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Title: A Phase 3, Multicenter, Open-Label, Single Arm Study of MR-100A-01 in Women of Childbearing Potential to Evaluate Contraceptive Efficacy and Safety

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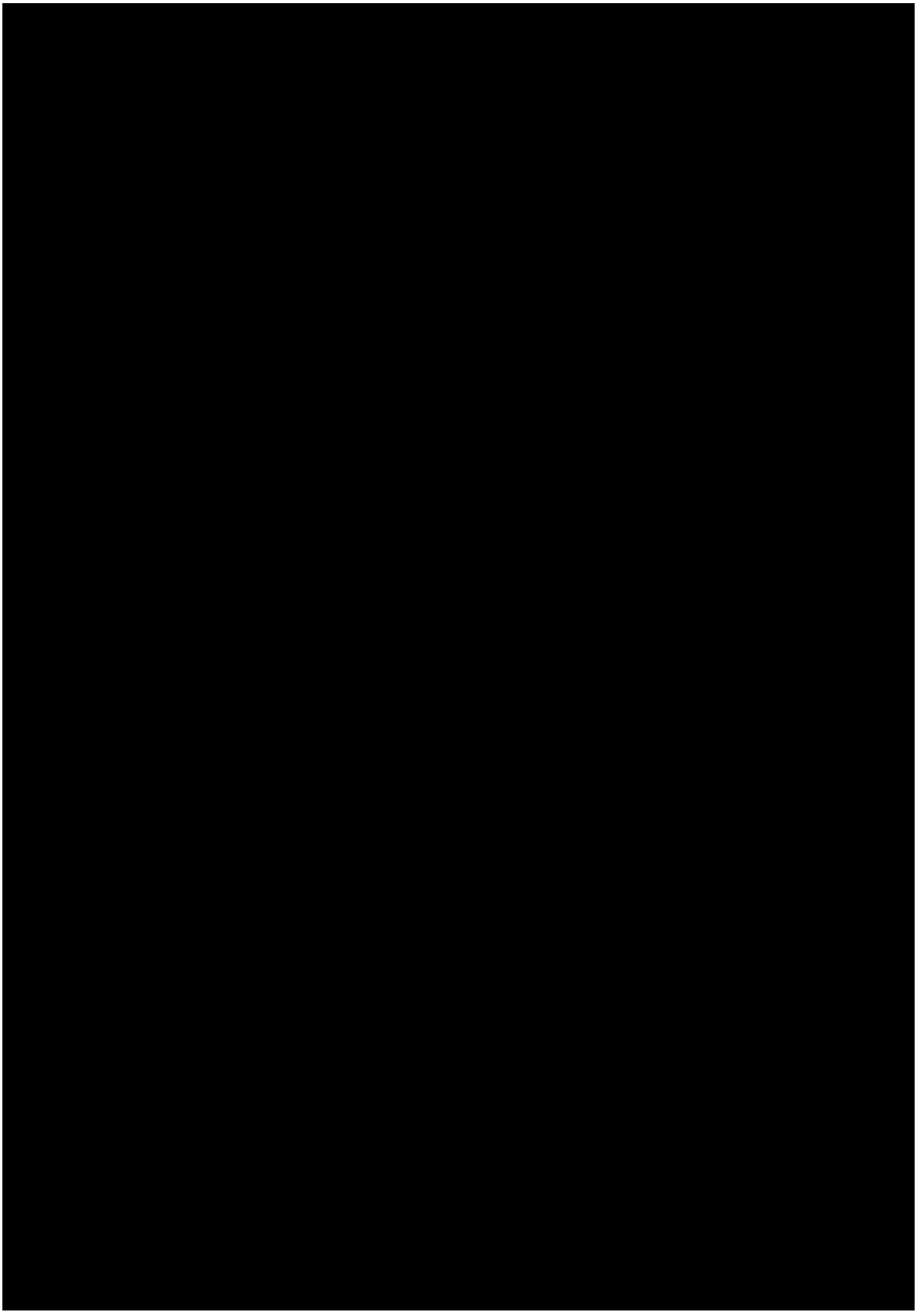
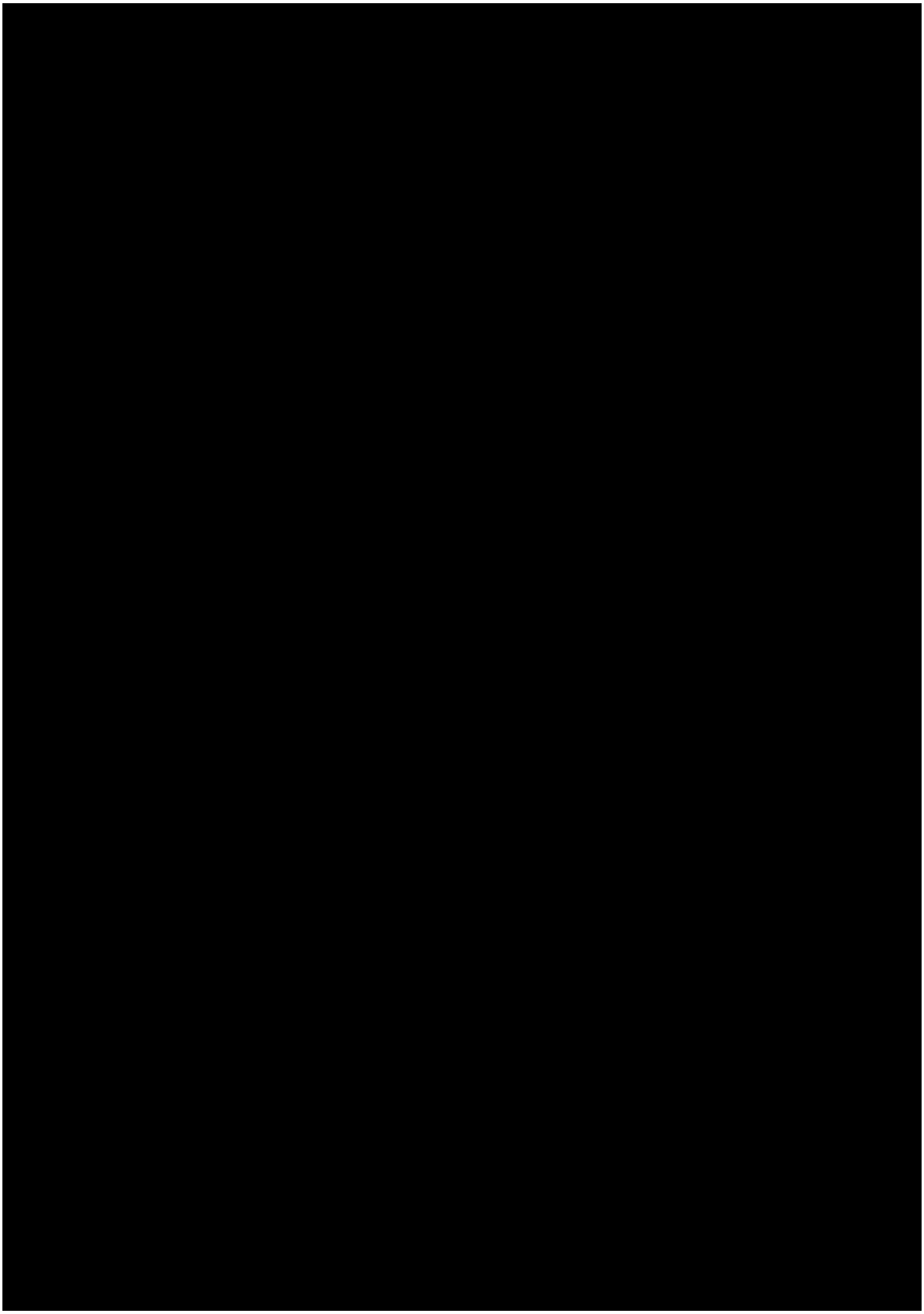
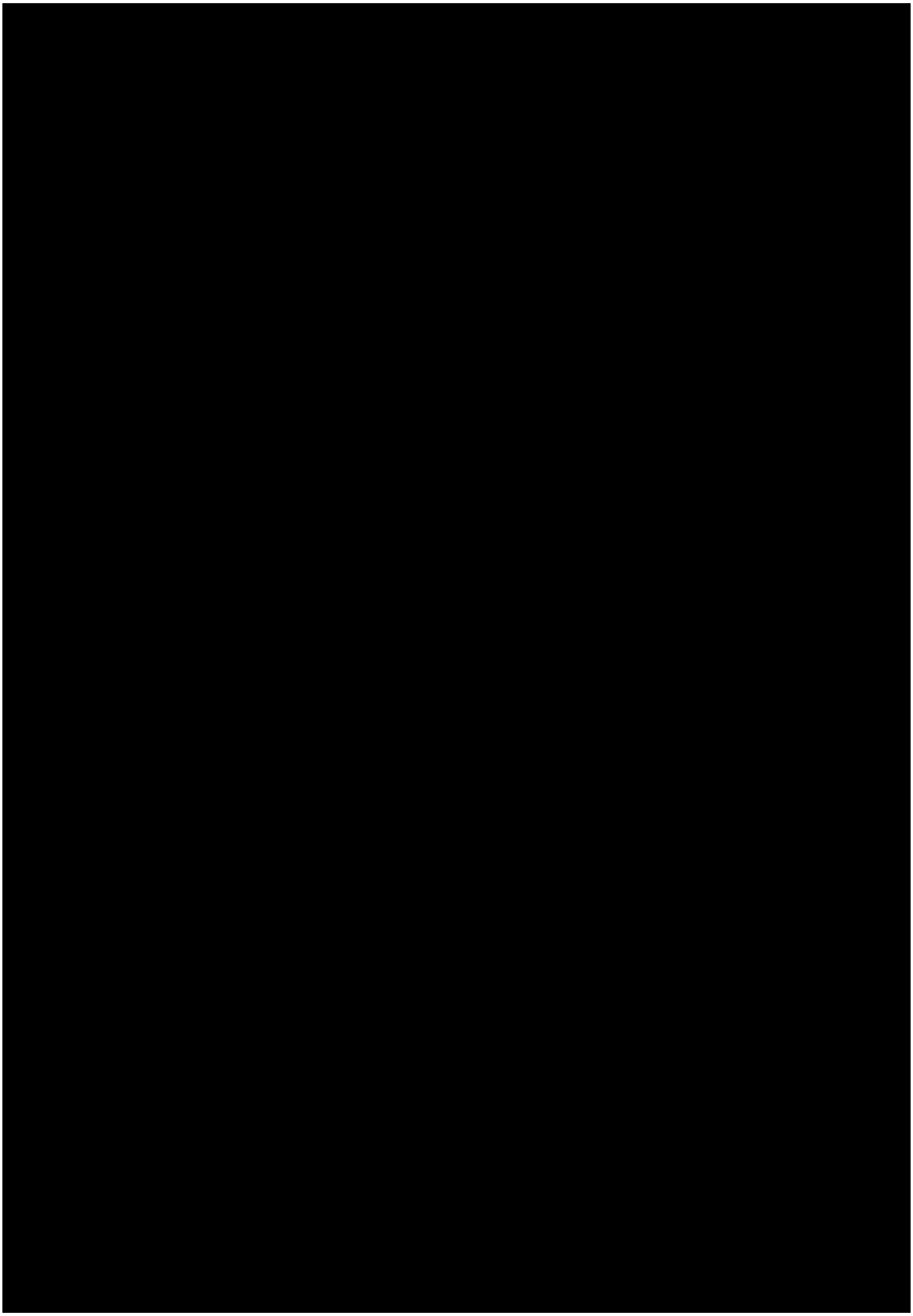
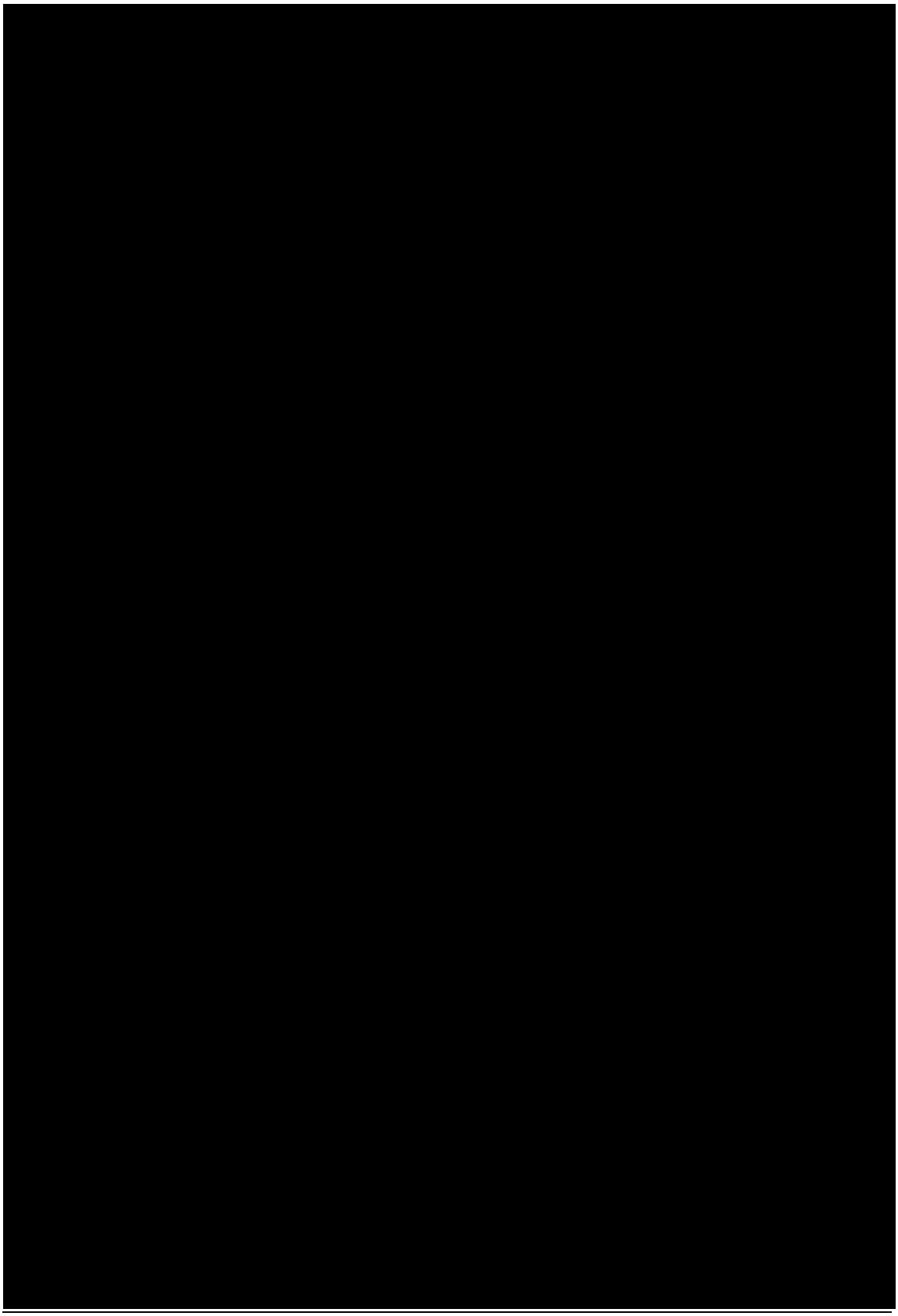
Protocol Title	A Phase 3, Multicenter, Open-Label, Single Arm Study of MR-100A-01 in Women of Childbearing Potential to Evaluate Contraceptive Efficacy and Safety
Protocol Number	MR-100A-01-TD-3001
Product	MR-100A-01 (Norelgestromin 4.86 mg/Ethinyl Estradiol 0.264 mg Transdermal System [TDS])
Study Type	Phase 3, Efficacy and Safety Study
[redacted]	[redacted]
Protocol Date	20 Jan 2023
IND no	[redacted]
Legal/Filing Sponsor	Mylan Technologies Inc., a Viatris Company 110 Lake Street St. Albans, VT 05478 USA

