenlafaxine up to 3 months before the start of screening[20], and not willing to stop these during their participation in the trial;

22. Not willing to stop any hormonal products as described in exclusion criteria 18, 19 and 20 during their participation in the trial;

23. Inadequately treated hyperthyroidism with abnormal TSH and free T4 at screening. Subjects with low or high TSH are allowed if free T4 at screening is within normal range[21];

24. History or presence of allergy/intolerance to the investigational product or drugs of this class or any component of it, or history of drug or other allergy that, in the opinion of the Investigator contraindicates subject participation;

25. For non-hysterectomized subjects: history or presence of allergy to peanuts[22];

26. History of alcohol or substance abuse (including marijuana, even if legally allowed) or dependence in the previous 12 months before the start of screening as determined by the Investigator, based on reported observations;

27. Sponsor or CRO employees or employees under the direct supervision of the Investigator and/or involved directly in the trial;

28. Subjects with known or suspected history of a clinically significant systemic disease, unstable medical disorders, life-threatening disease or current malignancies that would pose a risk to the subject in the opinion of the Investigator;

29. Participation in another investigational drug clinical trial within 1 month (30 days) or having received an investigational drug within the last month (30 days) before the start of screening;

[20] If not used for the treatment of VMS, this medication is allowed if on a stable dose for 3 months prior to the Screening visit and no change in the dose regimen is foreseen during the conduct of the trial.

[21] Reflex T4 test to be performed at screening only if TSH at screening is outside normal range

[22] P4 provided as part of this study contains peanut oil and should never be used by subjects with allergy to peanuts

30. Is judged by the Investigator to be unsuitable for any reason.

8.3. Subject Discontinuation and Replacement Procedures

Subjects may withdraw their consent and may discontinue from trial treatment and assessments at any time and for any reason. Subjects are free to discontinue their participation in the trial, without prejudice to further treatment.

In addition, a subject may be withdrawn by the investigator or Sponsor in the case of emerging effects of such a nature that the risk/benefit ratio is unacceptable, in the case of poor compliance or protocol violation, if enrollment into the trial is inappropriate or for administrative and/or other safety reasons.

If a subject does not complete the trial for any reason (including investigator discretion), the reason and circumstances for the subject's early termination must be fully documented in the electronic case report form (eCRF). Possible reasons for a subject discontinuing participation in the trial are (non-exhaustive list):

- SAE(s) that endanger the health of subjects, making it ethically unacceptable to continue or any SAE(s) that the subject finds intolerable
- Deterioration of the subject's clinical condition(s) that requires appropriate therapy/treatment during the trial period as per Investigator's or Sponsor decision
- Endometrium biopsy showing a disordered proliferative pattern, hyperplasia or worse, requiring treatment with a progestin
- Endometrial safety findings that preclude further treatment of non-hysterectomized subjects
- Withdrawal of consent due to lack of efficacy
- Withdrawal of consent for another reason
- Non-compliance to trial protocol: VMS count compliance
- Non-compliance to trial protocol: study drug intake compliance
- Non-compliance to trial protocol: others
- Lost to follow up
- Death
- Other

Wherever possible, subjects who discontinue should be seen and assessed by the investigator. Subjects should complete the early termination visit (Visit 7 Efficacy Study part /Visit 6 Safety Study part). Non-hysterectomized subjects who discontinue early, should also receive treatment with 200 mg P4 for 14 days and return to the clinic for the additional endometrial safety visit (Visit 8 Efficacy study part). If the endometrial event has not resolved by then, treatment with a progestin will be started according to local practice/guidelines. For any subject withdrawn or discontinuing the trial prematurely because of an adverse event (AE) related to one of the trial treatments, the investigator must strive to follow the subject until the AE has either resolved, becomes clinically insignificant, the event is stabilized, or the subject is lost to follow up.

Study site personnel will attempt to follow the progress of every subject admitted to the study through to study completion. If a subject fails to return for a scheduled visit, a reasonable effort should be made to contact the subject and ascertain the reason(s) for not returning. As a minimum, the site staff will contact the subject twice by phone and, if no response, will send a letter by registered mail.

Subjects who are discontinued prematurely from the trial may be replaced at the discretion of Sponsor, in case the total number subjects becomes too low for the evaluation of the primary objective of this trial (see Section 8.1). Investigational products and trial materials should be returned by the subject.

8.3.1. Criteria for Early Termination of the Study

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints or new information regarding the safety of the product becomes available that results in an unacceptable risk/benefit ratio for the trial population.

During the trial an independent Data Safety Monitoring Board (DSMB) will monitor the safety of E4 treatment (see Section 10.5). The study may be terminated early based on the advice of the DSMB.

In addition, further recruitment in the trial or at (a) particular trial center(s) may be stopped due to insufficient compliance with the protocol, good clinical practice (GCP) and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is considered to be too high.

If it becomes necessary to consider termination of the trial for any reason (e.g., safety, overestimation of the sample size, etc.) dosing may be suspended pending discussion between the investigator and Sponsor. Dosing will be stopped immediately on safety grounds.

The trial may also be terminated or suspended at the request of the local authorities or ethics committee (EC)/ institutional review board (IRB).

8.3.2. Stopping Criteria for Non-hysterectomized Women Only

Monitoring of endometrial safety is part of the ongoing safety monitoring by the DSMB. More details on this may be found in the DSMB charter.

9. TRIAL MEDICATION

9.1. Study Treatments

Efficacy Study part:

Once daily oral treatment with:

- E4 15 mg (Arm 1)
- E4 20 mg (Arm 2)
- Placebo (Arm 3)

Safety Study part

Once daily treatment with:

- E4 20 mg (Arm 4)

9.2. Timing of Administration

The trial medication should be taken once daily. Subjects will be instructed to take the trial medication at approximately the same time each day.

If a subject has missed a dose, she should be instructed to take the dose as soon as she remembers. It is acceptable to take a dose up to 12 hours late. If taken more than 12 hours late the subjects should omit dosing for that day and continue with the next dose as usual.

If study treatment is interrupted for 4 days and more per week, the Investigator will need approval from the Medical Monitor to restart the patient on study treatment if the subject has not received P4 200 mg (or other progestins).

9.3. Pharmaceutical Preparations

9.3.1. Active Treatment – Investigational Product

Active substance:	Estetrol monohydrate (E4)
Strength:	Efficacy Study part: E4 15 mg or E4 20 mg
	Safety Study part: E4 20 mg
Dosage form:	Film coated tablet
Excipients:	Lactose monohydrate
	Sodium starch glycolate type A
	Maize starch
	Purified Water
	Povidone 30LP
	Magnesium Stearate

	[redacted] (containing hypromellose, hydroxypropylcellulose, stearic acid, talc, titanium dioxide, Brilliant Blue, Indigo Carmine and Tartrazine)
Manufacturer:	[redacted]
Blinding primary packaging:	Blister pack (PVC/Aluminum) containing 28 tablets per blister
Supplier/secondary packaging:	Carton Wallet

9.3.2. Placebo (Visually Matching the Active Treatments)

Active substance	No active substance
Dosage form:	Film coated tablet
Excipients:	[redacted] (co-processed excipient containing lactose monohydrate and maize starch)
	Magnesium stearate
	[redacted] (containing hypromellose, hydroxypropylcellulose, stearic acid, talc, titanium dioxide, Brilliant Blue, Indigo Carmine and Tartrazine)
Manufacturer:	[redacted]
Blinding primary packaging:	Blister pack (PVC/Aluminum) containing 28 tablets per blister
Supplier/secondary packaging:	Carton Wallet

9.3.3. Progesterone Treatment

The 200 mg P4 treatment for the follow-up treatment of the non-hysterectomized subjects will be supplied by the Sponsor as commercially available medication in the original packaging.

For ad hoc treatment with a progestin, according to local practice/guidelines, the choice of the progestin is left at the discretion of the investigator and treatment will be supplied by the local pharmacy.

9.4. Packaging and Labelling

The E4 and placebo trial medication will be supplied as tablets. The once daily dose consists of one E4 or placebo tablet. All tablets will have a similar weight, shape and color. The tablets will be provided in blisters (28 tablets in one blister) and packed in wallets each containing one blister. The E4 or placebo trial medication will be provided at the study visits as shown in Table 1 (Efficacy Study part) and Table 2 (Safety Study part). One additional blister will be provided to the subjects at Visit 1 in a separate wallet as spare medication, in case the subject loses her

medication. Additional spare blisters may be provided at subsequent visits should the previous one be used. The packaging will be blinded for the Efficacy Study part and open-label for the Safety Study part.

The progesterone treatment (P4) will be supplied as a bottle of 100 capsules. The bottle should be provided entirely to the subject.

Table 1 Supply of E4/placebo and P4 trial medication per visit for Efficacy Study part

Visit number	Packages to be supplied for E4	Packages to be supplied for P4	Medication to be used for
Visit 1 (randomization)	2 blisters of 28 tablets + one spare blister	Not Applicable	Treatment for weeks 1 to 8
Visit 2 (week 5)	1 blister of 28 tablets + one spare blister if needed[1]	Not Applicable	Treatment for weeks 9 to 12
Visit 3 (week 9)	1 blister of 28 tablets + one spare blister if needed[1]	Not Applicable	Treatment for weeks 13 to 16
Visit 4 (week 13)	4 blisters of 28 tablets + one spare blister if needed[1]	Not Applicable	Treatment for weeks 17 to 32
Visit 5 (week 29)	3 blisters of 28 tablets + one spare blister if needed[1]	Not Applicable	Treatment for weeks 33 to 44
Visit 6 (week 41)	3 blisters of 28 tablets + one spare blister if needed[1]	Not Applicable	Treatment for weeks 45 to 56[2]
Visit 7 (Week 53) – EOT / Early Termination	Not Applicable	1 bottle of 100 capsules	Treatment for 14 days after Week 53[3]

[1] Only if previously dispensed spare blister has been used
[2] Only medication of week 45 to 53 is to be used as the next visit (the EoT visit) will be scheduled in week 53.
[3] Only medication for 14 days is to be used. The remaining medication will be returned at Visit 8.

Table 2 Supply of E4 and P4 trial medication per visit for Safety Study part

Visit number	Packages to be supplied for E4	Packages to be supplied for P4	Medication to be used for
Visit 1 (allocation to treatment)	2 blisters of 28 tablets + one spare blister	Not Applicable	Treatment for weeks 1 to 8
Visit 2 (week 5)	2 blisters of 28 tablets + one spare blister if needed[1]	Not Applicable	Treatment for weeks 9 to 16
Visit 3 (week 13)	4 blisters of 28 tablets + one spare blister if needed[1]	Not Applicable	Treatment for weeks 17 to 32
Visit 4 (week 29)	3 blisters of 28 tablets + one spare blister if needed[1]	Not Applicable	Treatment for weeks 33 to 44
Visit 5 (week 41)	3 blisters of 28 tablets + one spare blister if needed[1]	Not Applicable	Treatment for weeks 45 to 56[2]
Visit 6 (Week 53) – EOT / Early Termination	Not Applicable	1 bottle of 100 capsules	Treatment for 14 days after Week 53[3]

[1] Only if previously dispensed spare blister has been used
[2] Only medication of week 45 to 53 is to be used as the next visit (the EoT visit) will be scheduled in week 53.
[3] Only medication for 14 days to be used. The remaining medication will be returned at Visit 7.

Packaging and labelling will be carried out in accordance with the requirements of Annex 13 of the Good Manufacturing Practice (GMP) guidelines, ICH GCP requirements, Sponsor approved standard operating procedures (SOPs) and all applicable local regulations.

Final labelling and packaging of the products will be performed by the supplier [redacted] in accordance with their SOPs and international requirements. Product labels comply with applicable local regulatory requirements and languages.

9.5. Drug Accountability

The investigator is responsible for correct storage of the trial medication according to the manufacturer's recommendations and GMP and GCP requirements. Trial medication must be kept below 25°C/77°F, but not frozen, protect from light, in a locked and secured storage facility inaccessible to unauthorized personnel and stored in such a way that they will not be confused with supplies being used for another trial or any other purpose.

The investigator will ensure that the trial medication is used only in accordance with the approved protocol.

The designated CRO will provide the framework for documenting trial treatment accountability throughout the trial. The Investigator has to maintain an accurate written record of the shipment, dispensing, and return of trial treatments on the designated CRO drug accountability form. An accurate record of the date and amount of trial drug dispensed to each subject has to be available for inspection at any time. The designated CRO representatives will verify drug accountability during routine site monitoring visits and at the completion of the trial.

At the conclusion of the trial and as appropriate during the course of the trial, the Investigator will return all used and unused drug containers, drug labels, and a copy of the completed drug accountability form to Sponsor. Some sites may destroy medications locally at an appropriate time point, if previously agreed with the Sponsor.

9.6. Prior and Concomitant Medication

9.6.1. Prior Medication/Therapy

A washout period is required for the use of estrogens, progestins, androgens, and DHEA containing products for all subjects. For subjects in the Efficacy Study part a washout period is also required for the use of non-hormonal medication or OTC products that are used for the treatment of VMS (see also exclusion criteria, Section 8.2.2). These treatments need to be washed out before the start of screening.

Table 3 provides details on the washout period of each of these drugs.

Table 3 Washout of prior medication

Medication	Washout period before screening start [3, 4]
Estrogen/progestin containing drugs: - vaginal hormonal non-systemic products (rings, creams, gels) - vaginal or transdermal estrogen or estrogen/progestin products - oral estrogen and/or progestin and/or selective estrogen receptor modulator therapy - intrauterine progestin therapy - progestin implants and estrogen alone injectable drug therapy - estrogen pellet therapy or progestin injectable drug therapy	 1 week 4 weeks 8 weeks 8 weeks 3 months 6 months
Androgen or dehydroepiandrosterone (DHEA) containing drugs: - oral, topical, vaginal or transdermal androgen - implantable or injectable androgen	 8 weeks 6 months
- phytoestrogens, black cohosh used for the treatment of VMS	2 weeks
Non-hormonal prescription or over-the-counter treatments that are used for the treatment of VMS[1, 2]: - paroxetine, escitalopram, methyldopa, opioids, clonidine or others; - venlafaxine, desvenlafaxine	 4 weeks 3 months

[1] If used for other indications (e.g., for depressive disorders) this medication is allowed if on a stable dose for 3 months prior to the screening visit and no changes in the dose regimen is foreseen during the trial.

[2] In case it is clear that the subject will participate in the Safety Study part, washout of these medications is not required.

[3] If tapering off a medication is required per Investigator's medical judgement, the washout period should only start after last dose of such medication.

[4] When a subject starts a washout period, it's important to ensure that the subject will have sufficient time to randomize within the enrolment period.

9.6.2. Concomitant Medication/Therapy

The use of any concomitant medication taken during the trial will be recorded in the eCRF and will include the name of the drug, treatment regimen (dose, units, frequency, and route of administration), the date of initiation and discontinuation of the therapy, and the indication.

Lipid lowering drugs
If a subject is receiving a lipid-lowering therapy, then her dyslipoproteinemia has to be in line with the exclusion criteria, with LDL ≤190 mg/dL and triglycerides ≤300 mg/dL. The subject should be on a stable dose of lipid-lowering therapy for at least 1 month before the start of screening.

Thyroid treatment
Thyroid treatments are allowed as long as the subject has normal TSH levels or low or high TSH levels with normal free T4 at screening.

Treatment for VMS symptoms
Estrogen and/or progestin therapies are not allowed during the trial. A washout period is necessary as described in Section 9.6.1.

The use of non-hormonal medication (prescription medication or OTC) for the treatment of VMS is not allowed in the Efficacy Study part. A washout period is necessary as described in Section 9.6.1. If the medication is used for other indications (e.g., for depressive disorders) then participation is allowed if on a stable dose for at least 3 months prior to the start of screening and no changes in the dose regimen is foreseen during the study period.

To confirm compliance with the rules of unauthorized concomitant therapy, blood samples for the analysis of E2 concentrations will be taken during the treatment visits in the Efficacy Study part.

Antihypertensives

Subjects with mild to moderate hypertension who are controlled on a stable antihypertension regimen may be enrolled if they meet the blood pressure criteria at screening (systolic BP ≤130 mmHg, diastolic BP ≤80 mmHg). Subjects using methyldopa or clonidine containing antihypertensive medication may not be included in the Efficacy Study part.

9.6.3. COVID-19 vaccination

Subjects cannot be excluded from the trial based on vaccination status for COVID-19 consistent with restriction for other vaccinations, which may happen in the subjects (influenza, tetanus and other).