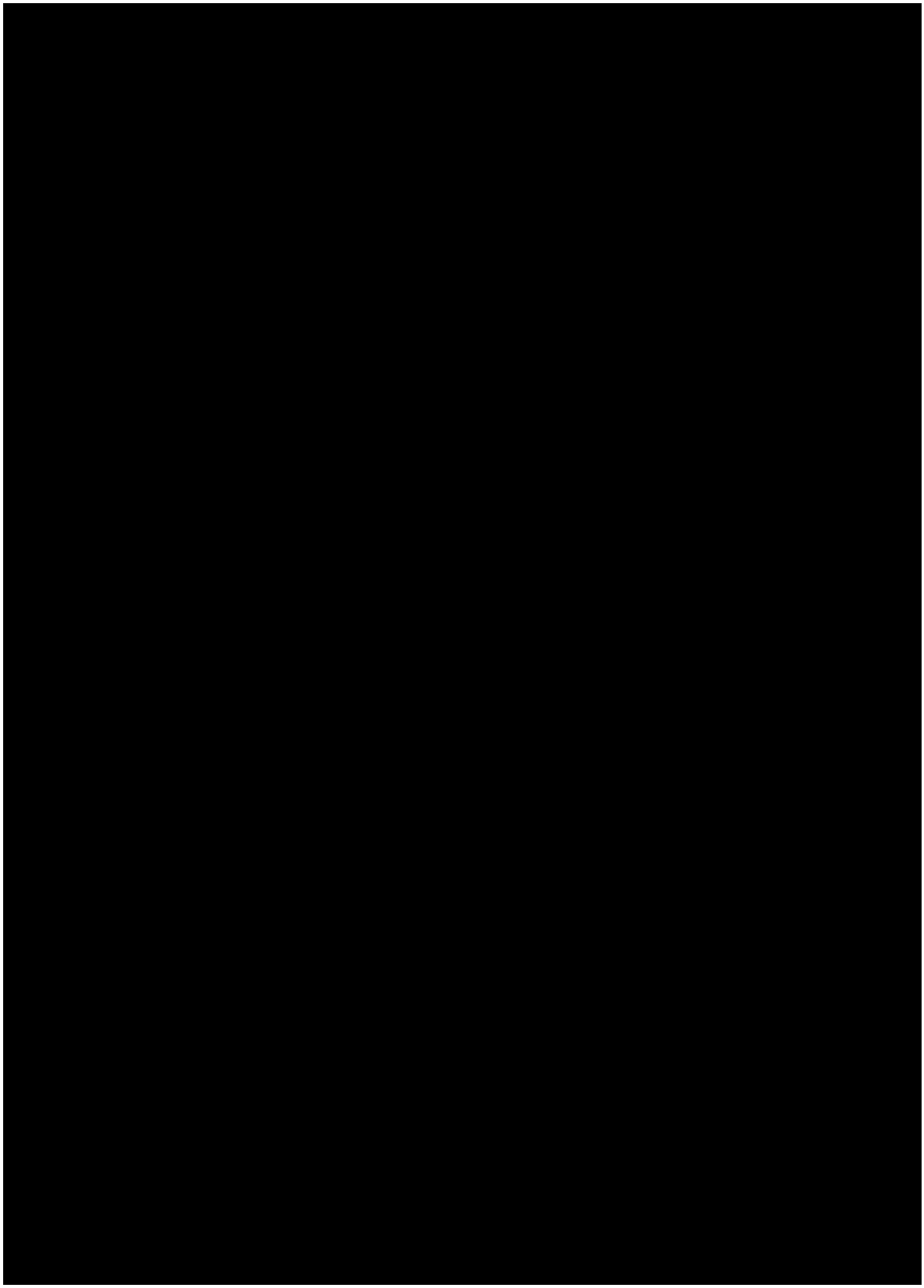
Confidentiality:

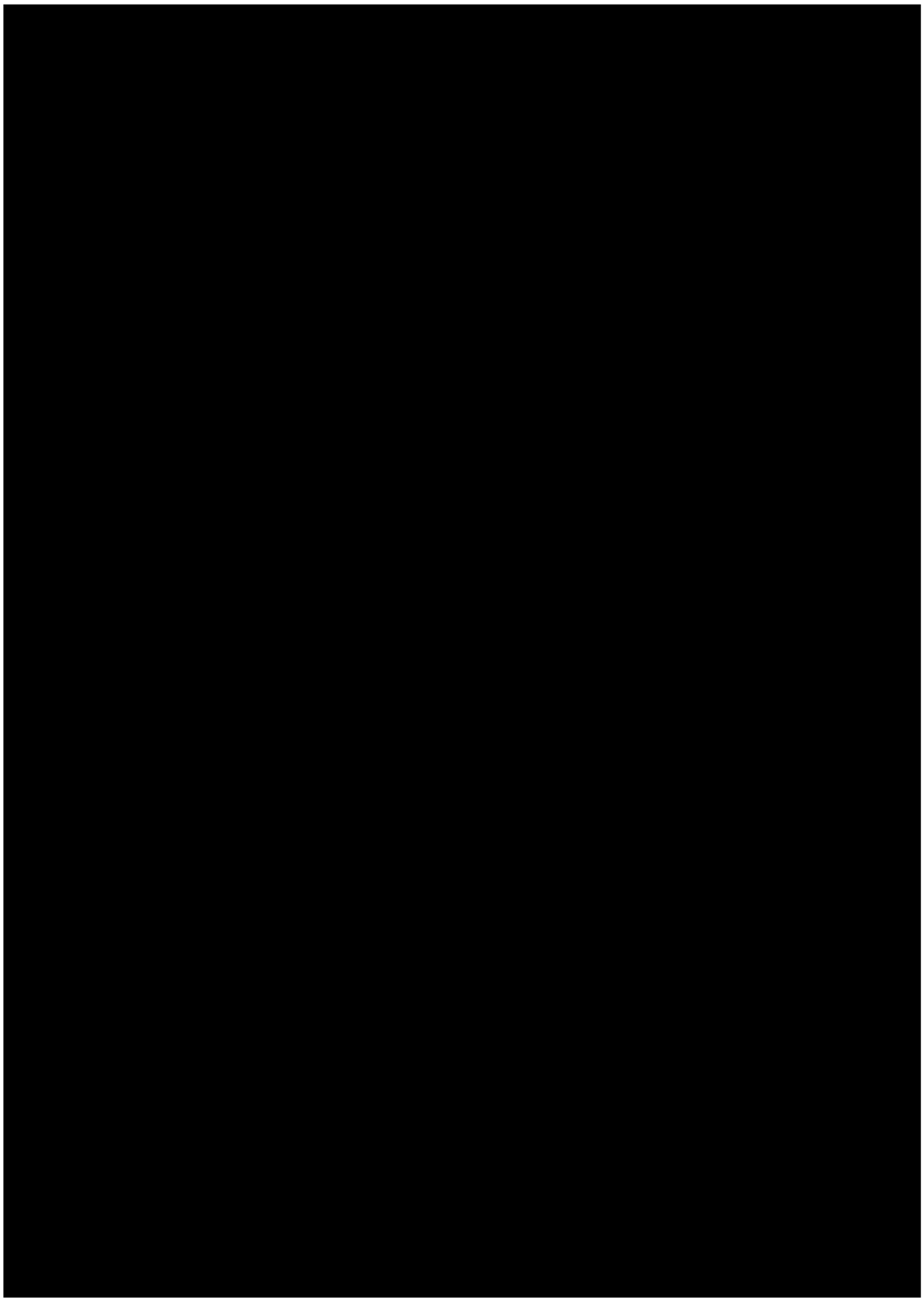


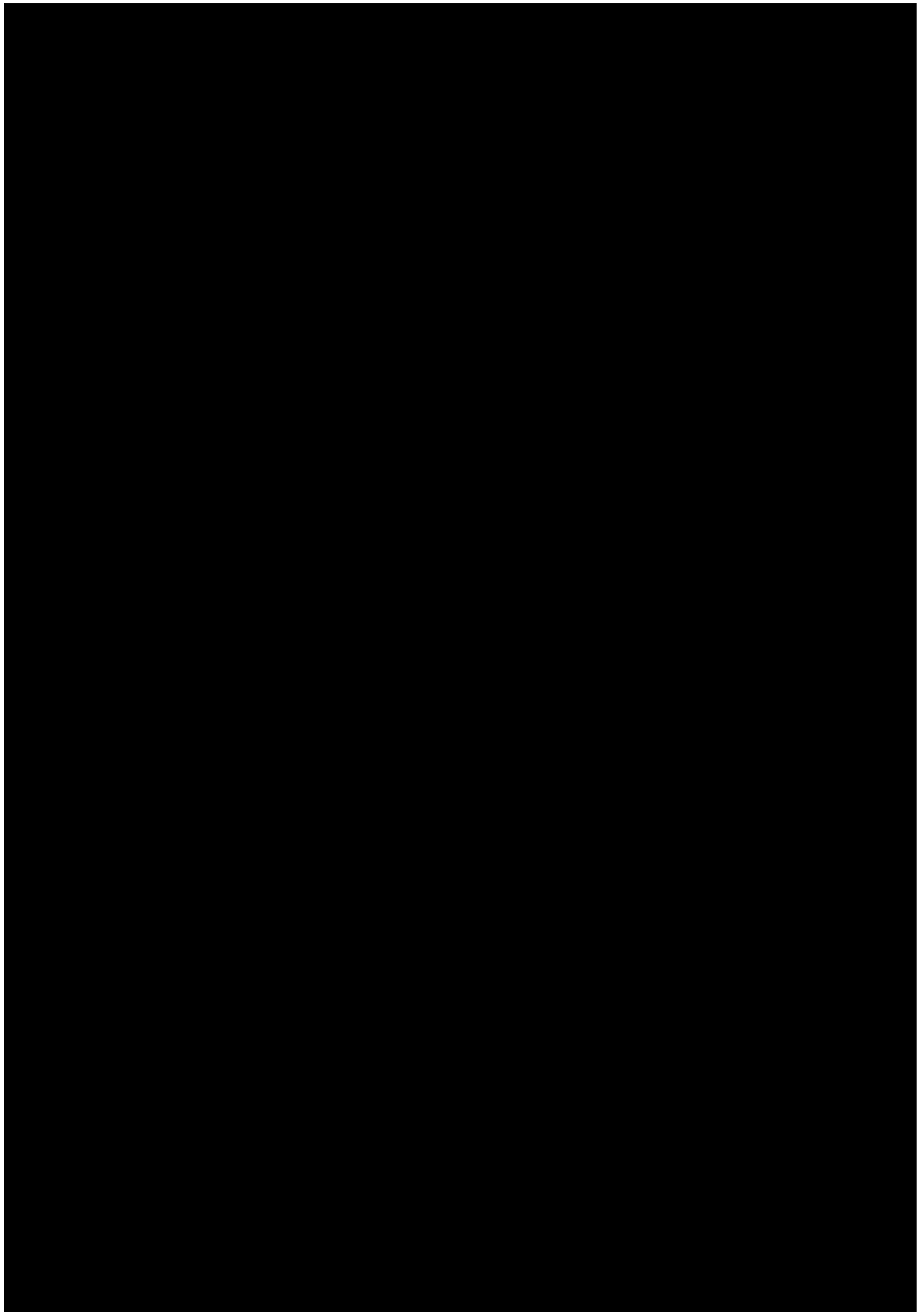


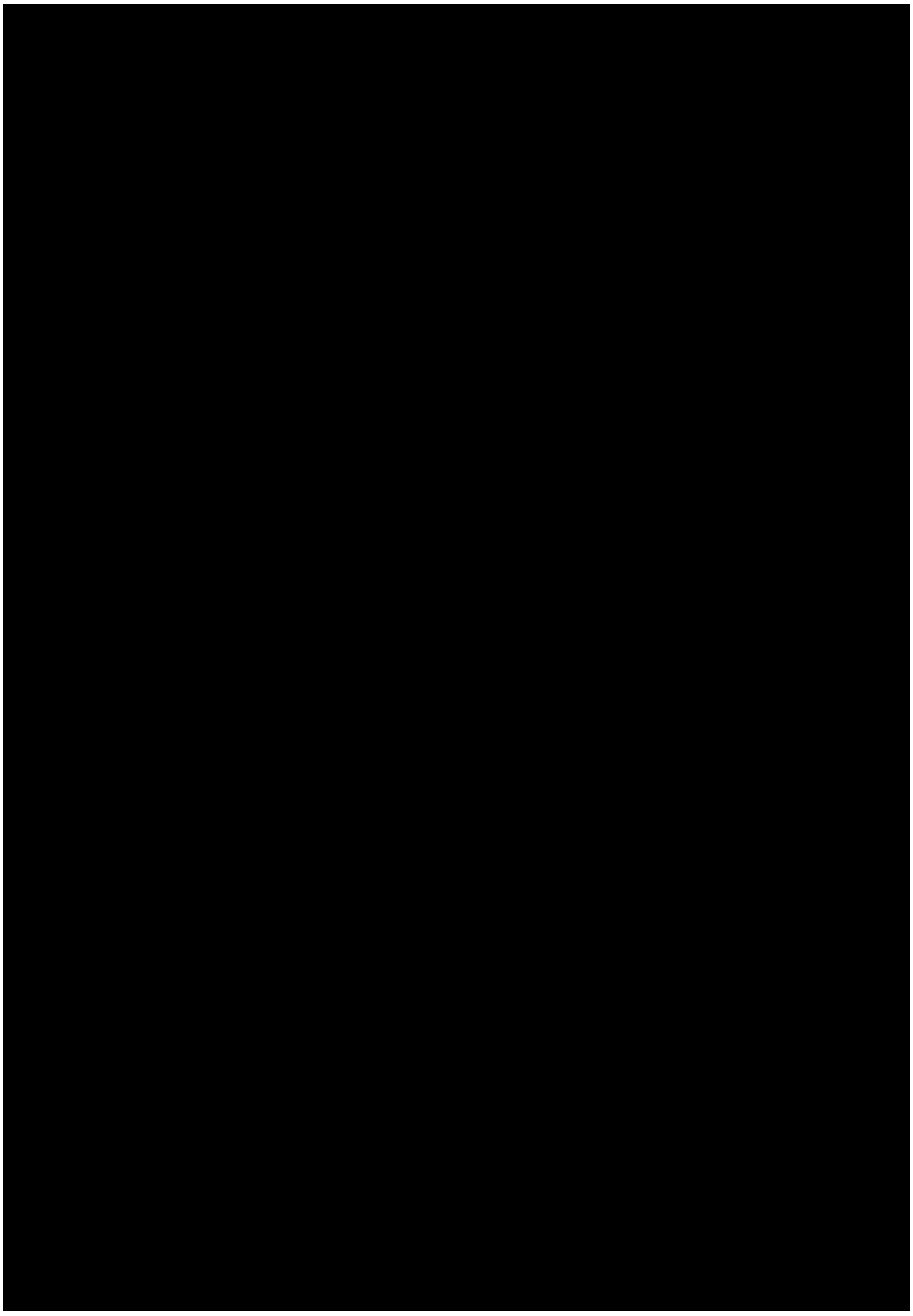


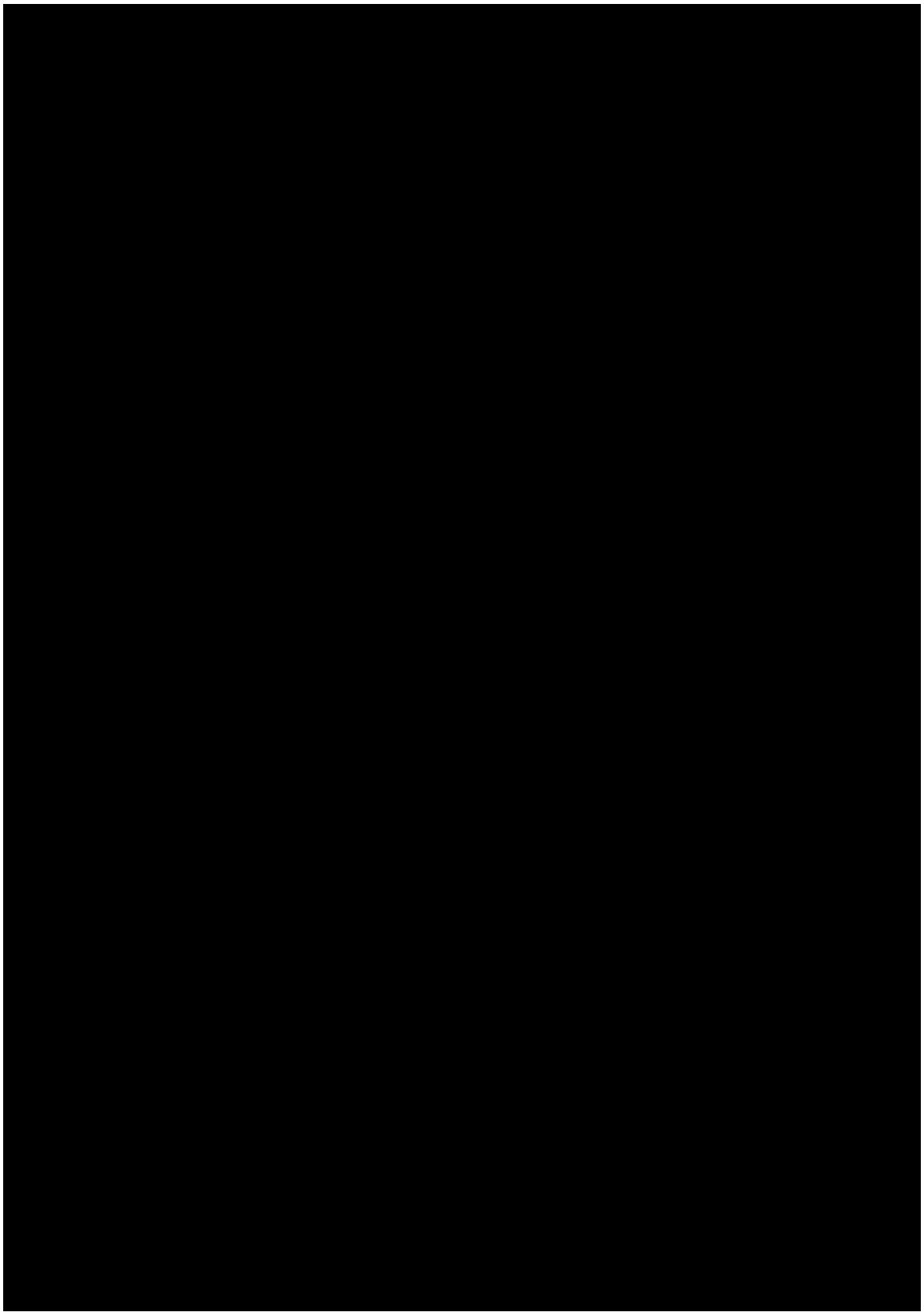


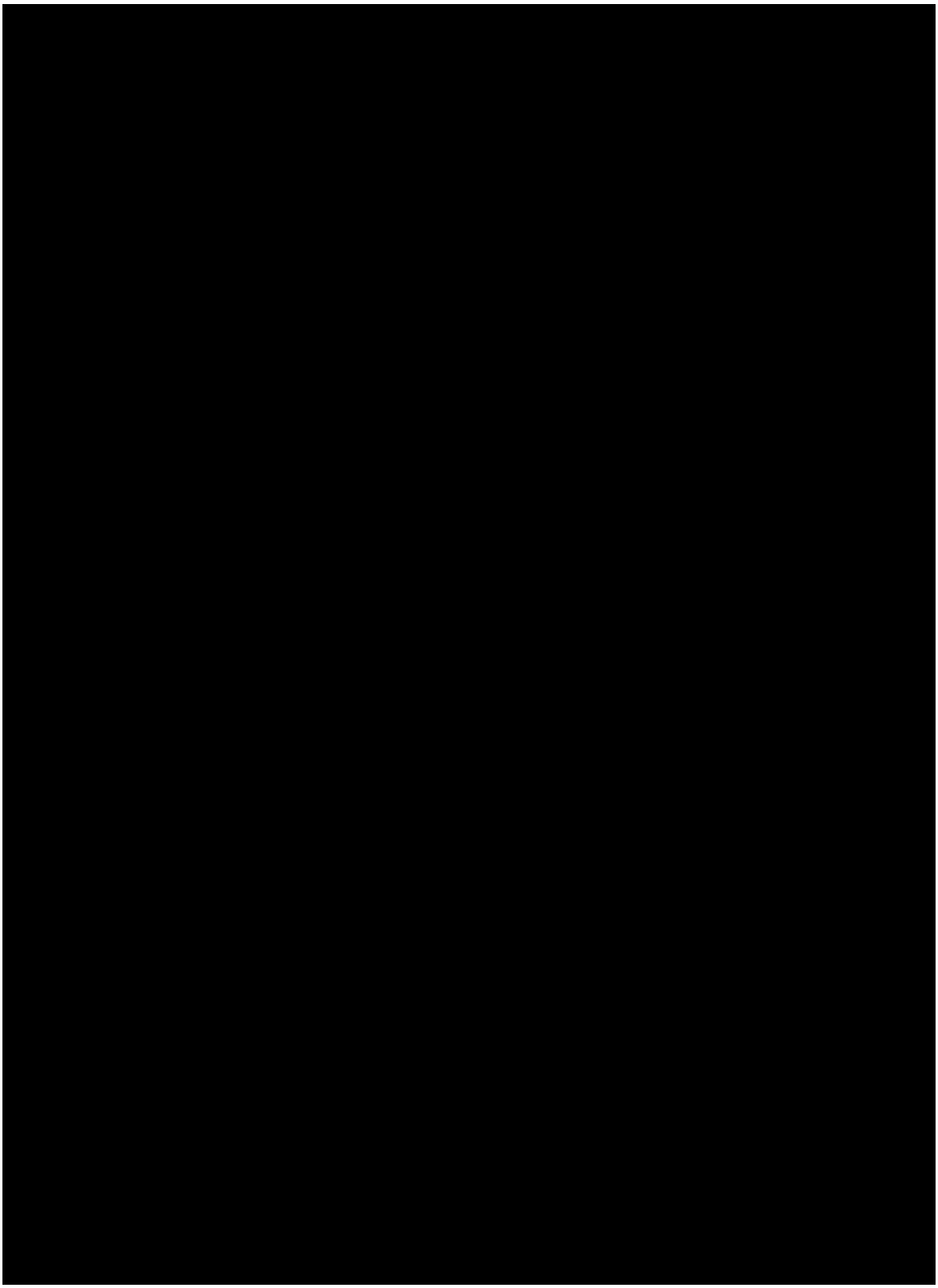












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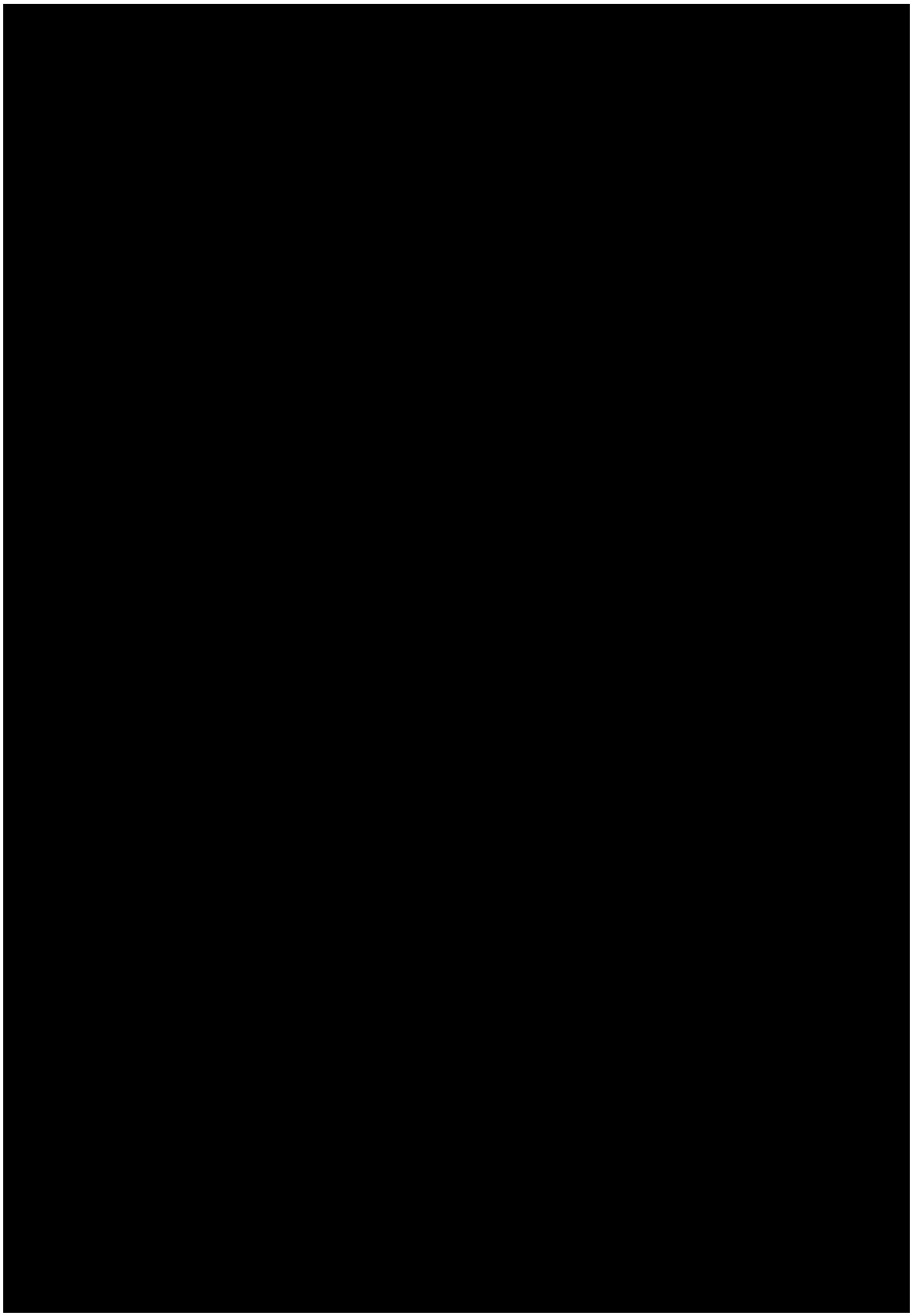

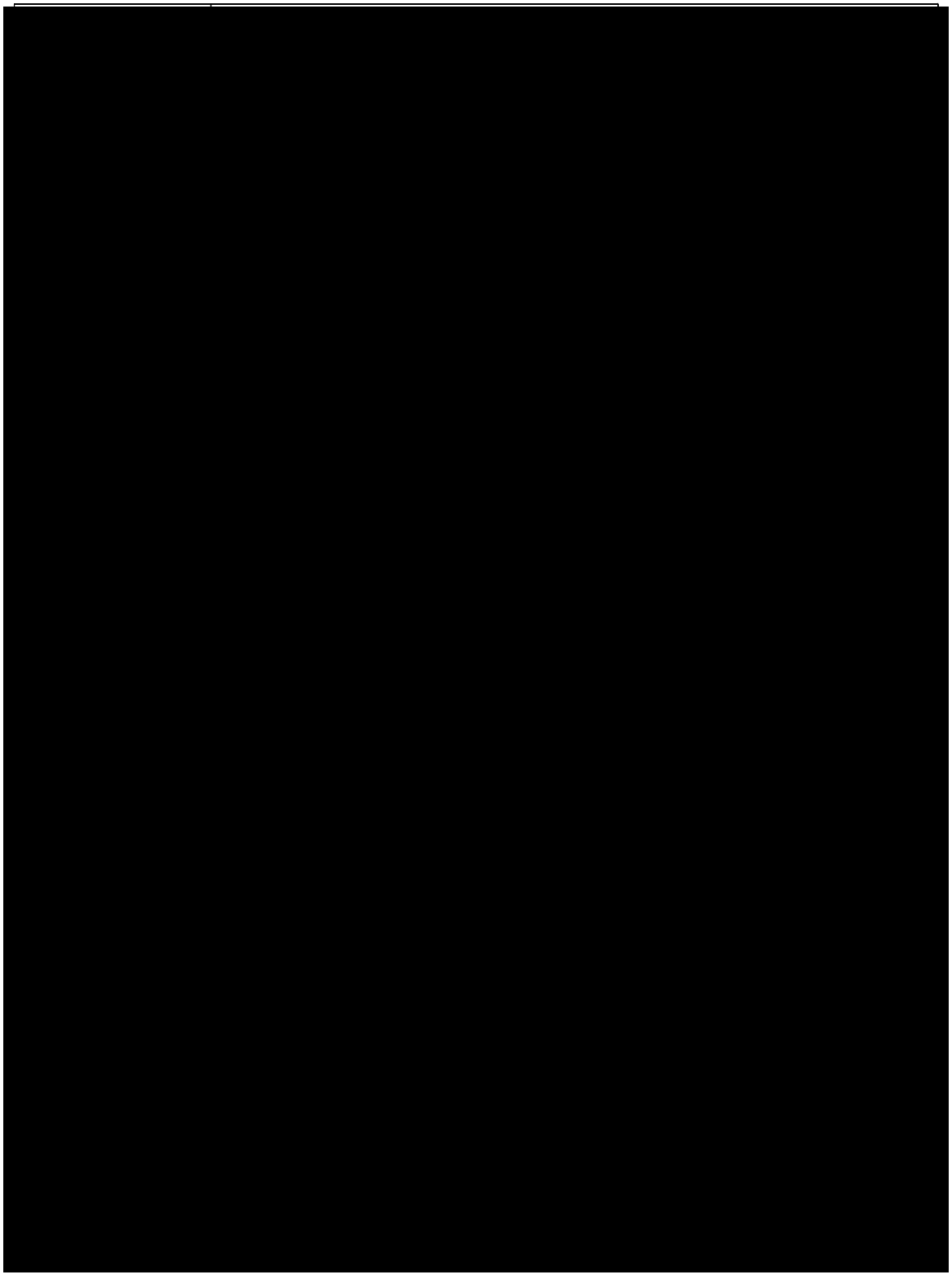

PROTOCOL SYNOPSIS

Protocol Title	A Phase 3, Multicenter, Open-Label, Single Arm Study of MR-100A-01 in Women of Childbearing Potential to Evaluate Contraceptive Efficacy and Safety
Study Sites	Approximately 75 clinical study sites based in the United States of America (US), including Puerto Rico, and Canada
Study Period Planned	~15 months
Duration of Individual Treatment	Enrolled subjects are expected to use the treatment for 13 cycles of 4-weeks (28 days).
End of Treatment	End of treatment will be the day of removal of the last patch in the study.
End of Study	The End of Study Visit will be performed at 14 (+5) days after the end of treatment (removal of last patch).
Background and Rationale	MR-100A-01 is a transdermal system (TDS) of norelgestromin (NGMN) 4.86 mg/ ethinyl estradiol (EE) 0.264 mg. This study will evaluate the contraceptive efficacy, cycle control, safety, and tolerability of MR-100A-01.
Investigational Product	MR-100A-01 (Norelgestromin 4.86 mg/Ethinyl Estradiol 0.264 mg TDS)
Primary Objective	To determine the contraceptive efficacy of MR-100A-01 when used over 13 cycles [of 4 weeks (28 days)] in healthy, post-menarcheal, premenopausal, heterosexually active female subjects of childbearing potential who are at least 16 years of age and at risk of pregnancy.
Secondary Objectives	To determine the overall safety and tolerability profile of MR-100A-01 in terms of incidence of adverse events (AEs), cycle control, and patch adhesion.
Primary Endpoint	The primary efficacy endpoint will be pregnancy rate described by Pearl Index (PI). PI is defined as the number of pregnancies per 100 women-years and will be calculated as follows: $Pearl\ Index = \frac{number\ of\ on\text{-}treatment\ \ pregnancies \times 13}{number\ of\ evaluable\ cycles} \times 100$

	where, • On-treatment pregnancy is defined as a pregnancy with an estimated date of conception (EDC) between the date of application of the first patch through 7 days after removal of the last patch in the study • Evaluable cycles are defined as the complete or incomplete 28-day cycles in which vaginal intercourse occurred and in which no back-up contraception was used based on the electronic diary (e-Diary) data, unless a pregnancy occurred in such a cycle
Secondary Endpoints	**Secondary Efficacy Endpoints:** 1. Cycle-wise and cumulative pregnancy rates over 1 year evaluated using life table analysis 2. Method failure PI **Secondary Safety Endpoints:** **a. Adverse Events and Tolerability:** 1. Incidence of AEs and serious adverse events (SAEs) 2. Incidence of application site reactions **b. Cycle Control and Patch Adhesion:** 1. Number of episodes and days of scheduled and unscheduled bleeding 2. Proportion of subjects reporting scheduled and unscheduled bleeding 3. Adhesion performance as measured by adhesion scores
Methodology and Treatments	This study is designed as a multicenter, open-label, single arm study in healthy, post-menarcheal, premenopausal, heterosexually active women of childbearing potential who are at least 16 years of age and at risk of pregnancy and seeking hormonal contraception for at least 12 months (13 cycles). The study is planned to be conducted in multiple (approximately 75) clinical sites in USA, including Puerto Rico, and Canada. Adequate number of subjects will be screened so that approximately 1,200 women meeting all study criteria will be enrolled. There will be a screening period of 7 to 60 days and a treatment period of approximately 12 months (13 cycles). **Screening:** Each subject and their guardian (if applicable) will be informed about the requirements for the participation in the study including the compliance requirements, at home Urine Pregnancy Tests (UPTs), prohibited medications, and the requirement to complete an e-Diary in real time with

	all necessary information. All screening assessments should be performed during the screening period of 7 to 60 days prior to enrollment. Screening can happen on multiple days across this period. Since the study will utilize an e-Diary, all eligible subjects will be trained to use the e-Diary. Subjects should demonstrate ability to complete the e-Diary to be eligible for enrollment. For this purpose, during the screening visit, an e-Diary application will be installed onto the subject's device (mobile or tablet). If the subject does not have a device, it may be possible for the sponsor to provide a device to only be used for this study and that will be retured at study completion. Subjects will be asked to enter data on sexual activity, contraception use and vaginal bleeding/spotting during the screening period and for at least 7 days. The screening period should be at least for 7 days before enrollment visit. **Enrollment:** Qualifying subjects with a negative UPT result and having a minimum of 70% e-Diary compliance will be enrolled into the study. If the screening period exceeds 28 days, the screening e-Diary compliance will be estimated based on the data entries either in the e-Diary for the initial 28 days from the date of activation of screening e-Diary (specifically if the compliance is less than 70% for a screening period that is longer than 28 days, then the compliance for the first 28 days can be calculated; if this meets the 70% threshold, then the criterion has been met). At first patch application, the subject will start completing the treatment daily e-Diary. Enrolled subjects will use the treatment for up to 13 cycles. The treatment regimen is a 4-week treatment cycle, with one MR-100A-01 patch to be applied every 7 days for 3 consecutive weeks followed by 1 week of a patch-free period. **Study Visits and Procedures:** During the treatment period, clinic visits will be performed anytime between Days 1 through 15 of cycles 2, 5, 8, and 12. Telephonic visits will be performed during Days 1 to 15 of Cycles 1, 3, 4, 6, 7, 9, 10, 11 and 13. End of Study (EOS) visit will be conducted at 14 (+5) days after the removal of the last study patch. Sexual activity and back-up/emergency contraception use will be monitored using the e-Diary. Subjects should use study treatment as the only method of contraception during the study. In case there arises a necessity to avoid sexually transmitted infections (STIs), subjects can use barrier methods such as condoms and spermicide. Emergency contraception (ie Morning After Pill/Plan B) can be used only in rare circumstances when the subject has

had a late patch application or partial or complete detachment and had intercourse.

During the study, pregnancy will be monitored using UPTs. UPTs will be performed at all clinic visits and whenever a subject is at risk of pregnancy or when pregnancy is suspected. An UPT and serum Pregnancy test (SPT) will be conducted at 14 (+5) days after removal of the last patch.

All subjects with an indeterminate or positive UPT result at any of the post first patch placement visits will undergo a Serum Pregnancy Test (SPT) and pelvic examination. In case of postive UPT,transvaginal ultrasonography will be performed at the earliest possible time, preferably the same day.

All pregnancies with an EDC between the date of the first patch application of the study and 7 days (inclusive) of the removal of the last patch of the study will be considered as 'on-treatment' pregnancies.

EDC will be separately estimated by the investigator, medical monitor and an independent Pregnancy Review Committee (PRC).

Medical monitor and the PRC will classify each confirmed pregnancy after placement of the first patch as pre-treatment, on-treatment, or post-treatment based on pre-specified definitions.

Evaluation of Contraceptive Efficacy:

Contraceptive efficacy will be evaluated by calculation of pregnancy rates using the PI. Cycle-wise and gross cumulative probability of pregnancy will also be measured using a life table analysis.

Evaluation of Contraceptive Safety:

Safety will be evaluated in the study by monitoring subjects for adverse events.

Assessment of patch adhesion:

Patch adhesion will be evaluated by subjects' daily self-assessment and investigator's assessment at all the clinic visits.

Self-reported adhesion will be evaluated by the subject for all days the patch is on and will be entered in the e-Diary. Subjects will record / rate the daily adhesion using the scoring system at around same time of the day. If the patch was detached during last 24 hours, subjects should be instructed to rate the patch adhesion status at the time of detachment, even if the patch was replaced later. Any possible reasons or risk factors for detachment should be noted in the e-Diary in case of complete

	detachment. Self-reported adhesion will be performed using a scoring system (Appendix 1). Investigator/Sub-investigator will perform evaluation of patch adhesion during the clinic visits using a scoring system as explained in the FDA draft guidance on Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs (Appendix 2). Adhesion performance should not be evaluated if the subject is not wearing the patch during the clinic visit. ***Assessment of patch irritaion:*** Local tolerability will be evaluated by self-reported irritation rated as none, mild, moderate or severe (Appendix 3). Self-reported irritation will be evaluated by the subject daily and will be entered in the e-Diary. At all clinic visits, the investigator/sub-investigator will perform assessment of the sites of patch application for skin irritation, with irritation rated as none, mild, moderate or severe (Appendix 4). ***Evaluation of Cycle Control:*** Cycle control will be evaluated by assessing incidence of bleeding and/or spotting episodes. The e-Diary will be used to determine the number of days of scheduled bleeding/spotting and unscheduled bleeding/spotting. Bleeding and spotting will be defined as per Mishell et al. (Mishell, 2007b) (Appendix 6). The e-Diary will also collect data on the severity of bleeding (light, normal, or heavy) (Appendix 7). **End of treatment** This will be the day of removal of the last patch in the study. **End-of-Study** The End-of-Study Visit will be performed at 14 (+5) days after the end of treatment. At this visit, a UPT, SPT, and safety assessments including hematology, chemistry and urinalysis will be performed. If urine or serum pregnancy test is positive, then a pelvic examination and transvaginal ultrasound should be performed and reviewed by the PRC to determine the on-treatment pregnancy status.
Inclusion/ Exclusion Criteria	**Inclusion criteria** 1. Healthy, post-menarcheal and premenopausal women at risk of pregnancy who are at least 16 years of age with no upper age limit.

Post-menarcheal female subjects who are at risk of pregnancy, and <18 years are eligible provided that:

a. Applicable national, state, and local laws allow the subject to consent to sexual intercourse,

b. Applicable national, state, and local laws allow subjects in this age group to consent/assent to receive contraceptive services, and

c. All applicable laws and regulations regarding the informed consent/assent of the subjects to participate in clinical trials are observed.

2. Desires to avoid pregnancy, is seeking to use hormonal contraception for at least 1 year, confirms no plans for pregnancy for the trial duration, understands the purpose of the trial and the need to report to investigator whenever she desires to get pregnant.
3. Has negative UPT results at screening and at enrollment visits.
4. Has normal, regular menstrual cycles that are between 21 and 35 days in duration with an intact uterus and both fallopian tubes and ovaries. If the subject has recently used hormonal birth control, historic data should be used to evaluate this criterion.
5. Engages in regular heterosexual vaginal intercourse (at least once per cycle), with a partner who is not known to be subfertile or infertile.
6. Agrees not to use other contraceptives or other methodology to prevent pregnancy during the study and willing to use study patch as only method of contraception except for use of back-up barrier contraception to prevent sexually transmitted infections or emergency contraception when necessary.
7. Able to understand and voluntarily provide written informed consent or assent (if the subject is adolescent prior to undergoing any trial-related procedure) to participate in the study.
8. Able to understand and willing to be compliant with study procedures such as patch applications, removals, and replacements, timely e-Diary entries, and all study visits as per the Investigator's assessment.
9. Willing to accept a risk of pregnancy.
10. Has demonstrated ability to complete e-Diary (at least 70% compliance) at enrollment visit.
11. Planning to reside within a reasonable driving/ public transport distance of the research site (approximately 150 miles) for around 12 months (13 cycles).

Exclusion Criteria

	1. Known or suspected pregnancy or planning pregnancy during next 12 months. 2. Subjects with known hypersensitivity or intolerance to estrogens, progestins, or any components of the MR-100A-01 product. 3. History or presence of dermal sensitivity to medicated patches or to topical applications including bandages, surgical tape. 4. Known infertility (current or known history) or history of sterilization in either partner. 5. Received injectable hormonal contraceptive therapy within 10 months of study enrollment or has had less than 2 consecutive, spontaneous menses after an injectable hormonal contraceptive therapy was received at least 10 months earlier. 6. Current use of hormonal contraceptive implants (still implanted or if an implant was removed, less than 3 consecutive spontaneous menses have occurred between removal and enrollment). 7. Has non-hormonal or hormonal intrauterine device (IUD) in place; or has had a recent IUD removal without one spontaneous menses after removal prior to the date of enrollment. 8. Recent surgical or medical abortion, miscarriage, ectopic pregnancy, or vaginal or cesarean delivery and have had less than 3 consecutive, spontaneous menses or withdrawal bleeding episodes prior to enrollment. 9. Subjects lactating at the time of screening into the study or has occurrence of less than 3 regular menstrual cycles after cessation of lactation. 10. Anticipates routine use of condoms or any other form of back-up contraception for protection from sexually transmitted infections during the study or for emergency contraception. 11. Subjects having a known contraindication to combined hormonal contraception as defined by category 3 or 4 conditions per Center for Disease Control and Prevention (CDC) recommendations on US Medical eligibility criteria for contaception use (US Medical Eligibility Criteria for Contraceptive Use, 2016) as listed below: a. Smoker who is ≥35 years old, or smoker who will turn 35 years old during the course of the trial (smoking includes cigarettes, cigars, smokeless tobacco, e-cigarettes, hookah, any form of nicotine replacement therapy). b. History or presence of ischemic heart disease, coronary artery disease, myocardial infarction, stroke, other cerebrovascular diseases including transient ischemic attacks (TIAs), valvular heart disease with complications (pulmonary hypertension,

	risk for atrial fibrillation, or history of subacute bacterial endocarditis), peripartum cardiomyopathy. c. History or presence of hypertension (including adequately controlled hypertension) or hypertension with vascular disease or elevated blood pressure (BP) defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, measured in sitting position after 5 minutes of rest, considering the average of two readings measured 1 to 2 minutes apart. d. History or presence of deep vein thrombosis/pulmonary embolism or superficial venous thrombosis. e. Has any comorbid condition that may require major surgery with prolonged immobilization during the study period. f. Subjects with known inherited or acquired hypercoagulopathy including thrombogenic mutations (e.g., antiphospholipid syndrome, factor V Leiden; prothrombin mutation; protein S, protein C, and antithrombin deficiencies). g. History or presence of systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies. h. History or presence of neurological conditions including migraine with aura at any age, migraine without aura in women ≥35 years age or in women who smoke, or multiple sclerosis with prolonged immobility. i. History or presence of or suspected carcinoma of breast. j. Has diabetes mellitus with nephropathy, retinopathy, neuropathy, or other vascular disease or diabetes of >20 years' duration. k. Has inflammatory bowel disease (ulcerative colitis or Crohn's disease) who are at increased risk for VTE (those with active or extensive disease, surgery, immobilization, systemic corticosteroid use, vitamin deficiencies, or fluid depletion) based on Investigator's discretion. l. Medically treated or presence of symptomatic gall bladder disease. m. History of CHC/pregnancy related cholestasis/jaundice. n. Presence of liver disease including acute or flare of viral hepatitis, severe (decompensated) cirrhosis, benign (e.g, hepatocellular adenoma) or malignant liver tumors. o. History of organ transplantation within 5 years before screening or chronic disease potentially necessitating organ transplantation during the anticipated course of the study.

p. Subject has requirement to be on treatment with medications prohibited during study (see section on prohibited medications 7.9).