Subjects can be vaccinated with a regulatory approved COVID-19 vaccine according to national guidelines but should not participate in a COVID-19 clinical trial.

Recommendation on the timing of the COVID-19 vaccination in relation to study assessments, due to possible acute reaction on vaccination:

- The vaccination should be performed preferably after regular visits with the planned blood collections.
- Otherwise minimum one week before regular visits with blood samples collections.

Rationale for timing restriction: the acute reaction on vaccination may cause transitory changes in biochemistry (liver enzymes, LDH etc.), it is not a common reaction but may happen. The possible transitory increase in temperature may cause changes in absorption of study drug, PK fluctuations etc.

In case of any acute condition, the scheduled visit should be postponed (if no safety issues) until the status of the subject improves.

The vaccination during the trial should be reported as concomitant medication. Any AE that occurs after vaccination should be properly reported.

9.7. Treatment Compliance

Subjects will be asked to bring all packages of used and unused trial medication, including empty blisters/bottles and wallets to each visit. Treatment compliance will be assessed by counting the returned trial medication at each visit. The counts of the returned trial medication will be recorded by the clinical staff in the subject drug accountability log. Any discrepancies between actual and expected amount of returned trial medication must be recorded and discussed with the subject at the time of the visit.

Additionally, for some subjects (see Section 10.1.7), intake of the trial medication will be recorded in a paper diary to check on treatment compliance. The diaries will be checked at each visit for any discrepancies in medication intake.

To confirm treatment compliance in the Efficacy Study part, blood samples for the analysis of E4 concentrations will be taken during Visits 2, 3 and 4.

10. TRIAL ASSESSMENTS

10.1. Experimental Flow

For the Efficacy Study part at least 9 visits are planned: a Washout visit followed by a Screening period which will start with a Screening visit, a Baseline visit (Visit 1), and 6 On-treatment visits (Visits 2 to 7). The last treatment visit (Visit 7) is also the end of treatment (EoT) Visit, which will also occur in case of early discontinuation. For non-hysterectomized women an additional endometrial safety follow-up visit (Visit 8) is planned after completion of the 14 days of P4 treatment, which will also occur in case of early discontinuation.

For the Safety Study part at least 8 visits are planned: a Washout visit followed by a Screening period which will start with a Screening visit), a Baseline visit (Visit 1), and 5 On-treatment visits (Visits 2 to 6). The last treatment visit (Visit 6) is also the end of treatment (EoT) Visit, which will also occur in case of early discontinuation. For non-hysterectomized women an additional endometrial safety follow-up visit (Visit 7) is planned approximately 10 days after completion of the 14 days of P4 treatment, which will also occur in case of early discontinuation.

The screening period requires at least one visit, to occur as per protocol, at the beginning of the period, but some assessments (e.g., mammography, biopsy, TVUS, ECG, and PAP test) may require additional visits to another clinic in case these assessments cannot be done by the study site.

An overview of the trial visits and time windows for each visit is presented in Table 4

Table 4 Visit schedule and permitted time window

Study part	Visit number	Week number	Time window
Efficacy Study part	Washout visit	Week - 12 to week - 4 [1]	n.a.
	Screening period	Week - 4 to week -1 [1]	n.a.
	Visit 1	Week 1	n.a.
	Visit 2	Week 5	Day 29 - 35
	Visit 3	Week 9	Day 57 - 63
	Visit 4	Week 13	Day 85 - 91
	Visit 5	Week 29	Day 197 - 203
	Visit 6	Week 41	Day 281 - 287
	Visit 7	Week 53	Day 365 - 371
	Visit 8 NH subjects only	Week 55/56	Day 379 - 392
Safety Study part	Washout visit	Week - 12 to week - 4 [1]	n.a.
	Screening period	Week - 4 to week - 1 [1]	n.a.
	Visit 1	Week 1	n.a.
	Visit 2	Week 5	Day 29 - 35
	Visit 3	Week 13	Day 85 - 91
	Visit 4	Week 29	Day 197 - 203
	Visit 5	Week 41	Day 281 - 287
	Visit 6	Week 53	Day 365 - 371
	Visit 7 NH subjects only	Week 55/56	Day 379 - 392

1 The week numbers for the Washout visit and Screening period may deviate. The washout visit is generally up to 8 weeks prior to the screening visit. The Screening period is up to 4 weeks, but may be extended to a maximum of 8 weeks.

An overview of the trial procedures and the timing of the assessments is provided in the Schedule of Trial Procedures (Section 2.1 for the Efficacy Study part and Section 2.2 for the Safety Study part). An overview of the procedures per visit is provided in the next sections. Details on the procedures can be found in Section 10.2 (demographics), Section 10.3 (efficacy assessments) and Section 10.4 (safety assessments).

10.1.1. Informed Consent Procedure

When a suitable candidate is identified by the Investigator among the outpatients coming to the trial site, the investigator or designated healthcare professional will ask the subject about her willingness to be included in the clinical trial. The subject is to be informed verbally and in writing about the nature, risks, benefits, and expectations of participating in the clinical trial and a copy of the subject informed consent form (ICF) is to be given to the subject in the appropriate language. Following this, subjects will be allowed sufficient time, in their own opinion, to consider trial entry, and will be offered the opportunity to ask any further questions prior to completing the ICF. The subject ICF is to be signed by the subject and countersigned by the attending investigator or designee prior to proceeding with the Washout/Screening visit and a copy of the signed ICF is provided to the subject.

10.1.2. Washout Visit

All subjects will be pre-screened at the Washout visit and Informed Consent (IC) is taken at this visit. After signing the ICF the following procedures will be performed:

- Check of already available inclusion/exclusion criteria
- Review of the drug treatments/therapy
- If lipid and/or glucose parameters could be a reason of concern in the judgement of the investigator, fasted blood sampling for lipid and glucose parameters assessment may be done during this visit. Otherwise, this assessment will be done during the Screening Period.
- Medical and gynecological history
- Obtain demographic data

In case the subject uses medication for which a washout is necessary (see Section 9.6.1) the screening procedures will be halted. The subject is asked to stop taking this medication and will return for screening after the required washout period (see Section 9.6.1).

In case no washout period is required the subject will immediately continue the procedures of the Screening Visit. For these subjects the Washout visit and Screening visit may occur at the same time.

10.1.3. Screening Visit (Within 4 weeks before Randomization/Treatment allocation)

After the washout period (if applicable) the participant will come to the Screening visit marking the beginning of the Screening period. The Screening period will last up to 4 weeks and the visit needs to occur within 4 weeks prior to Visit 1). The following procedures will be performed as screening procedures:

- Review of already available inclusion and exclusion criteria
- Physical examination
- Gynecological examination
- Breast examination
- Vital signs
- 12-lead ECG
- PAP test (unless a written normal result is available within 18 months before the start of screening)
- TVUS (for women who still have uterus and/or ovaries)
- Endometrial biopsy (for non-hysterectomized women only)
- Digitalized mammography (unless a written normal result is available within 9 months before the start of screening)
- Modified MENQOL questionnaire
- Fasted blood sampling for:
  - Routine hematology and chemistry
  - Lipid and glucose parameters for inclusion (if not done as Washout visit)
  - FSH, E2 and TSH for inclusion (fasting not required)
- Urinary pregnancy test (at the discretion of the Investigator)
- Dispense and explain paper diary
- Record prior medication and start recording concomitant medication.
- Start recording AEs.

The screening period may require additional visits for some assessments (i.e., mammography, biopsy, TVUS, ECG, PAP test) in case these assessments cannot be done during the Screening visit.

During screening the subjects will receive a paper diary and are instructed to record the severity and frequency of VMS until return for Visit 1. The study personnel will remind the subjects weekly (by phone, SMS, e-mail etc.) to complete the diary. The first reminder will be sent 5 ± 2 days after start of VMS recording (i.e. screening visit).

In case it is clear during screening that a subject will participate in the Safety Study part, either because she does not present a score of 4 to 6 on question 1 of the modified MENQOL questionnaire at screening, or based on current medical history, she will not reach the VMS requirements to participate in the Efficacy Study part or because the enrollment in the Efficacy Study part has been completed, the recording of VMS symptoms in the paper diaries may be skipped. The subject will return for Visit 1 after all screening results are available.

Subjects are required to come to the next visit in a fasted state (fasting for at least 8 hours), and take the diary with them.

Subjects presenting the required number of bothersome moderate to severe VMS/day or per week may participate in the Efficacy Study part. Bothersome is defined as a score of 4 to 6 on question 1 of the modified MENQOL questionnaire at screening. Women with at least 1 moderate to severe VMS/week may participate in the Safety Study part. The timing and number

of VMS and modified MENQOL score needed for allocation to the Efficacy Study part will not be disclosed to the study subjects to avoid bias in the VMS recording during the screening process.

Laboratory tests may be repeated once during the screening period, at the discretion of the investigator.

Cervical smears and endometrial biopsies may only be repeated once during the screening period in case of insufficient samples.

In the event screening requirements cannot be met within 4 weeks, the screening period may be extended with prior Medical Monitor approval, but screening period may not exceed 8 weeks. In case the screening period is extended, the site will provide additional/sufficient diary cards to the subject, to ensure completeness of diary cards until the end of the extended screening period. Repeat of entry laboratory parameters will need to be considered in case of extended screening period.

10.1.4. Subject Re-screening

This trial permits the re-screening of a subject who has discontinued the trial as a pre-treatment failure (i.e., subject has not been treated with the study medication); the reason for failure must be temporary and expected to resolve and not related to the primary endpoint (frequency of VMS). If re-screened, all assessments/procedures from the screening period need to be redone except:

- Gynecological examination, including breast examination (if done 2 months before re-screening)
- Mammography (if done 9 months before re-screening)
- Endometrial biopsy (if done 2 months before re-screening)
- PAP test (if a normal written result is available within 18 months before the start of screening)

10.1.5. Visits Efficacy Study part

10.1.5.1. Randomization Visit and Baseline Assessments (Visit 1 – Day 1)

Subjects will return to the trial site at the end of the Screening period (Study Day 1). The following observations/procedures are to be performed and checked at Randomization visit/Visit 1:

- Review of inclusion and exclusion criteria
- Vital signs
- MENQOL questionnaire
- Fasted blood sampling for:
  - Routine hematology and chemistry
  - Lipid metabolism
  - Glucose metabolism
  - Hemostasis

  - Bone turnover
  - Additional optional analysis (including a DNA sample)
  - E2 (fasting not required)
- Urinary pregnancy test (at the discretion of the Investigator)
- Collect diary for the Screening period
- Review of diary
- Randomization
- Dispense diary for treatment period
- Dispense trial medication
- Record prior medication
- Record AEs

Subjects who fulfil all of the inclusion and exclusion criteria will be randomized to trial treatment.

After randomization, the trial medication (E4 or placebo) for the first 8 weeks will be dispensed (see Section 9.4) and subjects need to start treatment on the day of randomization visit (= day 1 of week 1). The next visit will be scheduled and subjects are instructed to come to the next visit with all packages of used and unused trial medication, including empty blisters and wallets.

Subjects are instructed to record daily the severity and frequency of VMS and medication intake in the paper diary. During VMS recording the study personnel will remind the subjects weekly (by phone, SMS, e-mail etc.) to complete the diary. The first reminder will be sent 5 ± 2 days after start of treatment. Non-hysterectomized subjects are instructed to also record the vaginal bleeding events. Subjects need to take the diary to the next visit.

10.1.5.2. Visit 2: Primary Efficacy Visit (week 5)

Subjects will return to the trial site in week 5, after completion of 4 weeks of treatment. The following observations/procedures are to be performed and checked at Visit 2:

- Vital signs
- CGI questionnaire
- Blood sampling for E2 and E4
- Review of diary and collect completed pages
- Dispense trial medication
- Review of returned trial medication/drug accountability
- Record concomitant medication
- Record AEs

After completion of Visit 2 procedures, trial medication for weeks 9 to 12 will be dispensed (see Section 9.4) and the next visit will be scheduled. Subjects are instructed to come to the next visit with all packages of used and unused trial medication, including empty blisters and wallets.

Subjects are instructed to record daily the severity and frequency of VMS and medication intake in the paper diary. Non-hysterectomized subjects are instructed to also record the vaginal bleeding events. Subjects need to take the diary to the next visit.

10.1.5.3. Visit 3: Primary Efficacy Visit (week 9)

Subjects will return to the trial site in week 9, after completion of 8 weeks of treatment. The following observations/procedures are to be performed and checked at Visit 3:

- Vital signs
- Blood sampling for E2 and E4
- Review of diary and collect completed pages
- Dispense trial medication
- Review of returned trial medication/drug accountability
- Record concomitant medication
- Record AEs

After completion of Visit 3 procedures, trial medication for weeks 9 to 16 will be dispensed (see Section 9.4) and the next visit will be scheduled. Subjects are instructed to come to the next visit with all packages of used and unused trial medication, including empty blisters and wallets.

Subjects are instructed to record daily the severity and frequency of VMS and medication intake in the paper diary. Non-hysterectomized subjects are instructed to also record the vaginal bleeding events. Subjects are required to come to the next visit in a fasted state (fasting for at least 8 hours), and take the diary with them.

10.1.5.4. Visit 4: End of Primary Efficacy Period (week 13)

Subjects will return to the trial site in week 13 for Visit 4. This will be the end of the primary efficacy period. The following observations/procedures are to be performed and checked at Visit 4:

- Vital signs
- TVUS (for non-hysterectomized women only)
- MENQOL and CGI questionnaires
- Fasted blood sampling for:
  - Lipid metabolism
  - Glucose metabolism
  - Hemostasis parameters
  - Bone markers
  - E2 and E4 (fasting not required)
- Review of diary and collect completed pages
- Dispense trial medication
- Review returned unused medication/drug accountability
- Record prior/concomitant medication
- Record AEs

After completion of the Visit 4 procedures, trial medication for weeks 17 to 32 will be dispensed (see Section 9.4) and the next visit will be scheduled. Subjects are instructed to come to the next visit and take all packages of used and unused trial medication, including empty blisters and wallets. Non-hysterectomized subjects are instructed to continue daily recording of study drug intake and vaginal bleeding events in the diary and to take the diary to the next visit. Hysterectomized subjects will return their diary.

10.1.5.5. Visit 5: 6 Month Safety Visit (week 29)

Subjects will return to the trial site in week 29 after completion of 28 weeks of treatment. The following observations/procedures are to be performed and checked at Visit 5:

- Vital signs
- Breast examination
- TVUS (for non-hysterectomized subjects only)
- Review of diary and collect completed pages
- Dispense trial medication
- Review returned unused medication/drug accountability
- Record concomitant medication
- Record AEs

After completion of the Visit 5 procedures trial medication for weeks 33-44 will be dispensed (see Section 9.4) and the next visit will be scheduled. Subjects are instructed to come to the next visit and take all packages of used and unused trial medication, including empty blisters and wallets. Non-hysterectomized subjects are instructed to continue daily recording of study drug intake and vaginal bleeding events in the diary and to take the diary to the next visit.

10.1.5.6. Visit 6: 9 Month Safety Visit (week 41)

Subjects will return to the trial site in week 41 after completing 40 weeks of treatment. The following observations/procedures are to be performed and checked at Visit 6:

- Vital signs
- TVUS (for non-hysterectomized subjects only)
- Review of diary and collect completed pages
- Dispense trial medication
- Review returned unused medication/drug accountability
- Record concomitant medication
- Record AEs

After completion of the Visit 6 procedures, trial medication for weeks 45 to 56 will be dispensed (see Section 9.4). Only medication of week 45 to 53 is to be used as the next visit (the EoT visit) will be scheduled in week 53. Subjects are instructed to come to the next visit in a fasted state (fasting for at least 8 hours) and take all packages of used and unused trial medication, including empty blisters and wallets. Non-hysterectomized subjects are instructed to continue daily recording of study drug intake and vaginal bleeding events in the diary and to take the diary to the next visit.

10.1.5.7. Visit 7: End of Treatment/Early Termination Visit (week 53 or earlier)

Subjects will return to the trial site in week 53 for Visit 7. This will be the EoT and follow-up procedures will be performed. Subjects will take their last daily dose of the trial medication on the evening before or in the morning of the day of the EoT visit.

For subjects who terminate early, every reasonable effort should be made by the investigator to complete the final assessment procedures as specified in this section (see also Section 8.3). In case of early termination, treatment may have been stopped earlier.

The following observations/procedures are to be performed and checked at Visit 7:

- Physical examination
- Gynecological examination
- Breast examination
- Vital signs
- 12-lead ECG
- Endometrial biopsy if the subject has completed at least 12 weeks of treatment (for non-hysterectomized women only)
- TVUS (for women who still have uterus and/or ovaries)
- Digitalized mammography if the subject has completed at least 12 weeks of treatment and the last mammography was taken at least 9 months earlier
- MENQOL and CGI questionnaires
- Fasted blood sampling for:
  - Routine hematology, chemistry
  - Lipid metabolism
  - Glucose metabolism
  - Hemostasis parameters
  - Bone markers
  - Additional optional analysis
- Review of diary and collect completed pages (non-hysterectomized subjects)
- Dispense trial medication (P4 200 mg for non-hysterectomized subjects only)
- Review returned unused medication/drug accountability
- Record prior/concomitant medication
- Record AEs
- Complete end of trial form (hysterectomized subjects only)

For hysterectomized subjects: after completion of the Visit 7 procedures in the Efficacy Study part, the subject has completed the trial.

For non-hysterectomized subjects: after completion of Visit 7 procedures the subjects will start treatment with 200 mg P4 once daily for 14 days. Subjects should take the progestin medication as per investigator's instructions. Subjects are instructed to record the vaginal bleeding events and P4 intake in the diary. Subjects will return to the clinic approximately 10 days after completion of the progestin treatment for the endometrial safety follow-up visit.

10.1.5.8. Visit 8: Non-hysterectomized Subjects Only: Endometrial Safety Follow-up Visit (week 55/56 or earlier)

The following observations/procedures are to be performed and checked at Visit 8:

- TVUS
- Return of diary
- Review of diary
- Review returned unused medication/drug accountability
- Record concomitant medication
- Record AEs
- Complete end of trial form

After completion of the Visit 8 procedures in the Efficacy Study part, the subject has completed the trial.

10.1.6. Visits Safety Study part

10.1.6.1. Visit 1: Treatment Allocation Visit and Baseline Assessments (Day 1)

Subjects will return to the trial site at the end of the Screening period. The following observations/procedures are to be performed and checked at the Treatment allocation visit/Visit 1:

- Review of inclusion and exclusion criteria
- Vital signs
- MENQOL questionnaire
- Fasted blood sampling for:
  - Routine hematology and chemistry
  - Lipid metabolism
  - Glucose metabolism
  - Additional optional analysis (including a DNA sample)
- Urinary pregnancy test (at the discretion of the Investigator)
- Collect diary for Screening period
- Review of diary
- Allocation to treatment
- Dispense trial medication
- Dispense diary for treatment period (non-hysterectomized subjects only)
- Record prior medication
- Record AEs

Subjects who fulfil all of the inclusion and exclusion criteria will be allocated to trial treatment.

After treatment allocation, the trial medication (20 mg E4) for the first 8 weeks will be dispensed (see Section 9.4) and subjects need to start treatment on the day of treatment allocation visit (=

day 1 of week 1). The next visit will be scheduled and subjects are instructed to come to the next visit with all packages of used and unused trial medication, including empty blisters and wallets. Non-hysterectomized subjects are instructed to daily recording study drug intake and vaginal bleeding events in the diary and to take the diary to the next visit.

10.1.6.2. Visit 2: 4 Weeks Safety Visit (week 5)

Subjects will return to the trial site in week 5, after completion of 4 weeks of treatment. The following observations/procedures are to be performed and checked at Visit 3:

- Vital signs
- CGI questionnaire
- Review of diary and collect completed pages (non-hysterectomized subjects only)
- Dispense trial medication
- Review of returned trial medication/drug accountability
- Record concomitant medication
- Record AEs

After completion of Visit 2 procedures, trial medication for weeks 9 to 16 will be dispensed (see Section 9.4) and the next visit will be scheduled.

Subjects are instructed to come to the next visit in a fasted state (fasting for at least 8 hours) and take all packages of used and unused trial medication, including empty blisters and wallets. Non-hysterectomized subjects are instructed to daily recording of study drug intake and vaginal bleeding events in the diary and to take the diary to the next visit.

10.1.6.3. Visit 3: 12 Weeks Safety Visit (week 13)

Subjects will return to the trial in week 13 after completion of 12 weeks of treatment. The following observations/procedures are to be performed and checked at Visit 3:

- Vital signs
- TVUS (non-hysterectomized subjects only)
- MENQOL and CGI questionnaires
- Fasted blood sampling for:
  - Lipid metabolism
  - Glucose metabolism
- Review of diary and collect completed pages (non-hysterectomized subjects only)
- Dispense trial medication
- Review of returned trial medication/drug accountability
- Record concomitant medication
- Record AEs

After completion of the Visit 3 procedures, trial medication for weeks 17 to 32 will be dispensed (see Section 9.4) and the next visit will be scheduled. Subjects are instructed to come to the next

visit and take all packages of used and unused trial medication, including empty blisters and wallets. Non-hysterectomized subjects are instructed to daily recording of study drug intake and vaginal bleeding events in the diary and to take the diary to the next visit.

10.1.6.4. Visit 4: 6 Month Safety Visit (week 29)

Subjects will return to the trial site in week 29 after completion of 28 weeks of treatment. The following observations/procedures are to be performed and checked at Visit 4:

- Vital signs
- Breast examination
- TVUS (non-hysterectomized subjects only)
- Review of diary and collect completed pages (non-hysterectomized subjects only)
- Dispense trial medication
- Review of returned trial medication/drug accountability
- Record concomitant medication
- Record AEs

After completion of the Visit 4 procedures trial medication for weeks 33-44 will be dispensed (see Section 9.4) and the next visit will be scheduled. Subjects are instructed to come to the next visit and take all packages of used and unused trial medication, including empty blisters and wallets. Non-hysterectomized subjects are instructed to daily recording of study drug intake and vaginal bleeding events in the diary and to take the diary to the next visit.

10.1.6.5. Visit 5: 9 Month Safety Visit (week 41)

Subjects will return to the trial site in week 41 after completing 40 weeks of treatment. The following observations/procedures are to be performed and checked at Visit 5:

- Vital signs
- TVUS (for non-hysterectomized subjects only)
- Review of diary and collect completed pages (non-hysterectomized subjects only)
- Dispense trial medication
- Review of returned trial medication/drug accountability
- Record concomitant medication
- Record AEs

After completion of the Visit 5 procedures, trial medication for weeks 45 to 56 will be dispensed (see Section 9.4). Only medication of week 45 to 53 is to be used as the next visit (the EoT visit) will be scheduled in week 53. Subjects are instructed to come to the next visit in a fasted state (fasting for at least 8 hours) and take all packages of used and unused trial medication, including empty blisters and wallets. Non-hysterectomized subjects are instructed to daily recording of study drug intake and vaginal bleeding events in the diary and to take the diary to the next visit.

10.1.6.6. Visit 6: End of Trial/Early Termination Visit (week 53 or earlier)

Subjects will return to the trial site in week 53 for Visit 6. This will be the EoT and follow-up procedures will be performed. Subjects will take their last daily dose of the trial medication on the evening before the EoT visit.

For subjects who terminate early every reasonable effort should be made by the investigator to complete the final assessment procedures as specified in this section (see also Section 8.3). In case of early termination treatment may have been stopped earlier.

The following observations/procedures are to be performed and checked at Visit 6:

- Physical examination
- Gynecological examination
- Breast examination
- Digitalized mammography (in case of early termination, mammography may only be performed if subjects was treated for at least 12 weeks and last mammography was taken at least 9 months earlier)
- Vital signs
- 12-lead ECG
- Endometrial biopsy if the subject has at least completed 12 weeks of treatment (for non-hysterectomized women only)
- TVUS (for women who still have uterus and/or ovaries)
- MENQOL and CGI questionnaires
- Fasted blood sampling for:
  - Routine hematology, chemistry
  - Lipid metabolism
  - Glucose metabolism
  - Additional optional analysis
- Review of returned trial medication/drug accountability
- Dispense trial medication (P4 200 mg for non-hysterectomized subjects only)
- Record prior/concomitant medication
- Record AEs
- Complete end of trial form (hysterectomized subjects only)

For hysterectomized subjects: after completion of the Visit 6 procedures in the Safety Study part, the subject has completed the trial.

For non-hysterectomized subjects: after completion of Visit 6 procedures the subjects will start treatment with 200 mg P4 once daily for 14 days. Subjects should take the progestin medication as per investigator's instructions. Subjects are instructed to record the vaginal bleeding events and P4 intake in the diary. Subjects will return to the clinic approximately 10 days after completion of the progestin treatment for the endometrial safety follow-up visit (Visit 7).

10.1.6.7. Visit 7: Non-hysterectomized Subjects Only: Endometrial Safety Follow-up Visit (week 55/56 or earlier)

The following observations/procedures are to be performed and checked at Visit 7:

- TVUS
- Return of diary
- Review of diary
- Review returned unused medication/drug accountability
- Record concomitant medication
- Record AEs
- Complete end of trial form

After completion of the Visit 7 procedures in the Safety Study part, the non-hysterectomized subject has completed the trial.

10.1.7. Subject Diary

In the Efficacy Study part, subjects will complete a paper diary for:

- Daily VMS recording during the Screening period and during the 12 weeks treatment period (until Visit 4):
    - Amount of VMS
    - Severity of each VMS (mild, moderate, severe) (see Section 10.3.1 for definitions)
- Daily recording of trial drug intake, including P4 intake during the follow-up period for the non-hysterectomized subjects
- For non-hysterectomized subjects only: daily recording of the vaginal bleeding events (see Section 10.4.9 for definitions), until the end of study:
    - None
    - Spotting
    - Bleeding

During the VMS recording period subjects will be reminded weekly (by phone, e-mail, SMS etc.) of daily completion of the diary. The first reminder will be sent 5 ± 2 days after start of VMS count in the Screening period.

In the Safety Study part, only non-hysterectomized subjects will complete a paper diary for:

- Daily recording of the trial drug intake (including P4 intake)
- Daily recording of vaginal bleeding events (see Section 10.4.9 for definitions), including during the follow-up period:
    - None
    - Spotting
    - Bleeding

The subject will be instructed to bring the diary to the site at each subject visit. Review of the diary by the Investigator or designee for completeness and consistency is one of the procedures

to be followed on ongoing basis and at each subject's visit. Discrepancies and/or missing data need to be followed-up.

Completed sections of the subject diaries will be retrieved at each visit and the remaining pages will be collected at the end of the study and data will be entered in the eCRFs.

The hysterectomized subjects who continue into the safety follow-up or who are enrolled in the Safety Study part will not complete any diary.

10.2. Demographics and Subject Characteristics

Demographic data will be collected during washout visit and includes age, race, education level, and medical, surgical and gynecological history. Subject characteristics include body weight, height, BMI and smoking habits. BMI will be calculated from body weight and height [BMI = weight (kg)/height (m^2)] and will be rounded to one decimal point according to standard convention to judge inclusion.

10.3. Efficacy Assessments

VMS recording will be done as part of the screening, before assignment to the Efficacy Study part or the Safety Study part and during the Efficacy Study part.

The assessment of hemostatic parameters and bone markers are applicable for subjects in the Efficacy Study part only. Research on genetic coagulopathies is only planned in subjects in the Efficacy Study part.

The other efficacy assessments (lipid and glucose metabolism, HRQoL and TS) are applicable for subjects in the Efficacy Study part and subjects in the Safety Study part.

10.3.1. Frequency and Severity of Moderate and Severe VMS

VMS in postmenopausal women are commonly known as VMS or hot flashes/night sweats. The primary efficacy variables in this trial are the frequency and severity of moderate and severe VMS. Subjects will receive a paper diary to record the severity of any VMS on a daily basis during the Screening period (all subjects) and during the first 12 weeks of the treatment period in the Efficacy Study part. The severity scoring system of the VMS will be documented by the subjects in the diary using the following scores:

1. Mild = Sensation of heat without sweating.
2. Moderate = Sensation of heat with sweating. Able to continue activity.
3. Severe = Sensation of heat with sweating. Causes cessation of activity.

10.3.2. Health Related Quality of Life and Treatment Satisfaction Questionnaires

A modified MENQOL questionnaire will be completed by the subjects during the Screening visit in order to define if the subjects are suitable for the Efficacy Study part or not.

After that, the MENQOL questionnaire will be completed at Visit 1 (baseline), Visit 4 and Visit 7 in the Efficacy study part and at Visit 1 (baseline), Visit 3 and Visit 6 in the Safety Study part to assess the HRQoL. The CGI questionnaire for TS will be completed at Visit 2, Visit 4 and Visit 7 in the Efficacy Study part and at Visit 2, Visit 3 and Visit 6 in the Safety Study part.

Examples of the questionnaires are provided in Appendix16.1 (MENQOL) and Appendix 16.2 (GCI).

10.3.3. Laboratory Assessments for Efficacy

Samples for lipid and glucose metabolism will be taken for all subjects. Samples for hemostasis parameters and bone markers will be taken in the Efficacy Study part only.

Methods for blood sample collection, processing, and shipment are described in instructional materials provided to investigational sites. Leftover samples will be retained after this trial for optional additional analyses in the context of this program or any further research on E4; details of the sample retention for future research as well as subject's rights in regard to these samples are presented in the ICF.

Blood samples for the assessments mentioned below need to be taken in **fasting** conditions (at least 8 hours fast).

The following samples for lipid and glucose metabolism are to be collected at Visit 1 (baseline), Visit 4, and Visit 7 (EoT) in the Efficacy Study part and at Visit (baseline), Visit 3, and Visit 6 (EoT) in the Safety Study part.

- Lipid metabolism: triglycerides, HDL-cholesterol, LDL-cholesterol, total cholesterol, lipoprotein (a) and total cholesterol/HDL-cholesterol ratio.
- Glucose metabolism: fasting glycemia, insulin, glycated hemoglobin, and HOMA-IR.

The following samples for hemostasis and bone markers are to be collected at Visit 1 (Baseline) Visit 4 and Visit 7 (EoT) for subject in the Efficacy Study part:

- Hemostasis parameters: prothrombin fragment 1 + 2, ETP-based activated Protein C sensitivity ratio (APCsr ETP), activated aPTT based activated Protein C resistance (APCr), anti-thrombin III, Protein-C, free Protein-S, Factor VIII, angiotensinogen and SHBG.

  For subjects who gave consent for the DNA sampling only: Factor V Leiden mutation and prothrombin G20210A mutations.
- Bone markers: PINP, CTX-1, calcium and vitamin D

All samples will be processed in the central laboratory for analysis.

The results of these tests will not be reported or provided during the trial but will be included in the Clinical Study Report (CSR). After the end of the study, results will be provided to the investigator upon request.

10.3.4. Blood Sampling for Exploratory Research

In the context of future exploratory research on E4, three additional blood samples (including a DNA sample) will be taken. These extra samples are optional and will be taken only in subjects who provide their consent.

One of these samples is intended to be used as DNA sample (taken at Visit 1). The second and third samples (taken at Visit 1 and End of Treatment Visit) are intended to be used, at sponsor discretion, to perform any further analyses needed in the context of this program or any further research on E4, in order to better understand and assess how E4 works.

The results of these future possible exploratory analyses will be shared with the investigators, who may inform subjects of their results if requested by them.

These samples will be retained in a coded manner during storage and analysis process and will not be labeled with personal identifiers. Privacy and confidentiality of data generated in the future on stored samples is protected by the same standards applicable to all other clinical data as well as the long-term retention of samples for additional future research.

Details of the sample retention for future research as well as subjects' rights in regard to these samples are presented in the ICF.

10.3.5. Endocrine Assessment for Inclusion And Monitoring of Treatment Compliance

During screening a blood sample will be taken for assessment of FSH and E2 to confirm postmenopausal status and for the assessment of TSH to exclude inadequately treated hyperthyroidism. If TSH is outside the normal ranges, a reflex T4 will be done.

During the first 12 weeks of treatment with trial medication in the Efficacy Study part blood samples for E2 will be taken at each visit to continue monitoring the E2 levels and assess compliance with study requirements in terms of unauthorized concomitant therapies.

During the first 12 weeks of treatment with trial medication in the Efficacy Study part blood samples for E4 analysis will be taken at each visit (except at Visit 1) to confirm treatment compliance. E4 analyses will only be performed at the end of the study to avoid unblinding.