12. Known or suspected estrogen or progestin sensitive malignant or premalignant conditions including but not limited to carcinoma of endometrium, ovary or fallopian tubes.
13. History of any other condition that in the Investigator's opinion suggests an elevated risk of arterial or venous thromboembolic disease (e.g., any active malignancy except non-melanoma skin cancers, subacute bacterial endocarditis with valvular disease, atrial fibrillation).
14. Has uncontrolled thyroid disorder.
15. Has diagnosis of hereditary angioedema.
16. Has hyperlipidemia on screening (fasting cholesterol level >260 mg/dL; fasting triglyceride level >300 mg/dL).
17. Has uncontrolled diabetes mellitus as defined by Hemoglobin A1C (HbA1C) value of >7% at screening.
18. Subjects with abnormal significant liver function tests as measured by liver function tests; alanine aminotransferase (ALT) >3.0 times the upper limit of normal (ULN) or alkaline phosphatase >2.5 times ULN or aspartate aminotransferase (AST) >3.0 times ULN or blood bilirubin >1.5 times ULN.
19. Has a significantly abnormal cervical cancer screening test (cervical cytology with reflex human-papilloma-virus (HPV) testing or with HPV co-testing) performed at screening visit (for subjects aged ≥21 years) i.e., cervical dysplasia or invasive cervical cancer or has any abnormal cytology with/without HPV testing during 6 months prior to screening which may require additional screening or treatment during the study period per American Society of Colposcopy and Cervical Pathology (ASCCP) Screening Guidelines 2019 (Perkins RB, ASCCP, 2019). Specifically, the following are exclusionary:
    - Papanicolaou test (Pap test) with atypical squamous cells of undetermined significance (ASC-US), *unless*:
        - reflex HPV testing was performed and was negative for high risk oncogene HPV. Or
        - reflex HPV testing was performed and was positive for high risk oncogene HPV:
            - Subject is 21 to 24 years of age and will have repeat cytology in 12 months; at the investigator's discretion she may be included.
            - Subject is >24 years of age and has an adequate colposcopy and there are no

	lesions; at the investigator's discretion she may be included. ▪ Pap test with Low-Grade Squamous Intraepithelial Lesion (LSIL) ▪ Pap test with Atypical Squamous Cells - High (ASC-H), atypical glandular cells, high-grade intraepithelial lesion (HSIL) or malignant cells 20. Subjects with chlamydial or gonorrheal infection at screening (subjects who screen fail due to positive results may be re-screened and enrolled in the study after standard medical treatment). 21. Has unexplained vaginal bleeding within the past 6 months or any abnormal bleeding which is expected to recur during the study (e.g., bleeding from cervical polyp, recurrent bleeding after sex). 22. History of known or suspected hepatitis B or C infection or high risk for sexually transmitted disease (STD). 23. Known human immunodeficiency virus (HIV) infection or positive, confirmatory test at screening. 24. Current known active infection of coronavirus disease 2019 (COVID-19), or subjects with an increased risk of serious COVID-19 related morbidity as determined by the investigator at the time of screening and/or enrollment; subjects who have had previous COVID-19 infections but have recovered by the time of enrollment visit may be enrolled if there are no current COVID-19 symptoms as determined by the investigator; subjects who had previously received COVID-19 vaccine may be enrolled irrespective of the timing of vaccination. (Additional COVID-19 screening procedures that may be mandated by the study site do not need to be reported as protocol deviations.) 25. Within the past year, either suicidal ideation or attempt or severe depression requiring hospitalization. 26. Presence of any other concomitant disease or laboratory result that may worsen under hormonal treatment based on Investigator's discretion. 27. Positive urine drug screen for cocaine, methamphetamine, opiates, or phencyclidine unless there is a documented prescription with supporting medical history and diagnosis. 28. Recent history (within prior 12 months) of drug or alcohol abuse or at Investigator discretion, history greater than 12 months prior and at risk for noncompliance. Current or recent history of (recreational or medicinal) marijuana use is not exclusionary at the investigator's discretion upon assessment of any potential risk.

	29. Participation in an investigationalstudy within 30 days prior to enrollment or intention to participate within next 13 months.
Planned Number of Subjects	Adequate number of subjects will be screened so that approximately 1200 eligible women will be enrolled and treated for up to 13 cycles to provide at least 10,000 evaluable cycles for safety. The study population will be selected such that: • The proportion of non-white study participants will be at least 30% of the total study population to reflect the general population in the US • The proportion of women over the age of 35 years will represent approximately 10% of the total study population • The proportion of women with higher BMI ($\geq$30 kg/m^2) will be capped to a maximum of 10% of the total study population Based on the asumptions above, it is expected that approximately 1,000 enrolled women aged 16 to $\leq$35 years and with BMI <30 kg/m^2 will provide at least 5000 evaluable cycles (after excluding cycles with back-up contraception and abstinent cycles) for efficacy. [redacted]. At least 200 subjects will complete the study.
Statistical Methods	**Definitions of analysis populations**: 1. All-enrolled population: All subjects who were enrolled into the study (i.e. subjects who had a non-missing enrollment date on the enrollment page of the CRF). 2. Safety population: All subjects who had at least one patch application after enrollment. 3. Contraceptive efficacy population (CEP): All subjects in the safety population who have a negative serum β-hCG at enrollment visit. If the test was missed to be performed due to unforeseen reasons, results if available from UPT found to be negative at enrollment visit, can be considered for inclusion in the CEP. 4. Cycle control population: All subjects in CEP who provide information on bleeding and patch application. 5. Efficacy evaluable (EE) population: All subjects in CEP aged 16 to 35 years (inclusive) at enrollment who have baseline BMI < 30 kg/m^2 and have at least one efficacy evaluable cycle which meet the following criteria:

	i. Cycles in which vaginal intercourse occurred ii. Cycles in which no backup or emergency contraception was used based on e-Diary data, unless a pregnancy occurred in such a cycle **Statistical analysis:** The primary contraceptive efficacy endpoint used in this study will be PI. The PI and corresponding 95% CI will be calculated. The primary efficacy analysis will be performed on the EE population. The calculations will be also done for all women in CEP. For the primary efficacy analysis, PI will be calculated utilizing the number of on-treatment pregnancies adjudicated by the PRC. An additional analysis will be performed based on the medical monitor's determination of EDC. Sub-group analyses will be performed based on baseline weight and BMI in the EE population. Other sub-group analyses will be performed based on age, race, ethnicity, and previous hormonal contraceptive use. The method failure PI and corresponding 95% CI will be calculated in the EE population. A life-table analysis of cycle-wise and cumulative pregnancy rates up to 13 cycles will be performed as a supportive analysis on the EE population. The analysis will be done for all pregnancies and for all method failure pregnancies. An analysis of AEs will be performed in the safety population. An analysis of cycle control data will be performed in the cycle control population. Application site reactions and adhesion performance data will be reported descriptively.

STUDY DIAGRAM AND STUDY SCHEDULE OF ACTIVITIES

Figure 1: Study Diagram

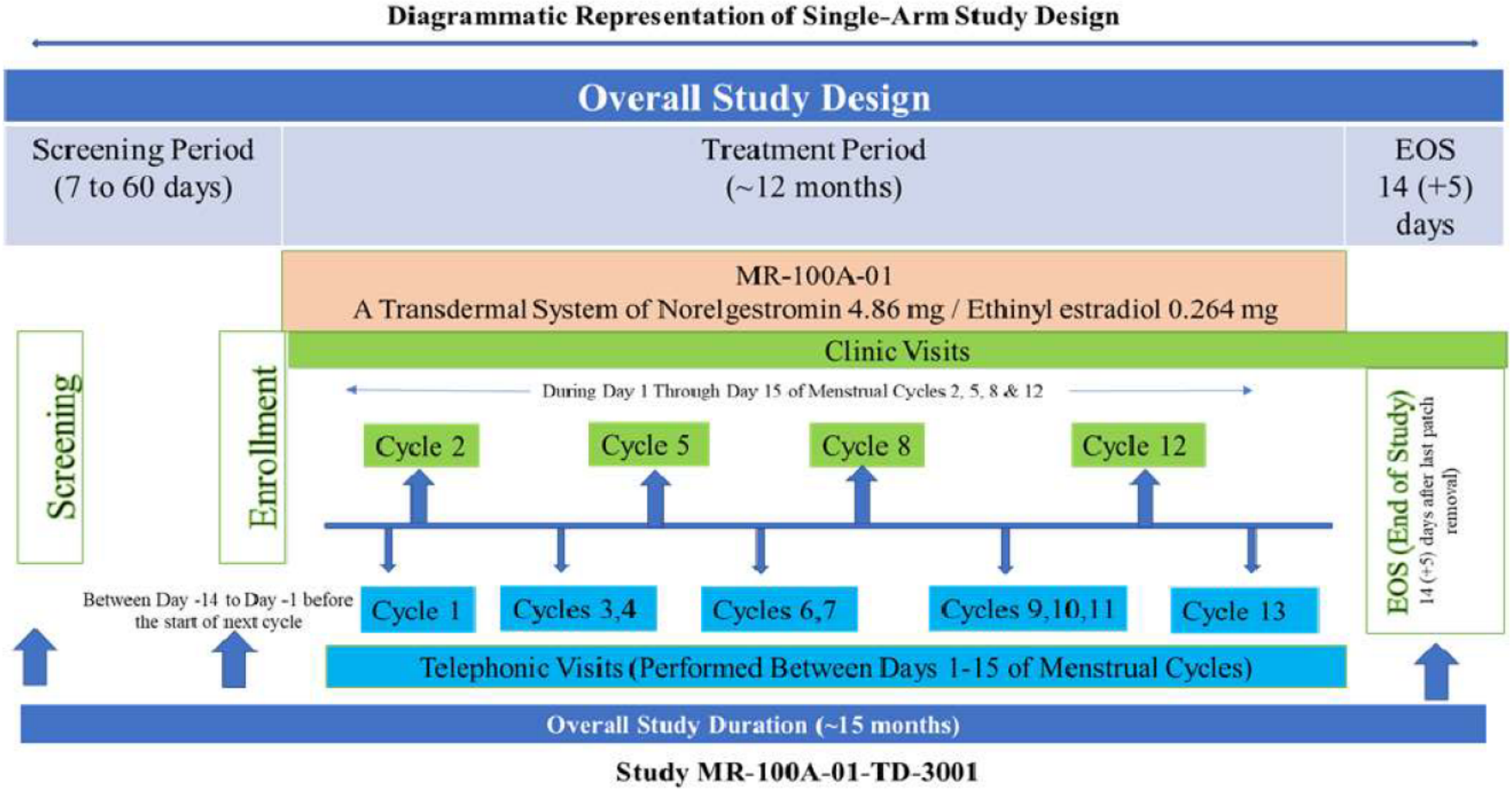

Table 1: Study Schedule

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the section Study Conduct Section for detailed information on each procedure and assessment required for compliance with the protocol.

Visits	Screening[1]	Enrollment[1]	Cycle 1/ TFU	Cycle 2	Cycle 3/ TFU	Cycle 4/ TFU	Cycle 5	Cycle 6/ TFU	Cycle 7/ TFU	Cycle 8	Cycle 9/ TFU	Cycle 10/ TFU	Cycle11/ TFU	Cycle 12	Cycle 13/ TFU	EOS/ ET[2]
Treatment Cycle Day	7 to 60 days prior to enrollment	Between Day -14 to Day -1 of Cycle 1 Day 1	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	14 (+5) days after patch removal
Informed consent/assent	✓															
Inclusion/ exclusion criteria	✓	✓														
IWRS Registration with assignment of Subject Identification Number	✓															
Demography[3]	✓															
Medical & Surgical and Medication History[4]	✓															
Gynecological, Obstetric, Menstrual & Contraceptive Use History[5]	✓	✓														
Alcohol abuse, Smoking & drugs of abuse history	✓															
Targeted Physical Examination including Gynecological examination	✓															✓
Height[6], Weight, BMI	✓	✓								✓						✓
Vital signs (BP, RR, PR, Temperature)	✓	✓		✓			✓			✓				✓		✓
Laboratory Investigations[7]	✓															✓
Urine drug screen	✓															
Testing for Chlamydia trachomatis and Neisseria gonorrhea	✓															
Cervical cancer screening[8]	✓															
Confirm and validate current cycle with e-Diary entry			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Confirm and validate Day 1 of the current cycle with e-Diary entry			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Urine Pregnancy Test (UPT)[9]	✓	✓	✓	✓			✓			✓				✓		✓
Serum Pregnancy test (SPT)[10]		✓														✓
Pregnancy determination[11]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medication			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Visits	Screening[1]	Enrollment[1]	Cycle 1/ TFU	Cycle 2	Cycle 3/ TFU	Cycle 4/ TFU	Cycle 5	Cycle 6/ TFU	Cycle 7/ TFU	Cycle 8	Cycle 9/ TFU	Cycle 10/ TFU	Cycle11/ TFU	Cycle 12	Cycle 13/ TFU	EOS/ ET[2]
Treatment Cycle Day	7 to 60 days prior to enrollment	Between Day -14 to Day -1 of Cycle 1 Day 1	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	1 to 15	14 (+5) days after patch removal
Dispense run-in e-Diary with subject training	✓															
Dispense condoms and spermicide [12]	✓													✓		
Collect unused condoms [13]																✓
Run-in e-Diary compliance check		✓														
Dispense Study Patch (including reserve patches as required) with instructions		✓[13]		✓			✓			✓				✓		
Dispense study e-Diary with subject training		✓														
Dispense home urine pregnancy kits[14]		✓		✓			✓			✓				✓		
Review compliance (including e-Diary use, patch use, back-up contraception, sexual activity) and re-training of subject as necessary			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Investigator's evaluation of patch application site				✓			✓			✓				✓		✓
Investigator's evaluation of patch adhesion[15]				✓			✓			✓				✓		
Adverse events recording	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intention to plan for pregnancy[16]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Review contact information	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Post-treatment contraceptive counselling														✓[17]		✓
Blood Samples for PK[18]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

C1D1: Cycle 1 Day 1; TFU: Telephonic Follow-up visit; EOS: End of Study; ET: Early Termination; IWRS: Interactive Web Response System; BMI: Body Mass Index; BP: Blood Pressure; RR: Respiratory Rate; PR: Pulse Rate; e-Diary: Electronic Diary

1. Screening period should be at least for 7 days before enrollment. Enrollment will be performed between Day -14 to Day -1 before the start of next expected menstural cycle; if the first study patch is applied at the site, this will be the Cycle 1 Day 1 for the subject If the first study patch was applied at the site during the enrollment visit, a follow-up telephonic visit still needs to be conducted until Day 15 of Cyle 1.