Methods for blood sample collection, processing, and shipment of these samples are described in instructional materials provided to investigational sites. Leftover samples will be retained after this trial for additional analyses in the context of this program or any further research on E4; details of the sample retention for future research as well as subject’s rights in regard to these samples are presented in the ICF.

10.4. Safety Assessments

Safety evaluations will include the following:

- General safety will be assessed in terms of occurrence of TEAS (including SAE monitoring)
- Physical and Gynecological examination (including TVUS for safety assessment)
- Breast examination
- Vital signs
- ECG
- Routine Clinical Laboratory Tests
- Mammography
- Endometrium thickness measured by TVUS (non-hysterectomized subjects only)
- Endometrial biopsies (non-hysterectomized subjects only)
- Vaginal bleeding events (non-hysterectomized subjects only)

10.4.1. Treatment Emergent Adverse Events

- All AEs that occur during the trial after the subject has signed the informed consent are to be documented in the eCRF, regardless of whether they are reported by the subject, elicited by Investigator questioning, detected through physical examination, or by other means.

For adverse events of special interest see Section 10.6.

As far as possible, each AE is described by:

- Duration (start and end dates);
- Start/end of trial medication;
- Severity grade (mild, moderate, severe);
- Investigation causality (relationship to the trial product);
- Action(s) taken (concomitant medication, change of trial medication etc.) including start and end of respective action;
- Concomitant diseases and respective medication in general;
- Start, end and dosage of rescue medication;
- Outcome.

Definition of terms:

AE

An AE is any untoward medical occurrence (change in anatomical, physiological, or metabolic function) in a subject, which does not necessarily have any causal relationship with the product under investigation. An AE may be an exacerbation of a pre-existing medical condition that was present before the subject was assigned to a treatment group.

TEAE

Treatment emergent AEs (TEAEs) are those AEs occurring from time point of first ingestion of investigational product until last visit or any event already present that worsens in either intensity or frequency following exposure to the treatment.

SAE or TESAE

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

- Results in death;
- Is life-threatening (Note: the term “life-threatening” refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically may cause death if it is more severe);
- Requires subject hospitalization or prolongation of existing hospitalization (for the purpose of this trial, a hospitalization is defined as a hospital stay of at least 8 hours and/or an overnight stay);
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Other medically important condition.

Events that require intervention to prevent one or more of the outcomes listed in the definition above are also to be considered as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsion that does not result in hospitalization, or development of drug dependency or drug abuse.

However, medical judgment has to be exercised in deciding whether an event is serious in any other situations considered medically relevant.

The evaluation of the AE as serious or not serious is made independently of any attribution of causality.

Events NOT considered to be SAEs are those that require:

- Treatment, which is elective or pre-planned, for a pre-existing condition that is unrelated to the indication under trial and does not worsen;
- Treatment of an emergency on outpatient basis for an event NOT fulfilling any of the definitions of serious given above and NOT resulting in hospital admission for the purpose of this trial, a hospitalization is defined as a hospital stay of at least 8 hours and/or an overnight stay).

Expected AE

The determination of whether an AE is expected is based on previous experience with the investigational product, as follows:

1. Expected AEs are AEs that have already been identified during the investigational product's use, or are a known complication of standard medical procedures that may be conducted as part of the clinical study. Expected AEs are described in the IB. If an event increases in intensity or severity from that described in the IB, it will be considered unexpected.
2. Unexpected AEs are all other AEs which are not deemed anticipated.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is any unexpected AEs assessed as related to treatment that at any dose:

1. Results in death;
2. Is life-threatening (Note: the term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically may cause death if it is more severe);
3. Requires subject hospitalization or prolongation of existing hospitalization (for the purpose of this trial, a hospitalization is defined as a hospital stay of at least 8 hours and/or an overnight stay);
4. Results in persistent or significant disability/incapacity;
5. Is a congenital anomaly/birth defect;
6. Other medically important condition.

AE intensity

AE intensity is determined by the clinical Investigator based on his/her direct observations or the subject's reporting:

- Mild: causes no limitation of usual activities; the subject may experience slight discomfort
- Moderate: causes some limitation of usual activities; the subject may experience annoying discomfort
- Severe: causes inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

AE causality (relationship guide)

Any AE has to be judged for causality (relationship to trial medication and relationship to trial procedure).

The relationship of an AE to the trial product is to be graded by the Investigator based on the following:

Table 5: Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug

Category	**Criteria**	**Final Reporting of Relationship to Study Drug**
Highly probable	• Event or laboratory test abnormality, with plausible time relationship to drug intake. • Cannot be explained by disease or other drugs. • Response to withdrawal plausible (pharmacologically, pathologically). • Event pharmacologically and/or phenomenologically related. • Rechallenge satisfactory, if necessary.	Related
Probable	• Event or laboratory test abnormality, with reasonable time relationship to investigational drug intake. • Unlikely to be attributed to disease or other drugs. • Response to withdrawal clinically reasonable. • Rechallenge not required.	
Possible	• Event or laboratory test abnormality, with reasonable time relationship to investigational drug intake. • Could also be explained by disease or other drugs. • Information on drug withdrawal may be lacking or unclear.	
Unlikely	• Event or laboratory test abnormality, with a time to investigational product intake that makes a relationship improbable (but not impossible). • Disease or other drugs provide plausible explanations.	Not Related
Not Related	• Event due to underlying or concurrent illness, complications, concurrent treatments or effect of another concurrent drug/therapy and is not associated to the investigational drug.	

Handling of AEs

If an AE occurs, appropriate diagnostic and therapeutic measures are to be taken and the trial product must be discontinued if appropriate. Follow up evaluations of the subject are to be performed until the subject recovers or until the clinical Investigator considers the situation to be no longer clinically significant, at the maximum of 30 days following completion of the trial.

If clinically significant laboratory abnormalities appear at the final visit, appropriate additional tests may to be performed to clarify the nature of any clinically significant laboratory abnormalities that occur.

AEs are monitored and registered on the AE form of the eCRF at each visit. The Investigator must make a determination of relatedness, seriousness, and intensity. All AEs during the study will be documented in the subject's medical record. This information will then be transcribed on the AEs form of the eCRF by designated study personnel. Required information includes a description of the event, date of onset, date of resolution, the outcome, the action taken to manage the AE, the impact on the study drug intake, as well as relatedness, seriousness and intensity. In the absence of a specific diagnosis, an individual AE form has to be filled in for each sign or symptom.

Persistent AEs will be entered once in the eCRF until they are resolved or if a new event has to be documented due to deterioration. These AEs will be carefully monitored; further details of monitoring of persistent AEs will be provided in the monitoring plan. If an AE is still not resolved at the end of the trial, this will be documented as ongoing.

For recurrent AEs, i.e., AEs of the same nature, but with a different date of onset, an individual AE form must be completed for each of them.

AEs occurring after the termination of the trial individually and/or of the trial in total are to be reported to the Sponsor even after the clinical trial has been finished if, in the judgment of the Investigator, there is an association between the event and the previous use of the product under investigation.

If the AE is classified as serious, Investigators or designated study site personnel must inform the appropriate CRO representatives of any SAEs that occur (whether or not related to the study drug) in the course of the study, within 24 hours of when he/she becomes aware of it.

All cases of VTE or arterial thromboembolism should be treated as SAE and reported in the same manner as SAEs.

SAEs will be entered by the site members into the eCRF, which contains specific questions for serious events. The CRO Drug Safety Department and the Sponsor will receive the alert through automated e-mail notification.

In case of technical problems in transmitting the SAE through the eCRF within the 24-hour timeline, the investigator/site representative shall complete the SAE form and e-mail to:

E-mail: [redacted]

Follow-up information on SAEs must also be reported by the investigator by entering this updated information into the eCRF within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to the CRO within 24 hours as described above.

At the earliest possible date, the SAE report must be followed by a detailed report and any documentation that may be available, e.g., hospital case records, autopsy reports, and/or other pertinent documents. No private and/or confidential data that allow identification of trial subjects are to be transmitted.

All the above documents will be sent by email to the Drug Safety Department of the designated CRO within 24 hours of receipt. The Investigator will be responsible for reporting the SAE to ethics committees or Institutional Review Board; the Sponsor will be responsible for reporting the SAE requiring expedited reporting to the respective health authorities, according to the national regulatory requirements. Serious adverse events are to be followed up until the subject recovers or until the clinical Investigator considers the situation to be no longer clinically significant, at the maximum of 30 days following completion of the trial. Subjects with disordered proliferative endometrium, hyperplasia or worse will be followed up until resolution.

Resolution of DPE and hyperplasia should be documented by TVUS with endometrial thickness ≤ 4 mm or an endometrial biopsy, if deemed necessary by the Investigator, repeated no earlier than 10-14 days after oral treatment with P4 200 mg/day for 14 days given after discontinuation of the subject.

10.4.2. Physical and Gynecological and Breast Examination

A physical examination will be performed for each subject during the Screening Period and at the EoT (Visit 7 Efficacy Study part/Visit 6 Safety Study part).

This evaluation will include an examination of general appearance, head, eyes, ears, nose, throat, skin neck, lungs, breast, lymph nodes, abdomen, and the cardiovascular musculoskeletal and neurological systems.

A gynecological and breast examination will be performed for each subject during the Screening Period and at the EoT (Visit 7 Efficacy Study part/Visit 6 Safety Study part). This evaluation will include a manual pelvic and breast. Additional breast examinations will be performed after 6 months of treatment (Visit 5 Efficacy Study part/Visit 4 Safety Study part). Gynecological and breast examinations will be done by trained and experienced personnel as per to local regulations.

All abnormal findings in the physical, gynecological and breast examinations that are considered by the Investigator to be clinically significant will be recorded as AEs (Section 10.4.1).

10.4.3. Vital Signs

Vital signs will include height, body weight, BMI, sitting systolic and diastolic BPs, and heart rate. BP will be taken at all visits; height will only be measured during screening, weight will

only be measured at during screening and at the EoT visit. The same equipment (e.g., scale) should be used for all measurements. BMI will be calculated from the subjects height and weight using the formula BMI = kg/m^2; where kg is the body weight in kilograms and m^2 is the body height in meters squared. BP measurements will be made using a sphygmomanometer with an appropriate cuff size for the individual subject. Measurements will be taken while the subject is seated after at least 5 minutes at rest. Other procedures should not be performed during the time of the blood pressure and pulse rate measurements. BP measurements at screening may be repeated if values are outside the inclusion criteria after sitting for an additional 5 to 10 minutes. The last reading will be used for eligibility.

All abnormal findings in vital signs that are considered by the Investigator to be clinically significant will be recorded as AEs (Section 10.4.1).

10.4.4. Electrocardiogram

A 12-lead ECG will be recorded for each subject during screening and at the EoT Visit (Visit 7 Efficacy Study part/Visit 6 Safety Study part). ECGs will be read locally. The ECG interpretation scheme will include the analysis of the morphology, rhythm, conduction, ST segment, PR, QRS, QT and QTc (according to QTcFrid) intervals, T waves, U waves and the presence or absence of any pathological changes.

All abnormal findings in ECG that are considered by the Investigator to be clinically significant will be recorded as AEs (Section 10.4.1).

10.4.5. Routine Clinical Laboratory Tests

Methods for blood collection, processing, and shipment are described in instructional materials provided to investigational sites. Leftover blood samples will be retained after this trial for optional additional analyses in the context of this program or any further research on E4; details of the sample retention for future research as well as subject's rights in regard to these samples are presented in the ICF.

Blood samples for the assessments lipids and glucose need to be taken in **fasting** conditions (at least 8 hours fast).

Samples for clinical blood tests will be taken during the Screening Period, at Visit 1 (baseline) and at the EoT (Visit 7 Efficacy Study part/Visit 6 Safety Study part). Samples will be processed in the central laboratory for analysis of the following parameters:

- Hematology: hematocrit, hemoglobin, erythrocytes, platelets, leukocytes, neutrophils, lymphocytes, basophils, eosinophils and monocytes
- Chemistry: urea, creatinine, total bilirubin, alkaline phosphatase, ALT, AST, sodium, potassium, chloride, bicarbonate, calcium, albumin, total protein, lactate dehydrogenase (LDH), LDH isoenzymes (I, II, III, IV, V), troponin, and blood glucose
- A urinary pregnancy tests may be performed at the discretion of the Investigator during the Screening visit and during the Randomization/Treatment allocation visit (Visit 1)

A sample for lipid and glucose parameters will be taken at washout visit or at screening visit and will be processed in the central laboratory for analysis of the following parameters:

- Lipid parameters: triglycerides, HDL-cholesterol, LDL-cholesterol, total cholesterol

- Glucose parameters: fasting glucose, glycated hemoglobin

The results of the above mentioned hematology, chemistry, lipid and glucose parameters will be analyzed during the trial on an ongoing basis and will be reported during the trial to the Investigator for safety monitoring. After review of the laboratory data, the Investigator must sign and date each laboratory report.

The laboratory will provide normal reference ranges for the laboratory results, and the laboratory report will flag all abnormal values. The Investigator will assess the clinical relevance of values outside the normal range and repeat, if needed, any clinically significant abnormal laboratory test.

Laboratory results should only be recorded and reported as AEs if they are considered as clinically significant, i.e., if they are associated with clinical symptoms, require active management, constitute SAEs or lead to discontinuation of treatment. As far as possible, the clinically significant abnormal laboratory value, as such, should not be recorded on the eCRF pages as an AE; rather, the etiology of the abnormality should be identified, and any clinical signs, symptoms or diagnoses which correspond to the laboratory abnormality should be recorded as an AE (Section 10.4.1).

Abnormal clinically significant laboratory values detected during screening are not considered AEs, but the underline disease needs to be reported in the medical history page, as appropriate.

10.4.6. Mammography

A digitalized mammogram will be performed during the Screening period unless a written report, preferably with digital imaging, demonstrating a normal result is available within 9 months before the Screening visit. Subjects must have a Breast Imaging-Reporting And Data System (BI-RADS) score of 1 or 2 to enroll in the study. An incomplete mammogram result, i.e., BI-RADS 0, is not acceptable and requires further assessment. The site must obtain a copy of the official report for the subject's study file, including the digital imaging if available.

An additional digitalized mammography will be performed at the EoT (Visit 7 Efficacy Study part/Visit 6 Safety Study part) or at early termination. In case of early termination, mammography may only be performed if the subject was treated for at least 12 weeks and the last mammography was taken at least 9 months earlier.

The mammogram will be used for exploratory evaluation of the change from baseline to EoT in breast density in subjects who have a paired digitalized mammography.

More information is to be found in the Imaging Manual.

10.4.7. Transvaginal Ultrasound in Non-hysterectomized Subjects

A TVUS will be performed during screening and at the EoT visit in all subjects who still have uterus and/or ovaries for general safety assessment.

In addition TVUS will be performed to monitor the endometrium thickness during the treatment at Visit 4, Visit 5 and Visit 6 in the Efficacy Study part and Visit 3, Visit 4 and Visit 5 in the Safety Study part. The TVUS will be done in the sagittal section showing the cervix including

the cervical canal. The TVUS will be assessed by the Investigator, gynecologist or designee and bi-layer endometrial thickness will be measured.

10.4.8. Endometrial Biopsy in Non-hysterectomized Subjects

Endometrial biopsies will be used for the evaluation of endometrial safety of non-hysterectomized subjects participating in the trial. An endometrial biopsy will be performed for all non-hysterectomized subjects at screening (Visit 1), at the EoT Visit (Visit 7 in the Efficacy Study part and Visit 6 in the Safety Study part) or upon early termination providing that the subject has been treated with E4 or placebo for at least 12 weeks.

Additional unscheduled endometrial biopsies will be performed in case a bi-layer endometrial thickness of >10 mm is detected on TVUS and/or in the presence of persistent and/or recurrent bleeding, confirmed by the investigator.

Detailed procedures for obtaining endometrial biopsies, tissue preparation and endometrial biopsy assessment will be described in separate study manuals to be provided to the sites, a summary is provided below.

Procedure for obtaining endometrial biopsy

The endometrial biopsy should be taken according to local procedures by a board-certified gynecologist or designee, preferably using the Pipelle technique. The “Pipelle de Cornier” is internationally used for endometrial biopsies, because it is adequate and safe. However, comparable devices may exist and be used, providing that they are adequate for sampling and not traumatizing. The screening biopsy should have sufficient endometrial tissue for diagnosis. If insufficient tissue specimen or if no tissue is obtained, the endometrial biopsy may be repeated once.