2. EOS Visit must be performed at 14 (+5) days after removal of last patch.
   In case of an early discontinuation from the study, whenever possible, it is recommended that ET visits be performed at 14 (+5) days after removal of last patch. However, this can be performed earlier based on subject's convenience in visiting the site and/or at the investigator's clinical decision.
3. Includes date of birth, age, race, ethnicity, educational status.
4. Medical History: Including check of VTE risk; Medication History: See section 5.8 on concomitant medications
5. At screening visit: Full details of contraceptive use history should be recorded for the year prior to screening. If relevant, medical/contraceptive history more than one year also need be collected; At enrollment visit: Only the history during screening period need to be collected.
6. Height is measured at screening visit (ONLY), for all subjects. At all other visits, height is measured only for adolescent subjects (i.e. < 18 years of age).
7. Blood samples for hematology, chemistry, HIV testing and urine samples for urinalysis will be obtained; samples for chemistry should be taken under fasting conditions; Note: HbA_1C and HIV testing ONLY at screening visit.
8. Cervical cancer screening: will not be performed for subjects < 21 years of age; for women aged 21 to 29 years, pap test will be performed, pap test may be followed by reflex HPV if needed; for ≥30 years, HPV and cytology will be performed; for all subjects, cervical cancer screen test results are acceptable from previous testing if they are available from testing within last 6 months of screening.
9. UPT will be performed at screening, at enrollment visit, before start of first ever study patch application (if applied at home), at all clinic visits and whenever subject is at risk of pregnancy or pregnancy is suspected (for example, any symptoms/signs suggestive of pregnancy, missed/ delayed patch application during that cycle without use of a back-up contraception as per requirements). In case of indeterminate or positive UPT result, SPT, pelvic examination and transvaginal ultrasound must be performed at the earliest possible time, preferably on the same day.
   Note: If subject has a positive UPT at screening or at enrollment visit, subject will be screen failed; such pregnancy would be designated as a pre-treatment pregnancy
10. Results of SPT testing at the enrollment visit may be available after the first patch has been placed. If subject has a positive SPT at enrollment visit, subject will be discontinued from study and counselled on continuation of pregnancy and on further standard medical care; such pregnancy would be designated as a pre-treatment pregnancy. If subject has a positive SPT at ET or EOS visit, subject will be asked to return to the study site and pelvic examination and transvaginal ultrasould will be performed at the earliest possible time, preferrably the same day. If the subject applies her first patch later than 7 days from the enrollment visit, the subject should contact the site immediately after first patch application to schedule a visit to peform a SPT (even if the UPT is negative before first patch application) within 7 days from the first patch application.
11. Pregnancy determination only if UPT is positive or indeterminate; SPT and pelvic examination will be performed at the earliest possible time, preferably on the same day whenever a UPT result is positive or indeterminate. In case of positive UPT, transvaginal ultrasound will be performed as early as possible, preferably the same day, it is highly recommended that an early transvaginal ultrasound examination is performed on the same day when UPT is positive.
12. For all women, condoms and spermicide will be dispensed at screening visit to be used during the screening period and up to first patch placement; based on the availability with subjects, condoms and spermicide will be dispensed at the cycle 12 visit for use after patch free week of cycle 13 in addition to any planned/actual start of any contraceptive method; Unused condoms will be collected at EOS visit. Subjects who prematurely terminate study drug will be asked to use barrier methods of contraception such as condoms and spermicide or diaphragm and spermicide until completion of the ET visit.
13. For subjects who will apply their first study patch later at home, a demonstration patch (no active ingredients) will be used to train the method of patch application.
14. UPT kits would be dispensed based on availability of UPT kit with the subject.
15. Adhesion performance should not be evaluated if the subject is not wearing the patch during the clinic visit.
16. The subject will be asked at each visit if she has a desire to become pregnant. In case of a positive answer, the subject will be discontinued from further study participation.
17. Includes instructions to use barrier contraceptives after the patch-free week of cycle 13 in addition to any planned/actual start of contraception including CHCs through the end of study visit.

18. All possible attempts should be made to collect PK samples as soon as possible in the event of any suspected or confirmed arterial or venous thromboembolic events. The blood samples will be analyzed for ethinyl estradiol and norelgestromin concentrations using fully validated analytical methods.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF COMMONLY USED ABBREVIATIONS

Abbreviation	Description
~	Approximately
ADRs	Adverse Drug Reactions
AE	Adverse Event
ALT	Alanine Aminotransferase
ANDA	Abbreviated New Drug Application
ASCCP	American Society Of Colposcopy And Cervical Pathology
ASC-H	Atypical Squamous Cells-High
ASC-US	Atypical Squamous Cells Of Undetermined Significance
AST	Aspartate Aminotransferase
β-hCG	Beta Human Chorionic Gonadotropin
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CDC	Center For Disease Control And Prevention
CEP	Contraceptive Efficacy Population
CHC	Combined Hormonal Contraceptives
CI	Confidence Interval
COC	Combined Oral Contraceptive
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
DHHS	Department Of Health And Human Services
ECG	Electrocardiogram
ECMC	Evaluable Cycles Monitoring Committee
e-CRF	Electronic Case Report Form
EDC	Estimated Date of Conception
e-Diary	Electronic Diary
EE	Ethinyl Estradiol
EE population	Efficacy Evaluable Population
EOS	End Of Study
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HbA_1C	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSIL	High-Grade Squamous Intraepithelial Lesion
hrs	Hours

ICF	Informed Consent Form
ICH	International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine Device
IWRS	Interactive Web Response System
LDL	Low-Density Lipoprotein
LEC	Local Ethics Committee
LSIL	Low-Grade Squamous Intraepithelial Lesion
mcg	Microgram(S)
MedDRA	Medical Dictionary For Regulatory Activities
MPPL	Mylan Pharmaceuticals Private Limited
NDA	New Drug Application
NGMN	Norelgestromin
Pap test	Papanicolaou Test
PE	Pulmonary Embolism
PI	Pearl Index
PR	Pulse Rate
PRC	Pregnancy Review Committee
PSRM	Product Safety And Risk Management
RBC	Red Blood Cell
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SGPT	Serum Glutamic Pyruvic Transaminase
SGOT	Serum Glutamic Oxaloacetic Transaminase
SID	Subject Identification Number
SOP	Standard Operating Procedure
SPT	Serum Pregnancy Test
STD	Sexually Transmitted Disease
STIs	Sexually Transmitted Infections
TDS	Transdermal System
TFU	Telephonic Follow-Up
TIAs	Transient Ischemic Attacks
ULN	Upper Limit Of Normal
UPT	Urine Pregnancy Test
US	United States
USPI	United States Prescribing Information
VTE	Venous Thrombo Embolism
WBC	White Blood Cell
WHO	World Health Organization

PROTOCOL SIGNATURE PAGE

Protocol Title	A Phase 3, Multicenter, Open-Label, Single Arm Study of MR-100A-01 in Women of Childbearing Potential to Evaluate Contraceptive Efficacy and Safety
Protocol Number	MR-100A-01-TD-3001
Protocol Version	[redacted]

The protocol identified above has been reviewed and the procedures outlined therein are in agreement with Sponsor's project objectives and applicable regulatory expectations.

Approved By:

Electronic Signature Manifestation Appended

[redacted]

Electronic Signature Manifestation Appended

[redacted]

Electronic Signature Manifestation Appended

[redacted]

INVESTIGATOR AGREEMENT

I, the undersigned, as Investigator for this study, have read the foregoing protocol, entitled "A Phase 3, Multicenter, Open-Label, Single Arm Study of MR-100A-01 in Women of Childbearing Potential to Evaluate Contraceptive Efficacy and Safety".

I agree to conduct the study as outlined herein and in accordance with all applicable requirements of the country where the study is being conducted, the country where the study will be submitted, and the Sponsor's requirements. Applicable guidelines and regulations include, but are not limited to:

1. Permission to allow the Sponsor and/or its agent or regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures subject confidentiality.
2. Immediate notification of the Sponsor and/or its agent of any regulatory inspection related to this study.
3. Submission of the proposed clinical investigation, including the protocol and consent/assent form, to a duly constituted IRB/Ethics Committee for approval, and acquisition of written approval for each, prior to study initiation.
4. Use of IRB/Ethics Committee-approved written informed consent/assent that is obtained prior to study initiation for each subject.
5. Submission of any proposed change in or deviation from the protocol to the IRB/Ethics Committee using a signed formal amendment document prepared by the Sponsor and/or its agent. Any proposed change(s) or deviation(s) from the protocol require that the informed consent/assent also reflect such change(s) or deviation(s), and that the revised informed consent/assent be approved by the IRB/Ethics Committee.
6. Documentation and explanation of the individual protocol deviations on the appropriate CRF page or other Sponsor-approved document.
7. Submission of written reports of serious or unusual adverse events to the Sponsor as defined in the protocol Section 'Adverse events and safety reporting'.
8. The Principal Investigator will individually assess the impact of all protocol deviations and adverse events on the conduct of the study, subject safety, and the suitability of the clinical data and provide to the Sponsor.

_____ _____

Investigator's Signature Date

_____

Investigator's Name (Please Print)

CLINICAL STUDY CONTACT LIST

Sponsor:	**Mylan Technologies Inc., a Viatris Company** 110 Lake Street St. Albans, VT 05478 USA
Sponsor Representative:	[redacted]
Sponsor Medical Monitor:	
Data Management:	
Sponsor Statistical Representative:	
Sponsor GCO Representative:	

	[redacted]
Sponsor Safety Reporting:	
Contract Research Organization :	

1.0 INTRODUCTION

1.1 Indication

The proposed indication for the MR-100A-01 Transdermal System (TDS) is the prevention of pregnancy in women of reproductive potential.

1.2 Background and Rationale

Unintended pregnancy is a significant health problem in the United States (US) (Guttmacher Institute, 2019). The rates of unintended pregnancy is significantly higher in the US than in many other developed countries (Singh S et al., 2010). Unintended pregnancies are either those that occurred when a woman wanted to become pregnant in the future but not at the time she became pregnant ("wanted later") or those that occurred when she did not want to become pregnant then or at any time in the future ("unwanted"). In 2011, nearly half (45%, or 2.8 million) of the 6.1 million pregnancies in the US were unintended. Specifically, 27% of all pregnancies were "wanted later" and 18% of pregnancies were "unwanted" (Finer and Zolna, 2016).

Nearly half of all unintended pregnancies are the result of inconsistent or improper use of contraceptives (Frost and Darroch, 2008). Women at risk for unintended pregnancy who use contraceptives consistently and correctly throughout the course of any given year account for only 5% of all unintended pregnancies. While the women at risk who use contraception but do so inconsistently account for 44% of all unintended pregnancies. Therefore, consistent and correct use of contraception is crucial to women's health (Guttmacher Institute, 2011).

The sponsor's Xulane TDS [norelgestromin (NGMN) and ethinyl estradiol (EE) 150/35 mcg/day] was approved by the US Food and Drug Administration (FDA) in April 2014 under Abbreviated New Drug Application (ANDA 200910) as bioequivalent to Ortho Evra® TDS (NDA 021180). A combined hormonal contraceptive (CHC) TDS Evra® (NGMN 6.0 mg & EE 0.6 mg), was approved and available in Canada since 2002 for the prevention of pregnancy Both Evra® and Xulane® TDS are applied weekly for 3 weeks, with 1 patch-free week in each cycle (Evra product monograph 2018).

The sponsor is developing MR-100A-01, a CHC TDS containing a lower estrogen dose than Xulane TDS.

The sponsor's MR-100A-01 is intended to offer the dual advantage of a minimally invasive transdermal contraceptive with a lower dose of estrogen, while providing adequate effectiveness and good safety profile.

The current pivotal study is designed to evaluate the contraceptive efficacy, cycle control, safety, and tolerability of the MR-100A-01 patch to support a 505(b)(2) New Drug Application (NDA) for MR-100A-01.

Complete information for MR-100A-01 may be found in the MR-100A-01 Investigator's Brochure (IB) Version 3.0 dated 18-Feb-2022.

1.3 Investigational Product

The investigational product to be used in this study is MR-100A-01 TDS which contains 4.86 mg of Norelgestromin and 0.264 mg Ethinyl Estradiol. The residual drug analysis studies to accurately determine the actual release rates of NGMN and EE from the MR-100A-01 TDS are being conducted. Preliminary data indicate that MR-100A-01 is expected to deliver EE at approximately [redacted] and norelgestromin at approximately [redacted] The IB will be updated when additional final data becomes available.

MR-100A-01 is a transdermal patch that contains EE as its estrogen component and NGMN as its progestin component. MR-100A-01 has been designed to deliver a reduced daily dose of EE compared to Xulane® (35 mcg/day) while maintaining the same dose of NGMN (Xulane USPI 2022).

2.0 OBJECTIVES AND ENDPOINTS

2.1 Study Population

Adequate number of subjects will be screened so that approximately 1,200 eligible women will be enrolled and treated for up to 13 cycles. Such is expected to provide at least 10,000 evaluable cycles for safety. The study population will be selected such that:

- The proportion of non-white study participants will be at least 30% of the total study population to reflect the general population in US.
- The proportion of women over the age of 35 years will represent approximately 10% of the total study population.
- The proportion of women with higher body mass index (BMI) ($\geq$30 kg/m^2) will be capped to a maximum of 10% of the total study population.

Based on the asumptions above, it is expected that approximately 1,000 enrolled women aged 16 to $\leq$35 years and with BMI <30 kg/m^2 will provide at least 5,000 evaluable cycles (after excluding cycles with back-up contraception and abstinent cycles) for efficacy. [redacted]. At least 200 subjects will complete the study.

2.2 Benefit-Risk Considerations

Potential Benefits and Advantages:

When the development of MR-100A-01 is complete, the benefits of MR-100A-01 are expected to be a reliable contraception with an efficacy and safety profile comparable to low-dose estrogen containing combined contraceptives with added advantages of less frequent administrations than oral contraceptives, and less invasive method compared to injections, implants, and intrauterine devices.

Although combined oral contraceptives (COCs) have been the gold standard in contraception, the use of pills requires a considerable commitment from the patient to realize their full potential for pregnancy prevention. A contraceptive patch may overcome the issue of non-compliance observed with a once-daily contraceptive pill, as well as possibly provide an alternative to women who are unable to take oral medication on an ongoing basis or temporarily because of gastrointestinal upset.

Potential Risks:

Complete information of the investigational medicinal product MR-100A-01 is available in the IB.

The noteworthy risks for an individual study subject are as follows:

Contraceptive failure is possible with all available contraceptive methods. MR-100A-01 is an investigational product, efficacy of which is not yet established. MR-100A-01-TD-3001 is the first study to evaluate the contraceptive effiacy and safety of MR-100A-01.

MR-100A-01 may be less effective in preventing pregnancy in obese women (BMI ≥30 kg/m^2). Clinical studies of CHCs have demonstrated a higher Pearl Index (PI) in a subpopulation of obese women (Yamazaki et al. 2015). Increased failure rate in obese women has been observed to be consistent in all forms of CHCs including the transdermal patch. According to Zieman M et al, effectiveness of Evra® patch might be reduced in women >90 kg (Zieman et al. 2002).

The adverse reactions which are expected with a CHC such as Xulane could be reasonably assumed to be associated with MR-100A-01, and therefore can be considered expected for the purposes of expedited reporting to regulatory authorities and investigators. The risks that are expected with any CHC product include serious cardiovascular events and stroke, vascular events including venous and arterialthromboembolic events, liver disease, impaired liver function, liver tumors, risk of liver enzyme elevations with concomitant hepatitis C treatment, high Blood Pressure (BP), gallbladder disease, carbohydrate and lipid metabolic effects, headache, bleeding irregularities, unscheduled bleeding and spotting, amenorrhea and oligomenorrhea, depression, carcinoma of breasts and cervix, rise in binding globulins, hereditary angioedema, chloasma.

The use of CHCs increases the risk of Venous Thrombo Embolisms (VTEs), such as Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). Risk factors for VTEs include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of CHCs. The risk of VTE may be greater in women with a BMI ≥30 kg/m^2 compared to women with a lower BMI (Xulane USPI 2022; Evra product monograph 2018). Use of CHCs and high BMI are independent risk factors for VTE risk. Many large cohort studies have observed a higher risk for VTE with obese women (BMI ≥30 kg/m^2) (Holst et al. 2010; Parkin et al. 2012; Kabrhel et al. 2009). The likelihood of obese women experiencing VTE is higher among those who use COCs than those who do not use COCs. Although the absolute risk for VTE in otherwise healthy women of reproductive age is small, obese women are at 2-3 times higher risk for VTE than normal weight women regardless of COC use (US Medical Eligibility Criteria for Contraceptive Use, 2016; WHO Medical Eligibility Criteria for Contraceptive Use, 2015).