Subjects can be given sedation and/or pain relief prior to the procedure under standard local care providing that the medications are not listed as unauthorized therapies in Section 9.6.2. and as per Investigator judgment. Women will receive counselling to include discharge instructions and to expect mild to moderate bleeding that can last for a few days and will be advised to call the site if they experience fever, pain or increased or prolonged bleeding. If an abnormal uterine bleeding occurs within 10 weeks after a first normal endometrial biopsy, a thorough gynecological examination, a TVUS, and – if necessary – a second endometrial biopsy will have to be performed.

Evaluation of endometrial tissue

The endometrial tissue obtained by endometrial biopsy at screening, during the conduct of the study, and at the end-of-study will be processed in the same manner by a central laboratory.

Biopsies obtained during screening and during the conduct of the study, including end-of-study biopsies, will be initially read by one safety pathologist for safety diagnosis only. The Investigator will decide inclusion or discontinuation of the subject from the study based on the initial reading. Screening biopsies will also be read by two other expert pathologists. Biopsy samples collected during the conduct of study and at the end-of-study will be read by three expert pathologists for the final (consensus) diagnosis. These three expert pathologists are independent and belong to different institutions. They are blinded to treatment and to each other’s readings.

The investigator will be informed if subsequent readings impact the initial decision. A reading of disordered proliferative endometrium, hyperplasia (simple or complex, with or without atypia) or carcinoma from any of the pathologists providing the safety readings will prompt the exclusion or discontinuation of the subject from the study.

The concurrence of two of the three pathologists who read the biopsy samples for final (consensus) diagnosis will be accepted as the Final Diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis, i.e., carcinoma > atypical complex hyperplasia > atypical simple hyperplasia > complex hyperplasia > simple hyperplasia > benign endometrium will be used as the final diagnosis. The Final Diagnosis will be used for the analysis of the endometrial safety objective.

Standardized criteria as provided in Blaustein's pathology text (Pathology of the Female Genital Tract 8, see Appendix 16.3) will be used for the characterization of the endometrial tissue. Endometrial polyps will be fully characterized as to the glandular proliferation and atypia (see Appendix 16.3 for additional histologic characteristics of the specimen).

Procedure in case of disordered proliferative endometrium, hyperplasia or worse

If a biopsy shows disordered proliferative endometrium, hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. If the endometrial event has not resolved, treatment with a progestin will be started according to local practice/guidelines. The subject will be followed up (i.e. collect diagnostic and therapeutic assessment(s)) until resolution, even if after study termination. The diagnostic assessment which proves resolution must be reported to the Sponsor even after study termination. In case of disordered proliferative endometrium, hyperplasia or worse, the event must be reported as an Adverse Event of Special Interest (AESI) (Section 10.6) and the Sponsor will be notified.

10.4.9. Vaginal Bleeding Events

The non-hysterectomized subjects will record daily the vaginal bleeding events in the paper diary for the evaluation of the bleeding pattern (spotting, presence, absence).

Absence or occurrence of vaginal bleeding/ spotting on a daily basis will be assessed using the scale below:

0 = Absence of vaginal bleeding or spotting;

1 = Spotting: evidence of minimal blood loss requiring none or at most one pad, tampon or panty liner per day;

2 = Bleeding: evidence of blood loss requiring more than one pad, tampon or panty liner per day.

Subjects are advised to inform the clinic in case of abnormal uterine bleeding.

Vaginal bleeding events grade 2 must be reported as AESIs (Section 10.6).

10.4.10. Endometrial Safety Assessment and Stopping Rules

A baseline endometrial biopsy will be obtained for all the non-hysterectomized subjects during the Screening period. An end-of-treatment endometrial biopsy is planned at the EoT Visit (Visit

7 in the Efficacy study part and Visit 6 in the Safety Study part) providing that the subject has been treated with E4 for at least 12 weeks.

Endometrial thickness will be measured at screening, Visit 4, Visit 5, Visit 6 and Visit 7 (EoT) in the Efficacy Study part and at screening, Visit 3, Visit 4, Visit 5 and Visit 6 (EoT) in the Safety Study part and subjects will record daily the vaginal bleeding events. If after the first 4 weeks of treatment, subject presents with a bi-layer endometrial thickness >10 mm as assessed by TVUS and/or presents with persistent and/or recurrent bleeding, confirmed by the investigator, an endometrial biopsy will be performed. If the biopsy shows disordered proliferative endometrium, hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. At approximately 10-14 days after completion of the progestin treatment, a new TVUS will be performed to measure endometrial thickness and a biopsy will be carried out if deemed necessary by the Investigator to demonstrate the resolution. If the endometrial event has not resolved, treatment will be started according to local practice/guidelines. The pathologic diagnoses of DPE, hyperplasia and worse will be reported as AESI and the subject will be followed up until the resolution of the event. Resolution of disordered proliferative endometrium and hyperplasia should be documented by TVUS with endometrial thickness ≤4 mm or an endometrial biopsy repeated no earlier than 10-14 days after oral treatment with P4 200 mg/day for 14 days given after discontinuation of the subject.

Information on the treatment (including surgical treatment) and any additional pathology results will be reported.

Endometrial safety will be monitored during the trial by a DSMB (see Section 10.5).

10.5. Data Safety Monitoring Board

An independent DSMB will be established to perform ongoing safety surveillance. The voting members on the DSMB are external to the Sponsor and are not involved with the trial in any other way and have no competing interests that could affect their roles with respect to the trial.

During the conduct of the study, the safety data of the study will be collected on an ongoing basis and provided to the DSMB. The DSMB will monitor the general safety and the endometrial safety of the trial at an appropriate frequency as provided in the DSMB charter and will make recommendations to the Sponsor regarding steps to ensure the safety of the trial subjects. The DSMB will be supported by a Clinical Event Committee who will adjudicate cardiovascular and thrombotic events in a consistent and unbiased manner throughout the course of the study.

More details on the DSMB, including the composition, responsibilities, timing and organization of the meetings and administrative structure will be described in a separate DSMB charter.

10.6. Adverse Events of Special Interest

AESIs are a subset of AEs that include the events listed below:

- Vaginal bleeding events grade 2 as assessed using the vaginal bleeding events scale (see section 10.4.9);
- Events resulting from endometrial biopsy reading limited to:

- Disordered proliferative endometrium;
- Simple hyperplasia without atypia;
- Complex hyperplasia without atypia;
- Simple hyperplasia with atypia;
- Complex hyperplasia with atypia;
- Carcinoma.

In order to facilitate the documentation of AESIs in the eCRF, the event term on the report should be listed as above. In addition, a standard questionnaire will be available to investigators in the eCRF in the SAE screen as guidance on the information to be reported.

The standard time period for collecting and recording of AESIs will begin at the first intake of study drug/placebo and will end at EoT visit. AESIs will be reported to the Sponsor within the same timeframes described for SAEs. AESI collection should start as of the Ministry of Health and/or IRB/EC approval date of Protocol Version 6.0 (Amendment 5). There is no need for retrospective reporting.

Once an onset of a new AESI or exacerbation of a pre-existing AESI is identified (serious or non-serious) in a study subject, the investigator (or designee) must complete the information in the SAE screens of the eCRF WITHIN 24 HOURS after he/she becomes aware of the diagnosis. A field on the SAE screen allows to specify that the event is an AESI and whether it is serious or non-serious. These screens will always be completed as thoroughly as possible with all available details of the event, in accordance with the AESI standard questionnaire provided in the eCRF. Even if the investigator does not have all information regarding an AESI, the screens should still be completed within 24 hours. Once additional relevant information is received regarding the AESI, the eCRF should be updated WITHIN 24 HOURS. The investigator will always provide an assessment of causality at the time of the initial report.

11. DATA COLLECTION, RECORD KEEPING AND QUALITY ASSURANCE

Detailed procedures will be separately provided in the data management, monitoring, and quality plans.

11.1. Data Collection

All subject data have to be reported on the eCRFs in an anonymous fashion. Subjects are identified only by screening number.

The Investigator will be responsible for the completeness, accuracy, and legibility of the information in the eCRF and other trial documents. In line with Good Documentation Practice, the source data should be accurate, legible, attributable, original, and contemporaneous. For documents other than eCRF, only ballpoint pen is to be used and any change of data is to be done by striking out the incorrect data with a single line and dating and initialing the changes made to provide an audit trail. Corrections should be explained in writing, where applicable. Correction fluid or pencils should not be used.

The trial monitors must check the eCRFs against the source documents for accuracy and validity as per the monitoring schedule, as applicable, which includes any data recorded directly on the eCRF (for example, no prior written or electronic record of data) which are considered source data. Also, any step in the creation of source data is to be identified, such as the computerized system used to create, modify, maintain, archive, retrieve, or transmit source data. The subject diary will remain as source at site and will only be source data verified by the monitors. Source data verification will include the eCRF data, and drug accountability. In addition, the diary data entered into the eCRF will be cross-checked against any additional documentation in the subjects' source data.

Upon completion of each visit, prompt eCRF completion is expected from each site to ensure quality of data and subject safety. Once eCRFs are completed, they will be available for remote review by the monitor and the designated CRO Clinical Data Management department. Completed eCRFs will be reviewed remotely for logical discrepancies. Missing data will be verified through comparison of eCRF and source data at on-site monitoring visits. If necessary, data queries will be used to make updates to the eCRF. The monitor will ensure that responses to all data queries and subsequent amendments in the eCRF documentation are made according to GCP guidelines.

After termination of the trial, the Investigator will be provided with an electronic copy of the eCRF to be archived together with the trial documents, source data, and laboratory records for the time required by the national regulation.

11.2. Protocol Deviations

A protocol deviation is defined as an instance of failure to follow, intentionally or unintentionally, the requirements of the protocol.

The Investigator has to conduct the study in accordance with the current protocol.

In the event that a protocol deviation occurs, the Investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. In no instance should this increase the subject's risk or affect the validity of the study data.

11.3. Confidentiality of Subject Records

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfil the objectives of the study.

All subject data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. The confidentiality of each record with subject identification is to be guaranteed by the clinical Investigator. This means that the clinical Investigator must respect subject confidentiality concerning all data collected, and that he has to code the data so that the subject identity will be replaced by a unique code (containing no element such as name initials, date of birth, etc.) before any type of data transmission outside the investigational site.

The IC obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study- related monitoring, audit, independent ethics committee (IEC)/IRB review, and regulatory inspection. The IC should also address the transfer of the data to other entities and to other countries.

11.4. Retention of Records

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s) in a secure place as long as needed to comply with national and international regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents. In the event the Investigator retires, relocates, or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records must be transferred to any other person who accepts responsibility for the records, e.g., the Sponsor, an EC, or another Investigator/institution. The sponsor must be notified in writing of the name and address of the new custodian prior to the transfer. Under no circumstance the investigator/institution shall relocate or dispose of any study documents before having obtained written approval from the Sponsor.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

These records must be made available for inspection upon reasonable request by a representative of the Sponsor or regulatory authorities.

11.5. Routine Monitoring

To provide a clear understanding of the trial protocol monitoring and to ensure protocol compliance, a Site Initiation Visit will be performed by a monitor prior to the start of subject enrollment. The aims of the trial, the trial protocol, eCRFs/patient diary, trial treatment supplies, and trial procedures and monitoring requirements will be explained in detail.

The purpose of monitoring is to verify the rights and well-being of human subjects are protected; that trial data are accurate, complete, and verifiable with source data; and that the trial is conducted in compliance with the protocol, GCP, and the applicable regulatory requirements. A monitor assigned by the CRO will conduct regular site visits for the purpose of trial monitoring. The monitoring strategy will be based on the importance of the data and will be performed on site and centrally. Risk based monitoring will be described in the monitoring plan and/or other appropriate documentation according ICH E6(R2) guideline (EMA/CHMP/ICH/135/1995).

The Investigator must agree to allow the trial monitor and authorized representatives of the CRO or the Sponsor to inspect all eCRFs and corresponding source documents (e.g., original medical records, subject records and laboratory raw data); to allow access to the clinical supplies, dispensing, and storage areas; and to agree to assist with their activities, if requested. The Investigator should provide adequate time and space for monitoring visits and visits of other Sponsor representatives.

The monitor will query any missing or spurious data with the Investigator, which should be resolved in a timely manner. A monitoring log will be maintained to record each visit, the reason for the visit, the monitor's signature, and the Investigator or designee's confirmation signature.

11.6. Site Audits

The Sponsor or its designee may carry out a site audit at any time. Investigators will be given adequate notice before the audit occurs. The purpose of an audit is to confirm that the trial is conducted as per protocol, GCP and applicable regulatory requirements, that the rights and well-being of the subjects enrolled have been protected, and that the data relevant for the evaluation of the investigational product have been captured, processed and reported in compliance with the planned arrangements. The Investigator will permit direct access to all trial documents, drug accountability records, medical records, and source data.

Regulatory authorities may perform an inspection of the trial, even up to several years after its completion. If an inspection is announced, the Investigator must inform the Sponsor immediately.

11.7. Database Management and Quality Control

The CRO will be responsible for the activities associated with the data management of this trial, including the production of an eCRF, setting up a relevant database, along with appropriate validation of data and generation of queries. The eCRF will be completed by site using the EDC system. Automated and manual checks will be made against the data entered into eCRF to

ensure completeness and consistency. Resolution of queries will be implemented in the database. The data will be converted into a Clinical Data Interchange Standards Consortium compliant format.

AEs will be standardized for terminology and classification, using the last version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be classified by site of action and therapeutic and clinical characteristics using the World Health Organization Medical Dictionary for Regulatory Activities. Versions of the dictionaries to be used will be documented in the Data Management Plan and the Statistical Analysis Plan (SAP).

11.8. Archiving of Data

The investigator/institution should maintain the trial documents according to the GCP guidelines and as required by the applicable regulatory requirements. The investigator must arrange for the storage of the trial file for the duration of at least 15 years after the completion or discontinuation of the trial or for at least two years after the granting of the last marketing authorization in an ICH region (when there are no pending or contemplated marketing applications) or for at least two years after formal discontinuation of clinical development of the investigational product. Storage of trial file may be prolonged if required by local regulations. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution, or private practice. The investigator should notify the Sponsor if archiving cannot be maintained for the required archiving period.

All data and documents must be made available if requested by relevant authorities.

12. STATISTICAL METHODS

12.1. Statistical populations

Analyses will be based on the Enrolled Set, the Safety Analysis Set, the Intent-to-treat (ITT) Set, the Endometrial Safety Analysis Set, the Per-protocol (PP) Set and the modified Intent-to-treat (mITT) Set. The definitions of the analysis sets, with the exception of the mITT, follow those given in the ICH E9 guideline (CMP/ICH/363/96).

Enrolled Set: All subjects who sign the ICF form the Enrolled Set.

Safety Analysis Set: Randomized subjects who receive at least one dose of randomized study medication form the Safety Set. The Safety Analysis Set will be used for all analyses of safety, tolerability, and background characteristics and all analyses on this set will be based on treatment received.

Endometrial Safety Analysis Set: All randomized subjects who received at least one dose of randomized study medication, had an evaluable biopsy at Baseline and at Month 12 (defined by a Visit window as on or after Day 326) or had a diagnosis of endometrial hyperplasia prior to Month 12.

Intent-to-treat (ITT) Set: The ITT Set consists of all randomized subjects who receive at least one dose of randomized study medication. The ITT Set will be the primary analysis population for the efficacy analyses and all analyses on this set will be based on randomized treatment.

Modified Intent-to-treat (mITT) Set: The mITT Set consists of all randomized subjects in the ITT Set excluding subjects presenting at least one of the following features:
- At least one post baseline E4 concentration level below the lower limit of quantification
- At least one post screening E2 concentration level is superior to 40 pg/mL

Per-protocol (PP) Set: Subjects in the ITT Set who do not have major protocol deviations will form the PP Set. The major protocol deviations will be defined at the time of the evaluability assessment between the database soft lock and hard lock before unblinding. The PP Set will be used for efficacy sensitivity analyses and all analyses on this set will be based on randomized treatment.

12.2. Baseline Values

Unless otherwise noted, baseline is defined as the last non-missing value recorded prior to the first dose of trial drug. Unscheduled visits will be used in the determination of baseline values, when applicable. This also applies to the primary efficacy variables derived from the VMS data collected in the subject diary, but on a weekly basis as described in the definition of the primary efficacy variables.

12.3. Handling of Dropouts or Missing Data

For days with missing VMS diary information, the number and intensity of VMS will be imputed with the mean values of the remaining days of the respective 7-day period, but only if at least 4 days with VMS data in this 7-day period are available. Otherwise, no calculation of the primary and related secondary efficacy variables will be done for this period.

No method of imputation is planned for the primary efficacy variable analysis since an MMRM model is used. As previously stated, sensitivity analyses of the primary efficacy variables may resort to imputation of missing data in order to assess the robustness of the MMRM results.

12.4. Primary Efficacy Variables

The weekly frequency of moderate to severe VMS at baseline, week 4 and week 12, respectively, is defined as the total number (sum) of all recorded moderate to severe VMS experienced during the last 7 consecutive days during the Screening period, days 22 to 28 (week 4) and days 78 to 84 (week 12), respectively.

The mean severity score of VMS is defined as the arithmetic mean of the daily severity score values of VMS (moderate or severe) observed from days -7 to -1 at baseline and the arithmetic mean of the daily severity score values of VMS (mild, moderate or severe) observed during the days 22 to 28 and days 78 to 84 for week 4 and week 12 respectively.

At baseline, the daily severity score is computed as [((2 x number of moderate VMS) + (3 x number of severe VMS))/ (total number of moderate + severe VMS)] if at least one moderate to severe VMS was recorded during the day. In case of documented absence of moderate to severe VMS during the day, the daily severity will be set to zero.

Post-baseline (days 22 to 28 [Week 4] and days 78 to 84 [Week 12]), the daily severity score is computed as [((1 x number of mild VMS) + (2 x number of moderate VMS) + (3 x number of severe VMS))/ (total number of mild + moderate + severe VMS)] if at least one mild to severe VMS was recorded during the day. In case of documented absence of VMS during the day, the daily severity will be set to zero.

The daily severity score as defined above will also be recomputed for post baseline weeks as [((2 x number of moderate VMS) + (3 x number of severe VMS)) / (total number of moderate + severe VMS)] if at least one moderate or severe VMS is recorded during the day.

The primary efficacy variables will be expressed as the changes from baseline computed as the differences between the estimated values at week 4 or 12 and the baseline values.

The analysis including the mild VMS will be used for submission to the FDA, the analysis without the mild VMS will be used for submission to the EMA.

12.5. Analysis of Primary Efficacy Variables

All statistical tests will be supported by presenting estimates and 95% CIs for the respective treatment effects (difference to placebo). These estimates and CIs will be based on the respective statistical models used for the analysis. Since all analyses of the efficacy variables are not exploratory in nature, adjustment for multiplicity will be performed (Dunnet adjustment for the comparison of each active dose versus placebo).
The primary efficacy comparison will test the following hypotheses for each treatment arm:

- H0: The average change from baseline in the primary efficacy endpoint in the treatment arm is greater (less pronounced) or equal to the average change from baseline in the placebo arm
- H1: The average change from baseline in the primary efficacy endpoint in the treatment arm is lower (more pronounced) to the average change from baseline in the placebo arm

The two dose groups of E4 will be compared to placebo regarding the four co-primary endpoints.

A comparison between treatment arms of the change from baseline at week 1 to week 12 in the weekly frequency of moderate to severe VMS and of the change from baseline in the weekly mean severity of moderate to severe VMS will be made by using Mixed-effect Models for Repeated Measures (MMRM). The MMRM models will include treatment, week, treatment by week interaction and pooled trial centers as fixed effects and baseline as a covariate. If the pooled center effect included in the model is significant, a treatment by center interaction will be included in the model. Treatment effects will be assessed at week 4 and 12 using two separate MMRM models (one on weekly frequency and another on weekly mean severity).

The primary analysis will use the data from the ITT population. Since an MMRM model is used, missing data imputation is not necessary. Additional sensitivity analyses will be implemented in order to assess the robustness of the results. These may include sensitivity with respect to:

- An imputation of missing data (last observation carried forward [LOCF] or other)
- The modelling strategy [analysis of covariance (ANCOVA) instead of MMRM]
- Confounders (for example ethnicity, hysterectomized status)
- Populations studied (mITT, PP)
- Any combination of the above

In addition, all primary efficacy variables will be tabulated at baseline and at each post-baseline time point.

12.6. Secondary Efficacy Variables

In addition to all the secondary efficacy endpoints previously described, all the variables described above for the assessment of the primary objectives are also considered as secondary efficacy variables when evaluated at other time points than Week 4 and Week 12.

In addition, three VMS weekly weighted scores, taking into account both the frequency and the severity of VMS, will be computed based on the diary data as:

- [(2 x number of moderate VMS) + (3 x number of severe VMS)] for baseline and post baseline visits if at least one moderate to severe VMS was recorded and zero otherwise.
- [(1 x number of mild VMS) + (2 x number of moderate VMS) + (3 x number of severe VMS) for baseline and post baseline visits if at least one mild to severe VMS was recorded and zero otherwise.
- [(2 x number. of moderate VMS) + (3 x number of severe VMS)] if at least one moderate to severe VMS was recorded for baseline visits and [(1 x number of mild VMS) + (2 x number of moderate VMS) + (3 x number of severe VMS)] for post baseline visits if at least one mild to severe VMS was recorded and zero otherwise.

Furthermore, the severity score will also be recomputed as [((1 x number mild VMS) + (2 x number of moderate VMS) + (3 x number of severe VMS)) / (total number of mild + moderate + severe VMS)] if at least one mild to severe VMS is recorded during the day for baseline and post baseline visits.

In case of documented absence of moderate to severe VMS during the day, the daily severity score will be set to zero. These additional efficacy variables will be derived for every week between baseline and week 12 based on the respective 7-day periods. All VMS related secondary efficacy variables will be expressed as changes from baseline computed as the differences of the estimated values at week 1 to 12 and the baseline values.

The percentage of subjects with a CID in the weekly frequency of moderate to severe VMS at weeks 4 and 12 will be assessed according to Gerlinger et al. (31).

12.7. Analysis of Secondary Efficacy Variables

All VMS related secondary efficacy variables will be analyzed using the same methodology as for the primary efficacy variables and will be based on the data from the ITT population.

All other secondary continuous efficacy variables will be analyzed using either an ANCOVA or an MMRM model depending on the type of endpoint considered. These models will be evaluated using data from the ITT, PP and mITT populations without imputation of data. Appropriate covariates may be included in the analyses.

The other categorical efficacy variables (scores, responder analysis) will be analyzed using appropriate statistical methods for the comparison of each treatment arm to the placebo arm.

In addition, all secondary efficacy variables will be tabulated at baseline and at each post-baseline time point.

12.8. Safety parameters (safety set)

All safety parameters will be summarized using data from the Safety Analysis Set if not indicated otherwise. No formal statistical test will be performed to determine statistical significance between treatment groups. Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, maximum), categorical variables will be presented in frequency tables using counts and percentages. The frequency of endometrial events will be computed on the evaluable biopsies of the endometrium. The incidence of spotting/bleeding will be analyzed by a 28-day period. The incidence rate of endometrial events will be computed on the evaluable endometrium. The 95% two-sided CI will be computed on the observed frequency of hyperplasia/carcinoma of the endometrium.

12.9. Timing of analysis

The final analysis of the primary efficacy objective and the secondary efficacy objectives 1 and 2 of the Efficacy Study part will be triggered when all subjects in the Efficacy Study part have completed Visit 4 and will be conducted by an independent statistician. The analyses of all other efficacy and safety objectives from the Efficacy and Safety Study parts will be triggered when the overall end of the trial is reached (i.e. when all subjects in the Efficacy Study part have completed Visit 8). The efficacy endpoints and the safety endpoints of the Safety Study will be analyzed separately from those of the Efficacy Study at the end of the Safety Study.

A firewall group, composed of Estetra SRL representatives independent of the E4 project will be appointed. This group will have access to the unblinded data of final and interim analyses of the Efficacy Study part. Further details regarding the composition and role of the firewall group

will be provided in a charter. The clinical team, the subjects and the site and sponsor personnel involved in the clinical evaluation of the subjects will remain blinded of the treatment assignment in the Efficacy Study part until the end of the study.

The analyses to be done after completion of Visit 4 will be performed by an independent statistician. Only the overall outcome of the results will be provided to the clinical team. The clinical team, the subjects and the site and sponsor personnel involved in the clinical evaluation of the subjects will remain blinded of the treatment assignment until the end of the study. Blinding for the data at subject and treatment group levels will be kept through a firewall process that will be put in place. No individual listings with the subject numbers' information or tables per treatment group will be disseminated at the time of final or interim triggered analysis of the Efficacy Study part.

No changes in the study conduct will be undertaken regardless of the primary efficacy analysis results. The study will continue until its completion in order to contribute to the safety profile of the study medication.

13. ETHICS

13.1. Independent Ethics Committee/Institutional Review Board

Site initiations will be undertaken only after the IEC/IRB has given full approval of the study including approval for all study related documents according to GCP and applicable local regulatory requirements, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

13.2. Ethical Conduct of the Study

This trial will be conducted in accordance with the Declaration of Helsinki, the ICH Guidelines for GCP and regulatory requirements as applicable. The Investigator agrees that the study will be conducted according to the protocol and these principles. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities. Study documents will be maintained in accordance with applicable regulations. During the pre-trial activities, the investigator and his staff must have confirmed a working knowledge of the regulatory requirements of the clinical trial.

13.3. Compensation, Insurance, and Indemnity

Information regarding compensation, insurance, and indemnity will be provided to the Investigator in the Clinical Trial Agreement. Country-specific insurance will be obtained in accordance with local regulations.

13.4. Subject Information and Consent

The investigator is responsible for ensuring that the subject fully understands the nature and purpose of the trial. Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time without giving any reason. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions.

The ICFs and any subsequent amended ICFs, as well as any other written information provided to the subjects must be submitted for review to the EC/IRB and a favorable opinion must be received in advance of use. The ICF(s) must be signed before performance of any study-related activity. The original signed ICFs will be retained by the investigator and made available (for review only) to the trial monitor and auditor on request. Subjects will be given a signed copy of

the informed consent. Source documentation will also document that IC was obtained prior to study related activity.

The investigator is responsible for ensuring that the subject fully understands the nature and purpose of the trial. In general, information should be given in both oral and written form whenever possible. No subject should be obliged to participate in the trial. Subjects, their relatives, guardians (or if applicable legal representatives) must be given ample opportunity to inquire about the details of the trial. The information must make clear that refusal to participate or withdrawal from the trial at any stage is without any prejudice to any subsequent care. Subjects must be allowed sufficient time to decide whether or not they wish to participate.

The ICFs and any subsequent amended ICFs, as well as any other written information provided to the subjects must be submitted for review to the EC/IRB and a favorable opinion must be received in advance of use. Informed consent will be obtained prior to the conduct of any trial-related procedures. The original signed ICFs will be retained by the investigator and made available (for review only) to the trial monitor and auditor on request. Subjects will be given a signed copy of the informed consent. Source documentation will also document that IC was obtained prior to the subject's participation in the trial.

13.5. Protocol Amendments

Any change of the clinical trial must be written and formally documented as an amendment to this protocol. Such amendments will be made jointly by the Sponsor and the CRO. No change to the protocol will be implemented until the Sponsor, have reviewed and approved the amendment. Amendments will be submitted to the EC/IRB as required by local regulations. If the subject information sheet and ICF are updated as a result of the amendment, the new approved versions will be used to re-consent currently enrolled subjects and must be provided to additional subjects prior to their entry into the trial.

14. CONFIDENTIALITY AND PUBLICATION POLICY

14.1. Confidentiality of Information

This protocol and other study documents contain trade secrets and commercial information that is privileged and confidential. Such information is not to be disclosed unless required by laws or regulations. The Investigator/CRO agrees to use this information only in conducting this study and is not allowed to use it for other purposes without written consent from the Sponsor. Results obtained from this study are the property of the Sponsor.

By signing this clinical trial protocol, the investigator/CRO reaffirms to the Sponsor that he/she will maintain in confidence all information provided to him/her during the present trial or resulting from this trial. The investigator will only divulge such information as may be necessary to the EC, the members of the staff and the subjects who are involved in this trial.

14.2. Reporting

The CRO will perform the statistical analysis and provide the Sponsor and the investigator with a written CSR. Except for compelling legal reasons, neither the Sponsor nor the investigator will communicate to third parties any result of the clinical trial before they have both agreed on the results of the analysis and its interpretation.

The final CSR of this clinical trial will be prepared and released by the Sponsor. A statement will be required of the investigator to confirm that the report accurately describes the conduct and results of the trial. This released final report may also be submitted to relevant health authorities to support a request for registration.

14.3. Publication and Disclosure Policy

The data that will be obtained in this trial will be the property of the Sponsor, who will make reasonable efforts to assure that the results are published in a peer-reviewed journal. As some of the information concerning the investigational product and development activities at the Sponsor may be of strictly confidential nature, any manuscript or other presentation of data must first be reviewed by the Sponsor before its submission.

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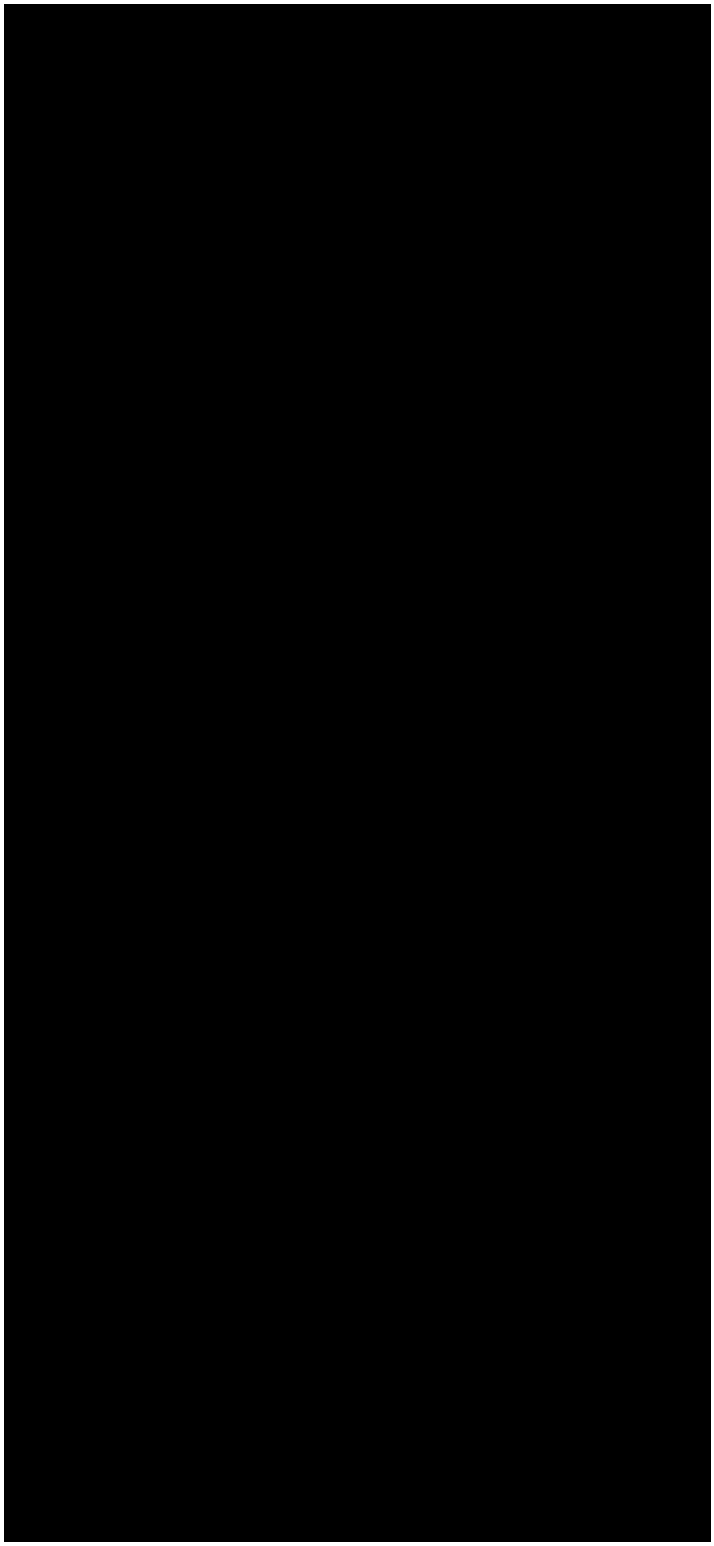
16. APPENDICES

16.1. Menopause Specific Quality of Life (MENQOL) Questionnaire

Modified MENQOL for screening



16.1 Menopause Specific Quality of Life (MENQOL) Questionnaire (continued)

MENQOL for during treatment assessments

[redacted]

16.2. Modified Clinical Global Impression

The Modified CGI to be used in this study is presented below

16.3. Histologic Descriptions Recommended for use when Reading Endometrial Biopsy Slides

Histologic Characteristics of the Endometrium

0. No tissue
1. Tissue insufficient for diagnosis
2. Atrophic
3. Inactive
4. Proliferative
   a. Weakly proliferative
   b. Active proliferative
   c. Disordered proliferative
5. Secretory
   a. Cyclic type
   b. Progestational type (including stromal decidualization)
6. Menstrual type
7. Simple hyperplasia without atypia
8. Simple hyperplasia with atypia
9. Complex hyperplasia without atypia
10. Complex hyperplasia with atypia
11. Carcinoma (specify type)

16.4. Histologic Descriptions Recommended for use when Reading Endometrial Biopsy Slides (Continued)

Additional Histologic Characteristics

If there are any polyps, please specify the type or types.