Since MR-100A-01 has not yet been evaluated in large clinical studies, investigators should carefully monitor for all Adverse Events (AEs), including those not described in the IB and should promptly document and report the AEs as per the protocol.

2.3 Objectives

2.3.1 Primary Objective

To determine the contraceptive efficacy of MR-100A-01 when used over 13 cycles [of 4 weeks (28 days)] in healthy, post-menarcheal, premenopausal, heterosexually active female subjects of childbearing potential who are at least 16 years of age and at risk of pregnancy.

2.3.2 Secondary Objectives

To determine the overall safety and tolerability profile of MR-100A-01 in terms of incidence of AEs, cycle control, and patch adhesion.

2.4 Endpoints

2.4.1 Primary Endpoint

The primary efficacy endpoint will be pregnancy rate described by PI.

PI is defined as the number of pregnancies per 100 women-years and will be calculated as follows:

$$Pearl\ Index = \frac{number\ of\ on\text{-}treatment\ \ pregnancies \times 13}{number\ of\ evaluable\ cycles} \times 100$$

where,

- On-treatment pregnancy is defined as a pregnancy with an estimated date of conception (EDC) between the date of application of the first patch through 7 days after removal of the last patch in the study
- Evaluable cycles are defined as the complete or incomplete 28-day cycles in which vaginal intercourse occurred and in which no back-up contraception was used based on the electronic diary (e-Diary) data, unless a pregnancy occurred in such a cycle.

2.4.2 Secondary Endpoints

Secondary Efficacy Endpoints:

1. Cycle-wise and cumulative pregnancy rates over 1 year evaluated using life table analysis
2. Method failure PI

Secondary Safety Endpoints

a. Adverse Events and Tolerability:

1. Incidence of AEs and serious adverse events (SAEs)
2. Incidence of application site reactions

b. Cycle Control and Patch Adhesion:

1. Number of episodes and days of scheduled and unscheduled bleeding
2. Proportion of subjects reporting scheduled and unscheduled bleeding
3. Adhesion performance as measured by adhesion scores

3.0 STUDY DESIGN

3.1 Overall Design

This study is designed as a multicenter, open-label, single-arm study in healthy, post-menarcheal, premenopausal, heterosexually active women of childbearing potential of at least 16 years of age, who are at risk of pregnancy and are seeking hormonal contraception for at least 12 months (13 cycles).

An adequate number of subjects will be screened so that approximately 1,200 women meeting all study criteria will be enrolled. [redacted] At least 200 subjects will complete the study.

There will be a screening period of 7 to 60 days and a treatment period of approximately 12 months (13 cycles).

Enrolled subjects will use the treatment for up to 13 cycles. The treatment regimen is a 4-week treatment cycle, with one MR-100A-01 patch to be applied every 7 days for 3 consecutive weeks followed by 1 week of a patch-free period. In the event of patch detachment or delayed patch application as described in Sections 5.1.3 and 5.1.4, the 4-week treatment cycle may be shortened.

3.2 Rationale for Study Design

Historically, contraceptives have been approved based on the PI obtained from the open-label single arm studies.

As explained in the FDA draft guidance on Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy, Guidance for Industry dated, July 2019, data from single-arm, open-label, historically controlled trials of at least 1 year's duration are generally sufficient to establish efficacy and safety of hormonal drug products intended to prevent pregnancy. A placebo control is not feasible because subjects in a contraceptive trial do not desire pregnancy.

MR-100A-01-TD-3001 utilizes a standard design for contraceptive effiacy and safety evaluation of multicenter, open-label, single arm study in women of childbearing potential to evaluate the study objective of evaluation of contraceptive effiacy and safety of MR-100A-01 TDS.

The current trial will include non-pregnant, postmenarcheal, premenopausal heterosexually active women of childbearing potential who are at least 16 years of age and at risk of pregnancy. The primary effiacy results will be calculated using the trial population of women younger than or equal to 35 years old at study enrollment, because the likelihood of pregnancy decreases with advancing age. Women with age older than 35 years will be included in the safety determinations. The other study design aspects are generally in line with US FDA feedback on the study design.

4.0 STUDY POPULATION

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Healthy, post-menarcheal and premenopausal women at risk of pregnancy who are at least 16 years of age with no upper age limit. Post-menarcheal female subjects who are at risk of pregnancy, and <18 years are eligible provided that:
   a. Applicable national, state, and local laws allow the subject to consent to sexual intercourse,
   b. Applicable national, state, and local laws allow subjects in this age group to consent/assent to receive contraceptive services, and
   c. All applicable laws and regulations regarding the informed consent/assent of the subjects to participate in clinical trials are observed.
2. Desires to avoid pregnancy, is seeking to use hormonal contraception for at least 1 year, confirms no plans for pregnancy for the trial duration, understands the purpose of the trial and the need to report to investigator whenever she desires to get pregnant.
3. Has negative Urine Pregnancy Test (UPT) results at screening and at enrollment visits.
4. Has normal, regular menstrual cycles that are between 21 and 35 days in duration with an intact uterus and both fallopian tubes and ovaries. If the subject has recently used hormonal birth control, historic data should be used to evaluate this criterion.
5. Engages in regular heterosexual vaginal intercourse (at least once per cycle), with a partner who is not known to be subfertile or infertile.
6. Agrees not to use other contraceptives or other methodology to prevent pregnancy during the study and willing to use study patch as only method of contraception except for use of back-up barrier contraception to prevent sexually transmitted infections or emergency contraception when necessary.
7. Able to understand and voluntarily provide written informed consent or assent (if the subject is adolescent prior to undergoing any trial-related procedure) to participate in the study.
8. Able to understand and willing to be compliant with study procedures such as patch applications, removals, and replacements, timely e-Diary entries, and all study visits as per the Investigator's assessment.
9. Willing to accept a risk of pregnancy.

10. Has demonstrated ability to complete e-Diary (at least 70% compliance) at enrollment visit.
11. Planning to reside within a reasonable driving/ public transport distance of the research site (approximately 150 miles) for around 12 months (13 cycles).

4.1.2 Exclusion Criteria

Subject candidates must not be enrolled in the study if they meet any of the following criteria:

1. Known or suspected pregnancy or planning pregnancy during next 12 months.
2. Subjects with known hypersensitivity or intolerance to estrogens, progestins, or any components of the MR-100A-01 product.
3. History or presence of dermal sensitivity to medicated patches or to topical applications including bandages, surgical tape.
4. Known infertility (current or known history) or history of sterilization in either partner.
5. Received injectable hormonal contraceptive therapy within 10 months of study enrollment or has had less than 2 consecutive, spontaneous menses after an injectable hormonal contraceptive was received at least 10 months earlier.
6. Current use of hormonal contraceptive implants (still implanted; or if an implant was removed, less than 3 consecutive spontaneous menses have occurred between removal and enrollment).
7. Has non-hormonal or hormonal intrauterine device (IUD) in place or has had a recent IUD removal without one spontaneous menses after removal prior to the date of enrollment .
8. Recent surgical or medical abortion, miscarriage, ectopic pregnancy, or vaginal or cesarean delivery and have had less than 3 consecutive, spontaneous menses or withdrawal bleeding episodes prior to enrollment.
9. Subjects lactating at the time of screening into the study or has occurrence of less than 3 regular menstrual cycles after cessation of lactation.
10. Anticipates routine use of condoms or any other form of back-up contraception for protection from sexually transmitted infections during the study or for emergency contraception.
11. Subjects having a known contraindication to combined hormonal contraception as defined by category 3 or 4 conditions per Center for Disease Control and Prevention (CDC) recommendations on US Medical eligibility criteria for contaception use (US Medical Eligibility Criteria for Contraceptive Use, 2016) as listed below:
    a. Smoker who is ≥35 years old, or smoker who will turn 35 years old during the course of the trial (smoking includes cigarettes, cigars, smokeless tobacco, e-cigarettes, hookah, any form of nicotine replacement therapy).
    b. History or presence of ischemic heart disease, coronary artery disease, myocardial infarction, stroke, other cerebrovascular diseases including transient ischemic attacks (TIAs), valvular heart disease with complications (pulmonary hypertension, risk for

atrial fibrillation, or history of subacute bacterial endocarditis), peripartum cardiomyopathy.

c. History or presence of hypertension (including adequately controlled hypertension) or hypertension with vascular disease or elevated blood pressure (BP) defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, measured in sitting position after 5 minutes of rest, considering the average of two readings measured 1 to 2 minutes apart.

d. History or presence of DVT/PE or superficial venous thrombosis.

e. Has any comorbid condition that may require major surgery with prolonged immobilization during the study period.

f. Subjects with known inherited or acquired hypercoagulopathy including thrombogenic mutations (e.g., antiphospholipid syndrome, factor V Leiden; prothrombin mutation; protein S, protein C, and antithrombin deficiencies).

g. History or presence of systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies.

h. History or presence of neurological conditions including migraine with aura at any age, migraine without aura in women ≥35 years age or in women who smoke, or multiple sclerosis with prolonged immobility.

i. History or presence of or suspected carcinoma of breast.

j. Has diabetes mellitus with nephropathy, retinopathy, neuropathy, or other vascular disease or diabetes of >20 years' duration.

k. Has inflammatory bowel disease (ulcerative colitis or Crohn's disease) who are at increased risk for VTE (those with active or extensive disease, surgery, immobilization, systemic corticosteroid use, vitamin deficiencies, or fluid depletion) based on Investigator's discretion.

l. Medically treated or presence of symptomatic gall bladder disease.

m. History of CHC/pregnancy related cholestasis/jaundice.

n. Presence of liver disease including acute or flare of viral hepatitis, severe (decompensated) cirrhosis, benign (e.g, hepatocellular adenoma) or malignant liver tumors.

o. History of organ transplantation within 5 years before screening or chronic disease potentially necessitating organ transplantation during the anticipated course of the study.

p. Subject has requirement to be on treatment with medications prohibited during study (see section on prohibited medications 7.9).

12. Known or suspected estrogen or progestin sensitive malignant or premalignant conditions including but not limited to carcinoma of endometrium, ovary or fallopian tubes.

13. History of any other condition that in the Investigator's opinion suggests an elevated risk of arterial or venous thromboembolic disease (e.g., any active malignancy except non-

melanoma skin cancers, subacute bacterial endocarditis with valvular disease, atrial fibrillation).

14. Has uncontrolled thyroid disorder.
15. Has diagnosis of hereditary angioedema.
16. Has hyperlipidemia on screening (fasting cholesterol level >260 mg/dL; fasting triglyceride level >300 mg/dL).
17. Has uncontrolled diabetes mellitus as defined by Hemoglobin A1C (HbA1C) value of >7% at screening.
18. Subjects with abnormal significant liver function tests as measured by liver function tests; alanine aminotransferase (ALT) >3.0 times the upper limit of normal (ULN) or alkaline phosphatase >2.5 times ULN or aspartate aminotransferase (AST) >3.0 times ULN or blood bilirubin >1.5 times ULN.
19. Has a significantly abnormal cervical cancer screening test (cervical cytology with reflex human-papilloma-virus (HPV) testing or with HPV co-testing) performed at screening visit (for subjects aged ≥21 years) i.e., cervical dysplasia or invasive cervical cancer or has any abnormal cytology with/without HPV testing during 6 months prior to screening which may require additional screening or treatment during the study period per American Society of Colposcopy and Cervical Pathology (ASCCP) Screening Guidelines 2019 (Perkins RB, ASCCP, 2019). Specifically the following are exclusionary:
    - Papanicolaou test (Pap test) with atypical squamous cells of undetermined significance (ASC-US), *unless*:
        - reflex HPV testing was performed and was negative for high risk oncogene HPV. Or
        - reflex HPV testing was performed and was positive for high risk oncogene HPV:
            - Subject is 21 to 24 years of age and will have repeat cytology in 12 months; at the investigator's discretion she may be included.
            - Subject is >24 years of age and has an adequate colposcopy and there are no lesions; at the investigator's discretion she may be included.
    - Pap test with Low-Grade Squamous Intraepithelial Lesion (LSIL)
    - Pap test with Atypical Squamous Cells - High (ASC-H), atypical glandular cells, high-grade intraepithelial lesion (HSIL) or malignant cells.
20. Subjects with chlamydial or gonorrheal infection at screening (subjects who screen fail due to positive results may be re-screened and enrolled in the study after standard medical treatment).
21. Has unexplained vaginal bleeding within the past 6 months or any abnormal bleeding which is expected to recur during the study (eg. bleeding from cervical polyp, recurrent bleeding after sex).

22. History of known or suspected hepatitis B or C infection or high risk for sexually transmitted disease (STD).
23. Known human immunodeficiency virus (HIV) infection or positive, confirmatory test at screening.
24. Current known active infection of coronavirus disease 2019 (COVID-19), or subjects with an increased risk of serious COVID-19 related morbidity as determined by the investigator at the time of screening and/or enrollment; subjects who have had previous COVID-19 infections but have recovered by the time of enrollment visit may be enrolled if there are no current COVID-19 symptoms as determined by the investigator; subjects who had previously received COVID-19 vaccine may be enrolled irrespective of the timing of vaccinationation. (Additional COVID-19 screening procedures that may be mandated by the study site do not need to be reported as protocol deviations).
25. Within the past year, either history of suicidal ideation or attempt or severe depression requiring hospitalization.
26. Presence of any other concomitant disease or laboratory result that may worsen under hormonal treatment based on Investigator's discretion.
27. Positive urine drug screen for cocaine, methamphetamine, opiates, or phencyclidine unless there is a documented prescription with supporting medical history and diagnosis.
28. Recent history (within prior 12 months) of drug or alcohol abuse or at Investigator discretion, history greater than 12 months prior and at risk for noncompliance. Current or recent history of (recreational or medicinal) marijuana use is not exclusionary at the investigator's discretion upon assessment of any potential risk.
29. Participation in an investigational, study within 30 days prior to enrollment or intention to participate within next 13 months.

4.1.3 Randomization Criteria

Not applicable as this is a single-arm study.

4.1.4 Criteria for Study Drug Termination, Withdrawal from the Study and Study Termination

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the clinical study site.

Every effort should be made to retain subjects in the study. When available, a reason for not completing the study will be recorded in the electronic case report form (e-CRF).

A subject may be required to terminate study drug for reasons including, but not limited to the following:

- The subject withdraws consent.

- Significant protocol deviations including violation of inclusion or exclusion criteria discovered during the study, if at the Investigator's discretion poses a safety risk to the subject upon continued participation in the study
- At Investigator's discretion, if it is in the subject's best interest due to occurrence of an AE or other finding considered to present a safety concern to continued dosing with study drug
- Persistent inadequate compliance potentially causing increased risk of non-compliance related pregnancy or inadequate safety monitoring based on Investigator's discretion (Investigator should document the rationale adequately). The non-compliance may be related to study medication, e-Diary, visits, or study procedures. Investigator is recommended to discuss such discontinuations with medical monitor.
- Subject becomes pregnant
- Subject expresses a desire to become pregnant
- Subject was lost to follow-up
- Sponsor's decision to terminate the study
- The subject takes prohibited treatment presenting a safety concern to continued dosing with study drug or impacting the efficacy of the study patch leading to increased risk of pregnancy.

The study will be terminated early if there are significant safety concerns and the IRB will be notified.