- Functional
- Atrophic
- Hyperplastic without atypia
- Hyperplastic with atypia
- Carcinomatous

If there is any stromal tissue, please specify the type or types.

- Smooth muscle tissue, normal
- Features suggestive of adenomyoma
- Features suggestive of stromal nodule
- Sarcoma (specify type)

If there is any metaplasia, please specify the type or types.

- Squamous
- Papillary
- Eosinophilic
- Ciliated
- Mucinous
- Syncytial
- Other type (specify type)

If there is any cervical tissue, please specify the type or types.

- Fragments of negative cervical epithelium
- Endocervical polyp
- Atypical endocervical glandular epithelium
- Atypical squamous metaplasia
- Squamous dysplasia
- Cervical carcinoma

16.5. Country Specific Requirements

16.5.1. Requirements for Canada

This appendix includes specific changes to the study protocol as required by Health Canada ([redacted]). These changes are to be implemented and taken into account in Canadian sites conducting the MIT-Do001-C302 study (E4Comfort Study II).

Concerning the STUDY POPULATION

In Canadian sites, only Hysterectomized women will be eligible to participate in both parts of the study, Efficacy and Safety study parts.

Concerning Section 6.1.3 on Exploratory Analyses of the Efficacy Study Part, second exploratory analysis

Subjects from Canadian sites will not participate in the second exploratory analysis of the Efficacy Study part intending *to evaluate the influence of E4 on the changes in the hemostasis parameters compared to placebo in women with inherited thrombophilia and women without this genetic disorder.*

Therefore, the following parameter of the efficacy endpoint for exploratory objective #2 will not be assessed in subjects from Canadian sites:

- *Change in hemostasis parameters in women with and without inherited thrombophilia (Factor V Leiden mutation and prothrombin G20210A mutations).*

The DNA sample taken at Visit 1, as mentioned in Section 10.3.4, will therefore not be collected.

Local ICF will reflect this change to the study protocol.

16.6. Protocol Amendment – Summary of changes

Modified sections in Protocol: MIT-Do001-C302 Amendment 7

This section summarizes the changes that have been performed between Protocol Version 7.1, date July 30, 2021, and Protocol Version 8, date June 21, 2022.

***Note*: wherever applicable, deleted text has been crossed out and added text has been printed in bold and italic characters.**

Minor changes involving grammar, wordsmithing, punctuation, and other editorial changes have been made throughout the document. All are clearly identified in the track-changes version of the amendment but are not shown in the Summary of changes.

[[Updates in Section "1. ADMINISTRATIVE INFORMATION" are also absent from the Summary of changes but are clearly identified in the track-changes version of the amendment.]]

2. STUDY SYNOPSIS

Study Design: […] Figure 1: Trial Schedule […] * […] If the biopsy shows ***disordered proliferative endometrium,*** hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. […]
Other trial medication (dose, and mode of administration): For non-hysterectomized subjects only: • P4, 200 mg, oral, once daily for 14 consecutive days (after completion or discontinuation of E4/placebo treatment) • Ad hoc treatment with a progestin according to local practice/guidelines if endometrial biopsy shows ***disordered proliferative endometrium,*** hyperplasia or worse
Endometrial Safety Assessment and Stopping Rules (non-hysterectomized subjects only): […] If the biopsy shows ***disordered proliferative endometrium,*** hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. At approximately 10-14 days after completion of the progestin treatment, a new TVUS will be performed to measure endometrial thickness and a biopsy will be carried out***, if deemed necessary by the Investigator,*** to demonstrate the resolution. If the endometrial event is not resolved, the subject will be further treated according to local practice/guidelines and she will be followed up until resolution. ~~In case of an AESI of DPE, the subject will be followed up in the trial with regular TVUS according to the Protocol. If a DPE persists at the end-of-study biopsy, treatment with P4 200 mg for 14 days will be given according to the Protocol and resolution should be documented by an endometrial biopsy repeated 10-14 days after treatment with P4. TVUS is to be performed before biopsy to measure endometrial thickness.~~ […]
Inclusion Criteria: […] 5. For non-hysterectomized subjects: Endometrial biopsy taken during screening that reveals no abnormal results, i.e., presence of hyperplasia (simple or complex, with or without atypia)***,*** ~~and~~ presence of carcinoma***, and presence of disordered proliferative endometrium findings***. The screening biopsy should have sufficient endometrial tissue for diagnosis. Biopsies without tissue or with insufficient tissue may be repeated once; […]
Exclusion Criteria: […] 4. For non-hysterectomized subjects: a) History or presence of uterine cancer ~~or~~***,*** endometrial hyperplasia***, or disordered proliferative***

endometrium; […]
Synopsis Final Version ~~7.1, July 30, 2021~~*8.0, June 21, 2022*

[…]

5.4. Risk-benefit Assessment

[…] An endometrial biopsy is part of the screening procedures in non-hysterectomized women and any findings indicating polyps, ***disordered proliferative endometrium,*** endometrial hyperplasia or cancer will result in exclusion from enrollment. […] If the biopsy shows ***disordered proliferative endometrium,*** hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study.

[…]

7. CLINICAL TRIAL PLAN

7.1. Clinical Trial Design and Justification

7.1.1. Trial Design

[…]

Figure 1: Trial Schedule

[…]

* […] If the biopsy shows ***disordered proliferative endometrium,*** hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. […]

[…]

8.2. Inclusion and Exclusion Criteria

8.2.1. Criteria for Inclusion

[…]

5. For non-hysterectomized subjects: endometrial biopsy taken during screening that reveals no abnormal result, i.e., presence of hyperplasia (simple or complex, with or without atypia)***,*** ~~and~~ presence of carcinoma***, and presence of disordered proliferative endometrium findings***. The screening biopsy should have sufficient endometrial tissue for diagnosis. Biopsies without tissue or with insufficient tissue may be repeated once;

[…]

8.2.2. Criteria for Exclusion

[…]

4. For non-hysterectomized subjects:

a. History or presence of uterine cancer~~ or~~***,*** endometrial hyperplasia***, or disordered proliferative endometrium***;

[…]

8.3. Subject Discontinuation and Replacement Procedures

[…]

- Endometrium biopsy showing ***a disordered proliferative pattern,*** hyperplasia or worse, requiring treatment with a progestin
- […]

10.4. Safety Assessments

[…]

10.4.1. Treatment Emergent Adverse Events

[…] Subjects with ***disordered proliferative endometrium,*** hyperplasia or worse will be followed up until resolution.

Resolution of ***DPE and*** hyperplasia should be documented by ***TVUS with endometrial thickness ≤ 4 mm or*** an endometrial biopsy***, if deemed necessary by the Investigator,*** repeated ***no earlier than*** 10-14 days after oral treatment with P4 200 mg/day for 14 days given after discontinuation of the subject.

~~In case of an AESI of DPE, the subject will be followed up in the trial with regular TVUS according to the Protocol. If a DPE persists at the end of study biopsy, treatment with P4 200 mg for 14 days will be given according to the Protocol and resolution should be documented by an endometrial biopsy repeated 10-14 days after treatment with P4.~~

[…]

10.4.8. Endometrial Biopsy in Non-hysterectomized Subjects

[…]

The investigator will be informed if subsequent readings impact the initial decision. A reading of ***disordered proliferative endometrium,*** hyperplasia (simple or complex, with or without atypia) or carcinoma from any of the pathologists ***providing the safety readings*** will prompt the exclusion or discontinuation of the subject from the study.

[…]

Procedure in case of ***disordered proliferative endometrium,*** hyperplasia or worse

If a biopsy shows ***disordered proliferative endometrium,*** hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. […]

10.4.10. Endometrial Safety Assessment and Stopping Rules

[…] If the biopsy shows ***disordered proliferative endometrium,*** hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. At approximately 10-14 days after completion of the progestin treatment, a new TVUS will be performed to measure endometrial thickness and a biopsy will be carried out ***if deemed necessary by the Investigator*** to demonstrate the resolution. If the endometrial event has not resolved, treatment will be started according to local practice/guidelines. The pathologic diagnoses of DPE, hyperplasia and worse will be reported as ~~an~~ AESI and the subject will be followed up until the resolution of the event. Resolution of ***disordered proliferative endometrium and*** hyperplasia should be documented by ***TVUS with***

endometrial thickness ≤4 mm or an endometrial biopsy repeated ***no earlier than*** 10-14 days after oral treatment with P4 200 mg/day for 14 days given after discontinuation of the subject.

~~In case of an AESI of DPE, the subject will be followed up in the trial with regular TVUS according to the Protocol. If a DPE persists at the end of study biopsy, treatment with P4 200 mg for 14 days will be given according to the Protocol and resolution should be documented by an endometrial biopsy repeated 10-14 days after treatment with P4. TVUS is to be performed before biopsy to measure endometrial thickness.~~ […]

10.5. Data Safety Monitoring Board

[…] During the conduct of the study, the safety data of the study will be collected on an ongoing basis and provided to the DSMB. The DSMB will monitor the general safety and the endometrial safety of the trial at an appropriate frequency as provided in the DSMB charter and will make recommendations to the Sponsor regarding steps to ensure the safety of the trial subjects. ***The DSMB will be supported by a Clinical Event Committee who will adjudicate cardiovascular and thrombotic events in a consistent and unbiased manner throughout the course of the study.***

[…]

Modified sections in Protocol: MIT-Do001-C302 Amendment 6.1

This section summarizes the changes that have been performed between Protocol Version 6.0, date September 23, 2020, and Protocol Version 7.1, date July 30, 2021.

***Note*: wherever applicable, deleted text has been crossed out and added text has been printed in bold and italic characters.**

Minor changes involving grammar, wordsmithing, punctuation, and other editorial changes have been made throughout the document. All are clearly identified in the track-changes version of the amendment but are not shown in the Summary of changes.

Updates in Section "1. ADMINISTRATIVE INFORMATION" are also absent from the Summary of changes but are clearly identified in the track-changes version of the amendment.

2. STUDY SYNOPSIS

Study Design:

[…]

Figure 1: Trial Schedule

[…]

* [...] If the biopsy shows ~~disordered proliferative endometrium,~~ hyperplasia or worse, ***the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. If the endometrial event has not resolved,*** treatment with a progestin will be started according to local practice/guidelines ~~and the subject will be withdrawn from the study~~.

Other Trial Medication (dose, and mode of administration):

For non-hysterectomized subjects only:

- P4, 200 mg, oral, once daily for 14 consecutive days (after completion ***or discontinuation*** of E4/placebo treatment)

Ad hoc treatment with a progestin according to local practice/guidelines if endometrial biopsy shows ~~disordered proliferative endometrium,~~ hyperplasia or worse

Conduct of the Trial:

[…]

Washout and screening procedures for the Efficacy Study part and Safety Study part

[…]

The length of the Screening period is generally up to 4 weeks, but can be extended (with prior Medical Monitor approval) without exceeding ~~6~~***8*** weeks.

[…]

Endometrial Safety Assessment and Stopping Rules (non-hysterectomized subjects only):
[…]

If the biopsy shows ~~disordered proliferative endometrium,~~ hyperplasia or worse, ***the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days*** ~~treatment with a progestin will be started according to local practice/guidelines and the subject will be withdrawn from the study~~. At approximately 10***-14*** days after completion of the progestin treatment, a new TVUS will be performed to measure endometrial thickness ***and a biopsy will be carried out to demonstrate the resolution***. ~~In case of disordered proliferative endometrium, hyperplasia or worse~~***If the endometrial event is not resolved,*** the subject will be ***further*** treated according to local practice/guideline***s*** and she will be followed up until resolution. ***In case of an AESI of DPE, the subject will be followed up in the trial with regular TVUS according to the Protocol. If a DPE persists at the end-of-study biopsy, treatment with P4 200 mg for 14 days will be given according to the Protocol and resolution should be documented by an endometrial biopsy repeated 10-14 days after treatment with P4. TVUS is to be performed before biopsy to measure endometrial thickness.***
[…]

Objectives and Endpoints of the Efficacy Study part (Arms 1-3):
[…]

Secondary Objectives and Endpoints:

1. To measure the effect of treatment with E4 15 mg or E4 20 mg compared to placebo on the frequency and severity of ***mild,*** moderate ~~to~~***and*** severe VMS in postmenopausal women weekly up to 12 weeks
   Efficacy endpoints for secondary objective #1
   1.1. […]
   1.2. […]
   1.3. Percentage of subjects with 50% and 75% reduction from baseline in the weekly frequency of moderate to severe VMS at weeks ***1, 2, 3,*** 4***, 5, 6, 7, 8, 9, 10, 11*** and 12
   1.4. Percentage of subjects with 50% and 75% reduction from baseline in the weekly frequency of mild, moderate and severe VMS at weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12

[…]

3. […]
   3.1. Change from baseline to week 12 and week 52 in prothrombin fragment 1 + 2, endogenous thrombin potential (ETP)-based activated Protein C sensitivity ratio (APCsr ETP) ~~(in a subset of subjects in selected study centers)~~, […]
   w)
7. To evaluate the effect of treatment with E4 15 mg or E4 20 mg on vaginal bleeding in non-hysterectomized subjects compared to placebo

   Safety endpoints for secondary objective #7
   7.1. […]
   7.2. ***Number of days with bleeding and/or spotting during each 28-day cycle of treatment based on recording in the patient diary***
   7.3. ~~7.2~~ […]
   7.4. ***Cumulative rates of amenorrhea defined as the percentage of women who reported consecutive cycles of amenorrhea for a given cycle of time***

Objectives and Endpoints of the Safety Study part (Arm 4):
[…]

Secondary Objectives and Endpoints:
[…]

4. To evaluate the effect of treatment with E4 20 mg on vaginal bleeding in non-hysterectomized subjects

   Safety endpoints for secondary objective #4

4.1. […]
4.2. ***Number of days with bleeding and/or spotting during each 28-day cycle of treatment based on recording in the patient diary***
4.3. ~~4.2.~~ […]
4.4. ***Cumulative rates of amenorrhea defined as the percentage of women who reported consecutive cycles of amenorrhea for a given cycle of time***

Inclusion Criteria:
[…]

5. For non-hysterectomized subjects: Endometrial biopsy taken during screening that reveals no abnormal results, i.e., presence of hyperplasia (simple or complex, with or without atypia), ***and*** presence of carcinoma~~, and presence of disordered proliferative findings~~. The screening biopsy should have sufficient endometrial tissue for diagnosis. […]

Exclusion Criteria:
[…]

3. PAP test with atypical squamous cells undetermined significance (ASC-US) or higher (low-grade squamous intraepithelial lesion [LSIL], atypical squamous cells- cannot exclude high-grade squamous intraepithelial lesion [HSIL] [ASC-H], HSIL dysplastic or malignant cells) in sub-totally hysterectomized and non-hysterectomized subjects[1]. Note: ASC-US is allowed if a reflex human papilloma virus (HPV) testing is performed and is negative for high risk oncogene HPV ***subtypes 16 and 18***;
x)
4. For non-hysterectomized subjects:
f) History or presence of uterine cancer~~,~~ ***or*** endometrial hyperplasia~~, disordered proliferative findings~~;

[…]

23. Inadequately treated hyperthyroidism with abnormal TSH and free T4 at screening. Subjects with low ***or high*** TSH are allowed if free T4 at screening is within normal range[10];

[…]

Statistical populations:
Analyses will be based on the Enrolled Set, the Safety Analysis Set, the Intent-to-treat (ITT) Set, ***the Endometrial Safety Analysis Set***, the Per-protocol (PP) Set and the modified Intent-to-treat (mITT) Set.
[…]

Statistical Methods:
[…]
Safety parameters (safety set):
[…] The 95% two-sided CI will be computed on the observed frequency of hyperplasia/carcinoma of the endometrium ~~in order to show that the frequency is not superior to 2% (upper bound lower than the 2% threshold)~~.

Timing of analysis
The final analysis of the primary efficacy objective ***and the secondary efficacy objectives 1 and 2*** of the Efficacy Study part will be triggered when all subjects in the Efficacy Study part have completed Visit 4. ~~An interim analysis of the safety objectives of the Efficacy Study part will be triggered at the same time (i.e. when all subjects in the Efficacy Study part have completed Visit 4).~~ […]

2.1 Schedule of Trial Procedures Efficacy Study Part

[…]
y) In the event screening requirements cannot be met within 4 weeks, the screening period may be extended with prior Medical Monitor approval, but screening period may not exceed ***8***6 weeks.
[…]

2.2 Schedule of Trial Procedures Safety Study part

[…]
u) In the event screening requirements cannot be met within 4 weeks, the screening period may be extended with prior Medical Monitor approval, but screening period may not exceed ***8*** weeks.

5.4. Risk-benefit Assessment

[…]

To monitor the effect of E4 on the endometrium, transvaginal ultrasounds (TVUS) will be performed at multiple time points during E4 treatment to measure the endometrial thickness and subjects will record daily the vaginal bleeding pattern. If, after the first 4 weeks of treatment, a non-hysterectomized subject presents with a bi-layer endometrial thickness > 10 mm as assessed by TVUS or presents with persistent and/or recurrent bleeding, confirmed by the investigator, an endometrial biopsy will be performed. ~~In case of disordered proliferative endometrium,~~ ***If the biopsy shows*** hyperplasia or worse, ***the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. If the endometrial event has not resolved,*** treatment with a progestin will be started according to local practice/guidelines ~~and study drug will be discontinued~~. Subjects will be followed up until resolution.

[…]

6. OBJECTIVES AND ENDPOINTS

[…]

6.1.2 Secondary Objectives and Endpoints:

1. To measure the effect of treatment with E4 15 mg or E4 20 mg compared to placebo on the frequency and severity of ***mild,*** moderate ***and*** ~~to~~ severe VMS in postmenopausal women weekly up to 12 weeks

   Efficacy endpoints for secondary objective #1

   1.1. […]
   1.2. […]
   1.3. Percentage of subjects with 50% and 75% reduction from baseline in the weekly frequency of moderate to severe VMS at weeks ***1, 2, 3,*** 4***, 5, 6, 7, 8, 9, 10, 11*** and 12
   1.4. Percentage of subjects with 50% and 75% reduction from baseline in the weekly frequency of mild, moderate and severe VMS at weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12

[…]

3. […]

   3.1. Change from baseline to week 12 and week 52 in prothrombin fragment 1 + 2, endogenous thrombin potential (ETP)-based activated Protein C sensitivity ratio (APCsr ETP) ~~(in a subset of subjects in selected study centers)~~, […]

7. To evaluate the effect of treatment with E4 15 mg or E4 20 mg on vaginal bleeding in non-hysterectomized subjects compared to placebo

   Safety endpoints for secondary objective #7

   7.1. […]
   7.2. Number of days with bleeding and/or spotting during each 28-day cycle of treatment based on data in the patient diary
   7.3. ~~7.2~~ […]
   7.4. Cumulative rates of amenorrhea defined as the percentage of women who reported consecutive cycles of amenorrhea for a given cycle of time

[…]

6.2 Objectives and Endpoints of the Safety Study Part (Arm 4)

[…]

Secondary Objectives and Endpoints:

[…]

2. To evaluate the effect of treatment with E4 20 mg on vaginal bleeding in non-hysterectomized subjects

   Safety endpoints for secondary objective #4

   4.1 Frequency of women with vaginal bleeding and/or spotting during each 28-day cycle of treatment with E4 based on data in the patient diary
   4.2 ***Number of days with bleeding and/or spotting during each 28-day cycle of treatment based on data in the patient diary***
   4.3 Frequency of women with amenorrhea (absence of any bleeding or spotting) during each 28-day cycle of treatment with E4 based on data in the patient diary
   4.4 Cumulative rates of amenorrhea defined as the percentage of women who reported consecutive cycles of amenorrhea for a given cycle of time

[…]

7. CLINICAL TRIAL PLAN

7.1 Clinical Trial Design and Justification

7.1.1 Trial Design

[…]

Figure 2: Trial Schedule

[…]

* […] If the biopsy shows ~~disordered proliferative endometrium~~***hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. If the endometrial event has not resolved***, treatment with a progestin will be started according to local practice/guidelines ~~and the subject will be withdrawn from the study~~. […]

[…]

Washout screening procedures for the Efficacy Study part and Safety Study part
[…]

The length of the Screening period is generally up to 4 weeks, but can be extended (with prior Medical Monitor approval) without exceeding ~~6~~***8*** weeks. […]

7.4.1 Blinding after analysis of data up to Visit 4 in the Efficacy Study part

The final analysis of the primary ***and secondary*** efficacy ~~objective of the Efficacy Study part and the interim analysis of the safety endpoints~~***objectives 1 and 2*** of the Efficacy Study part are to be triggered when all subjects in the Efficacy Study part have completed Visit 4 and will be conducted by an independent statistician. […]

8. SUBJECT SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

[…]

8.2. Inclusion and Exclusion Criteria

8.2.1. Criteria for Inclusion

[…]

5. For non-hysterectomized subjects: endometrial biopsy taken during screening that reveals no abnormal result, i.e., presence of hyperplasia (simple or complex, with or without atypia)~~,~~ ***and*** presence of carcinoma~~, and presence of disordered proliferative findings~~. […]

8.2.2. Criteria for Exclusion

[…]

3. PAP test with atypical squamous cells undetermined significance (ASC-US) or higher (low-grade squamous intraepithelial lesion [LSIL], atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion [HSIL] [ASC-H], HSIL dysplastic or malignant cells) in sub-totally hysterectomized and non-hysterectomized subjects[1]. Note: ASC-US is allowed if a reflex human papilloma virus (HPV) testing is performed and is negative for high risk oncogene HPV ***subtypes 16 and 18***;
4. For non-hysterectomized subjects:
   a) History or presence of uterine cancer~~, or~~ ***or*** endometrial hyperplasia~~, disordered proliferative findings~~;

[…]

23. Inadequately treated hyperthyroidism with abnormal TSH and free T4 at screening. Subjects with low ***or high*** TSH are allowed if free T4 at screening is within normal range[21];

[…]

8.3. Subject Discontinuation and Replacement Procedures

[…] Possible reasons for a subject discontinuing participation in the trial are (non-exhaustive list):

- […]
- […]
- Endometrium biopsy showing ~~disordered proliferative pattern,~~ hyperplasia or worse, requiring treatment with a progestin

[…]

Wherever possible, subjects who discontinue should be seen and assessed by the investigator. Subjects should complete the early termination visit (Visit 7 Efficacy Study part /Visit 6 Safety Study part). Non-hysterectomized subjects who discontinue early, should also receive treatment with 200 mg P4 for 14 days and return to the clinic for the additional endometrial safety visit (Visit 8 Efficacy study part). ***If the endometrial event has not resolved by then, treatment with a progestin will be started according to local practice/guidelines.*** […]

9.2. Timing of Administration

[…]

If study treatment is interrupted for 4 days and more per week, the Investigator will need approval from the Medical Monitor to restart the patient on study treatment if the subject has not received P4 200 mg (or other progestins).

[…]

9.6.2. Concomitant Medication/Therapy

[…]

Thyroid treatment

Thyroid treatments are allowed as long as the subject has normal TSH levels or low ***or high*** TSH levels with normal free T4 at screening.

[…]

9.6.3 COVID-19 vaccination

Subjects cannot be excluded from the trial based on vaccination status for COVID-19 consistent with restriction for other vaccinations, which may happen in the subjects (influenza, tetanus and other).

Subjects can be vaccinated with a regulatory approved COVID-19 vaccine according to national guidelines but should not participate in a COVID-19 clinical trial.

Recommendation on the timing of the COVID-19 vaccination in relation to study assessments, due to possible acute reaction on vaccination:

- ***The vaccination should be performed preferably after regular visits with the planned blood collections.***
- ***Otherwise minimum one week before regular visits with blood samples collections.***

Rationale for timing restriction: the acute reaction on vaccination may cause transitory changes in biochemistry (liver enzymes, LDH etc.), it is not a common reaction but may happen. The possible transitory increase in temperature may cause changes in absorption of study drug, PK fluctuations etc.

In case of any acute condition, the scheduled visit should be postponed (if no safety issues) until the status of the subject improves.

The vaccination during the trial should be reported as concomitant medication. Any AE that occurs after vaccination should be properly reported.

10.1. Experimental Flow

[…]

Table 4 Visit Schedule and Washout of prior medication

[…]

[1] The week numbers for the Washout visit and Screening period may deviate. The washout visit is generally up to 8 weeks prior to the screening visit. The Screening period is up to 4 weeks, but may be extended to a maximum of ~~6~~ ***8*** weeks.

[…]

10.1.3. Screening Visit (Within 4 weeks before Randomization/Treatment Allocation)

[…]

In the event screening requirements cannot be met within 4 weeks, the screening period may be extended with prior Medical Monitor approval, but screening period may not exceed ~~6~~ ***8*** weeks.

[…]

10.3.3. Laboratory Assessments for Efficacy

[…]

The following samples for hemostasis and bone markers are to be collected at Visit 1 (Baseline) Visit 4 and Visit 7 (EoT) for subject in the Efficacy Study part:

- Hemostasis parameters: prothrombin fragment 1 + 2, ETP-based activated Protein C sensitivity ratio (APCsr ETP) ~~(in a subset of subjects in selected study centers)~~, […]

10.4.1. Treatment Emergent Adverse Events

[…]

Handling of AEs

[…]

Subjects with ~~disordered proliferative endometrium,~~ hyperplasia or worse will be followed up until resolution.

Resolution of hyperplasia should be documented by an endometrial biopsy repeated 10-14 days after oral treatment with P4 200 mg/day for 14 days given after discontinuation of the subject.

In case of an AESI of DPE, the subject will be followed up in the trial with regular TVUS according to the Protocol. If a DPE persists at the end-of-study biopsy, treatment with P4 200 mg for 14 days will be given according to the Protocol and resolution should be documented by an endometrial biopsy repeated 10-14 days after treatment with P4.

10.4.5. Routine Clinical Laboratory Tests

[…]

Samples will be processed in the central laboratory for analysis of the following parameters:
[…]

- Chemistry: urea, creatinine, total bilirubin, alkaline phosphatase, ALT, AST, sodium, potassium, chloride, bicarbonate, calcium, albumin, total protein, lactate dehydrogenase ~~1~~ (LDH~~1~~), LDH~~2~~ ***isoenzymes (I, II, III, IV, V)***, troponin, and blood glucose

[…]

10.4.8 Endometrial biopsy in Non-hysterectomized subjects

[…]

Evaluation of endometrial tissue

The endometrial tissue obtained by endometrial biopsy during screening, during the conduct of the study, and at the end-of-study will be processed in the same manner by a central laboratory ~~and will be evaluated by three independent expert pathologists from different institutions, blinded to treatment group and to each other's readings~~.

Biopsies obtained during screening and during the conduct of the study***, including end-of-study biopsies,*** will be initially read by one ***safety*** ~~expert~~ pathologist ***for safety diagnosis only***. The Investigator will decide inclusion or discontinuation of the subject from the study based on the initial reading. ***Screening biopsies will also be read by two other expert pathologists.*** Biopsy samples ***collected during the conduct of study and at the end-of-study*** will ~~then~~ be read by ~~the two other~~ ***three expert*** pathologists ***for the final (consensus) diagnosis. These three expert pathologists are independent and belong to different institutions. They are blinded to treatment and to each other's readings.***

~~and t~~***T***he investigator will be informed if subsequent readings impact the initial decision. A reading of ~~disordered proliferative endometrium,~~ hyperplasia ***(simple or complex, with or without atypia)*** or carcinoma from any of the ~~three~~ pathologists will prompt the exclusion or discontinuation of the subject from the study.

The concurrence of two of the three pathologists ***who read the biopsy samples for final (consensus) diagnosis*** will be accepted as the Final Diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis, i.e, ***carcinoma*** > atypical ***complex*** hyperplasia > ***atypical simple hyperplasia*** > complex hyperplasia > simple hyperplasia >

benign endometrium, will be used as the final diagnosis. The Final Diagnosis will be used for the analysis of the endometrial safety objective.

[…]

Procedure ~~in case of disordered proliferative endometrium or~~ in case of hyperplasia or worse
If a biopsy shows ~~disordered proliferative endometrium,~~ hyperplasia or worse, ***the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. If the endometrial event has not resolved,*** treatment ***with a progestin*** will be started according to local practice/guidelines ~~and the subject will be withdrawn from the study~~. […]

10.4.10. Endometrial Safety Assessment and Stopping Rules

[…] If the biopsy shows ~~disordered proliferative endometrium~~***hyperplasia or worse, the study drug will be discontinued, and the subject will be withdrawn from the study. The subject will be treated with P4 200 mg once daily for 14 days. At approximately 10-14 days after completion of the progestin treatment, a new TVUS will be performed to measure endometrial thickness and a biopsy will be carried out to demonstrate the resolution. If the endometrial event has not resolved***, treatment will be started according to local practice/guidelines ~~and the subject will be withdrawn from the study~~. The pathologic ~~diagnosis prompting discontinuation~~ ***diagnoses of DPE, hyperplasia and worse*** will be reported as ***an*** AESI and the subject will be followed up until the resolution of the event. ***Resolution of hyperplasia should be documented by an endometrial biopsy repeated 10-14 days after oral treatment with P4 200 mg/day for 14 days given after discontinuation of the subject.***
In case of an AESI of DPE, the subject will be followed up in the trial with regular TVUS according to the Protocol. If a DPE persists at the end-of-study biopsy, treatment with P4 200 mg for 14 days will be given according to the Protocol and resolution should be documented by an endometrial biopsy repeated 10-14 days after treatment with P4. TVUS is to be performed before biopsy to measure endometrial thickness.

[…]

10.6. Adverse Events of Special Interest

[…]

The standard time period for collecting and recording of AESIs will begin at the first intake of study drug/placebo and will end at EoT visit. AESIs will be reported to the Sponsor within the same timeframes described for SAEs. ***AESI collection should start as of the Ministry of Health and/or IRB/EC approval date of Protocol Version 6.0 (Amendment 5). There is no need for retrospective reporting.***

[…]

12.1. Statistical populations

Analyses will be based on the Enrolled Set, the Safety Analysis Set, the Intent-to-treat (ITT) Set, ***the Endometrial Safety Analysis Set***, the Per-protocol (PP) Set and the modified Intent-to-treat (mITT) Set.

[…]

Endometrial Safety Analysis Set: All randomized subjects who received at least one dose of randomized study medication, had an evaluable biopsy at Baseline and at Month 12 (defined by a Visit window as on or after Day 326) or had a diagnosis of endometrial hyperplasia prior to Month 12.
[…]

12.8. Safety parameters (safety set)

[…] The 95% two-sided CI will be computed on the observed frequency of hyperplasia/carcinoma of the endometrium ~~in order to show that the frequency is not superior to 2% (upper bound lower than the 2% threshold)~~.

12.9. Timing of analysis

The final analysis of the primary efficacy objective ***and the secondary efficacy objectives 1 and 2*** of the Efficacy Study part ~~and the interim analysis of the safety endpoints of the Efficacy Study part are to~~***will*** be triggered when all subjects in the Efficacy Study part have completed Visit 4 and will be conducted by an independent statistician. ***The analyses of all other efficacy and safety objectives from the Efficacy and Safety Study parts will be triggered when the overall end of the trial is reached (i.e. when all subjects in the Efficacy Study part have completed Visit 8). The efficacy endpoints and the safety endpoints of the Safety Study will be analyzed separately from those of the Efficacy Study at the end of the Safety Study.***

[…]