At the investigator's discretion, the study patch use can be temporarily stopped at least 4 weeks before and through 2 weeks after major surgery or any other surgeries known to have an elevated risk of VTE. Also, during periods of prolonged immobilization, the study patch can be temporarily discontinued and resumed based on clinical judgment. Investigator can also decide to terminate such subjects and manage their safety and contraception needs outside the study.

Subjects who prematurely terminate study will have to complete an Early Termination (ET) visit. Whenever possible, it is recommended that the ET visit be scheduled at 14 (+5) days after the removal of the last study patch. However, this can be performed earlier based on the subject's convenience in visiting the site and/or at the investigator's clinical decision.

4.2 Replacement Policy

Subjects who are withdrawn from the study will not be replaced.

4.3 Lifestyle Guidelines

Participants should maintain their normal daily activities like bathing, swimming, and exercising while wearing the patch, but they are instructed not to apply oils, creams, or cosmetics on or around the area of patch placement.

5.0 STUDY DRUG

5.1 Investigational Drug

MR-100A-01 is a 14 cm² square TDS with rounded corners consisting of a tan-colored backing film printed in brown ink with "Norelgestromin / Ethinyl Estradiol XXXXXXXXXX", an adhesive layer [redacted] removable release liner. Each individual TDS is placed between two pieces of protective film and packaged in a sealed pouch which is imprinted with lot number and manufacturing date. The pouches and cartons will be labelled with a clinical trial label in accordance with local regulations. Each TDS contains two active pharmaceutical ingredients norelgestromin (NGMN) and ethinyl estradiol (EE) [redacted]

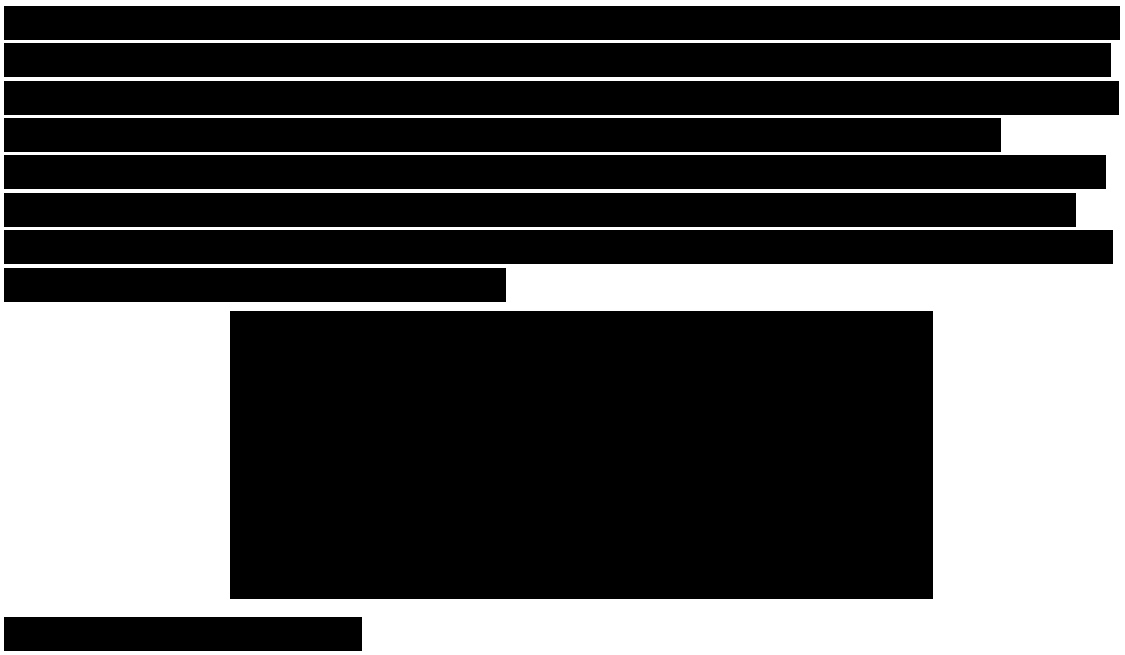

Figure 2: Schematic Diagram of Sponsor's Norelgestromin 4.86 mg and Ethinyl Estradiol 0.264 mg Transdermal System

5.1.1 Patch Application Guidelines

CHOOSING A PLACE ON THE BODY TO PUT THE PATCH:

The patch may be placed on the upper outer arm, abdomen, buttock or back, in a place where it won't be rubbed by tight clothing. For example, it should not be placed under the waistband of clothing.

- The patch should not be placed on the breasts, on cut or irritated skin or on the same location as the previous patch.

BEFORE APPLYING THE PATCH:

- The woman should make sure the skin is clean and dry.
- She should not use lotions, creams, oils, powders, or make-up at the patch site. It may cause the patch to fail to stick properly or to become loose.

HOW TO APPLY THE PATCH

- Tear open the pouch at the top edge **and** one side edge. Peel open the foil pouch. Gently remove the contents of the foil pouch and discard the additional pieces of film above and below the MR-100A-01 patch.
- Peel away one piece of the clear plastic and discard such. The woman should avoid touching the sticky surface with fingers.
- Apply the sticky side of the MR-100A-01 patch to clean, dry skin. Remove the other piece of the clear plastic. Apply the entire patch to the skin. Discard the clear plastic film.
- Press firmly on the MR-100A-01 patch with the palm of your hand for 10 seconds, making sure that the whole patch sticks to the skin.
- Run fingers over the entire surface area to smooth out any "wrinkles" around the outer edges of the MR-100A-01 patch.
- The woman should check her patch every day to make sure all edges are sticking correctly.

In the event of any significant dosing errors, the Medical Monitor, or Sponsor's study contact should be contacted immediately.

5.1.2 Patch Application – Initiation and Schedule

Initiation:

Study patches will be dispensed at the enrollment visit (Day -14 to Day -1 before the start of next cycle).

Scenario 1: For subjects who are not current users of hormonal contraception (oral pill, transdermal patch or vaginal ring):

Subjects will be instructed to apply the first transdermal patch within 24 hours of the start of the next menstrual bleeding. Subjects will be trained on the method of patch application using a demonstration patch which has no active ingredients.

Scenario 2: For subjects who are current users of hormonal contraception (oral pill, transdermal patch or vaginal ring):

The first transdermal patch can be applied at the site on the day of enrollment visit or later at home (requires training by demonstration patch):

a. At any day* during the active regimen-taking interval OR
b. On the day after the last hormone-containing pill/day after patch or ring removal OR

c. Within 24 hours of onset of withdrawal bleeding following an active cycle (if there is no withdrawal bleed, then within 4 days of last active drug)

* Subject should be instructed to discontinue former hormonal contraceptive method before application of first study patch.

Note: If the patch was applied at the site on the day of enrollment visit, this will be the Cycle 1 Day 1 for the subject.

In all cases, the date of first study patch application should be accurately recorded by the Investigator along with scenario applicable for the subject.

Schedule:

The treatment regimen is a 4-week treatment cycle, with one MR-100A-01 patch to be applied every 7 days for 3 consecutive weeks followed by 1 week of a patch-free period. In every 4-week treatment cycle, weeks 1, 2 and 3 will be ***patch-on weeks*** and week 4 will be a ***patch-free week***.

Table 2: Patch Application Schedule

Week	Cycles 1 – 13		Patch Application Schedule
Week 1	Day 1	Patch on	New patch should be applied
Week 2	Day 8	Patch change	Previous patch should be removed and a new patch should be applied
Week 3	Day 15	Patch change	Previous patch should be removed and a new patch should be applied
Week 4	Day 22	Patch removal	Previous patch should be removed (Days 22-28 will be patch-free)

5.1.3 Patch Replacement Guidelines

Subjects will be provided with reserve patches to be used in cases where unscheduled patch replacement will be required.

Whenever the patch edge lifts up, the subject should press down firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. She should run her fingers over the entire surface area to smooth out any “wrinkles” around the edges of the patch. If the patch does not stick completely, she should remove it and apply a replacement patch. She should not tape or wrap the patch to her skin or reapply a patch that is partially adhered to clothing. The woman should not try to reapply a patch if it is no longer sticky, if it has become stuck to itself or another surface, or if it has other material stuck to it.

Whenever a partial (more than half of the patch lifts off the skin, but undetached) or complete patch detachment is noticed within 24 hours of the detachment, the subject should try to immediately reapply the patch. If the patch does not adhere completely, the subject will be

instructed to apply a new replacement patch immediately, to be worn for the remainder of that week. The patch change day will remain same and no back-up contraception is required in this case.

However, when a partial (more than half of the patch lifts off the skin, but undetached) or complete patch detachment was noticed at 24 hours or later, or if the subject was not sure how long the patch had been detached, subjects should start a new 4-week cycle immediately by applying a new patch. Back-up contraception with condom and spermicide or diaphragm and spermicide should be used for 7 days in addition. The date of new patch application will become a new patch change day for the woman.

Any possible reasons or risk factors for detachment should be noted in the e-Diary in case of complete detachment.

5.1.4 Procedures for Delayed/Missed Patch Application/Change/Removal

At start of patch cycle - Week 1/Day 1 (Cycle 1):

- If the scheduled first patch application was planned at home AND if the subject did not apply the patch within 24 hours of menstruation (for naive users) or during the planned Cycle 1 Day 1 date (current hormonal contraception users) recommended by the investigator, she should not apply the first study patch whenever she remembers. The subject should immediately contact the site and discuss with the investigator for the next possible date for initiation of study patch. This may require re-scheduling the first patch application to the next menstrual cycle or may necessitate withdrawal of subject from study if the screening period extends beyond 60 days or for any other reason as per investigator's discretion.
- If subject is a naive user of hormonal contraception, during the time until application of the first study patch, she MUST use back-up methods of contraception to prevent pregnancy.
- If subject is a current user of any hormonal contraceptive, subject must continue using the current hormonal contraceptive for the current cycle or until the day before the study patch will be initated as per the Investigator's advice. It is also highly recommended that subjects use additional back-up methods of contraception during times of sexual activity during this period.

At start of patch cycle Week 1/Day 1 (Cycles 2 through 13):

- If the woman forgets to apply her patch during the Day 1 of week 1, she may not be protected from pregnancy. She should apply the first patch of her new cycle as soon as she remembers. There is now a new "Patch Change Day" and a new "Day 1." The woman must use back-up contraception, such as a condom and spermicide or diaphragm and spermicide, for the first week of the new cycle.

At middle of the patch cycle - Week 2/Day 8 (<u>All Cycles</u>):

- If the woman forgets to change her patch for 1 or 2 days (up to 48 hours), she should apply a new patch immediately. The next patch change should happen on the usual "Patch Change Day." No back-up contraception is needed.
- If the woman forgets to change her patch for more than 2 days (48 hours or more), SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new 4-week cycle immediately by putting on a new patch. There is now a new "Patch Change Day" and a new "Day 1." The woman must use back-up contraception for 1 week.

At middle of the patch cycle - Week 3/Day 15 (<u>All Cycles</u>):

- If the woman forgets to change her patch for 1 or 2 days (up to 48 hours), she should apply a new patch immediately. Subsequently, the scheduled patch removal should be performed on the usual "Patch removal Day." No back-up contraception is needed.
- If the woman forgets to change her patch for more than 2 days (48 hours or more), SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new 4-week cycle immediately by putting on a new patch. There is now a new "Patch Change Day" and a new "Day 1." The woman must use back-up contraception for 1 week.

At the end of the patch cycle - Week 4/Day 22 (<u>Cycles 1 through 12</u>):

- If the woman forgets to remove her patch, she should take it off as soon as she remembers. The next cycle should be started on the usual "Patch on Day," which is the day after Day 28. No back-up contraception is needed.

At the end of the patch cycle - Week 4/Day 22 (<u>Cycle 13</u>):

- If the woman forgets to remove her patch, she should take it off as soon as she remembers. After the patch-free week of cycle 13, irrespective of the post-trial contraception planned/used, subject must use back-up methods of contraception until completion of End of Study (EOS) visit.

5.2 Drug Inventory

Sponsor will supply the study drug. The study drug must be kept in appropriate conditions in a locked and secure place at the clinical study site. The individual containers will be labeled.

One study medication kit for each 28 day cycle will be supplied. Each study medication kit will include 3 foil pouches each containing one MR-100A-01 patch.

Each subject will be supplied with a replacement medication kit. Each replacement medication kit will contain 4 foil pouches each containing one MR-100A-01 patch. These patches can be used in case the patch placed loses proper adherence prior to completion of the week's dosing.

5.3 Study Medication Complaints

In the event the subject has a complaint/concern during study participation regarding the supplied study medication, they should contact the site.

In the event of a complaint/concern regarding any study medication provided by Sponsor for this study, as a minimum the following information should be sent by the site via e-mail to MGRG.study.medication.complaints@Viatris.com.

- Study number
- Principal Investigator name
- Subject ID
- Date of occurrence of incident/complaint
- Description of incident/complaint (facts)
- Confirmation if the complaint caused or resulted in a SAE? If "Yes", confirmation that the SAE has been reported

Additional information and potentially the return of study medication may be requested by Sponsor in order to investigate the complaint.

5.4 Storage, Disposition of Unused Study Drug and Drug Accountability

The Investigator, or an authorized designee, e.g., pharmacist, will ensure that all investigational products are stored in a secured area under recommended storage conditions and in accordance with applicable regulatory requirements while at the investigator site.

Study drug should be stored in accordance with the drug label.

Temperature of storage facilities should be monitored and recorded on a daily basis using validated devices that record maximum and minimum temperatures. Should the storage facility experience any excursion of temperature outside of the labelled storage condition this must be reported immediately to the Sponsor or designee. At sites where daily monitoring and recording is not possible at weekends, then on the next working day after the weekend the temperature (e.g. max/min) should be checked immediately for any temperature excursions. Devices used for temperature monitoring should be regularly calibrated. Affected material must be placed into quarantine until the impact of the excursion has been assessed and confirmed by the Sponsor.

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the study drug. If the Sponsor supplies drug accountability forms, these must be used. Alternatively, the Sponsor or designee may approve use of standard institution forms. In either case, the forms must identify the study drug, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to the Sponsor or designee.

At the end of the study, the Sponsor will provide instructions for disposition of any unused investigational product. If the Sponsor authorizes destruction at the study site, the investigator

must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor. Destruction must be adequately documented.

5.5 IWRS System

Assignment of Subject Identification number (SID), study medication, as well as site drug inventory control will be managed by an automated Interactive Web Response system (IWRS). A manual containing complete instructions for Web access and use will be provided to each site prior to study start. At their first clinic visit, the IWRS will assign a SID. Each SID will be unique and serve as the primary subject identifier throughout the study. The SID must appear on all CRF pages, source documents, laboratory data, and e-Diary data.

The IWRS will be set-up such that

- The proportion of non-white study participants will be at least 30% of the total study population to reflect the general population in the US
- The proportion of women over the age of 35 years will represent approximately 10% of the total study population
- The proportion of women with higher BMI ($\geq$30 kg/m^2) will be capped to a maximum of 10% of the total study population

Subjects will be permitted for enrollment as allowed by the given allocation ratio.

5.6 Breaking the Blind

As this is a open label study with a single treatment arm, the breaking of blind is not applicable.

5.7 Rescue Medication

Not applicable.

5.8 Concomitant Medications

All concomitant medications taken during the study (from signing informed consent/assent to post-study follow-up) must be recorded with indication, dose, and start and stop dates of administration in the CRF. All subjects will be questioned about concomitant medication at each visit.

Medications taken prior to first application of study medication will be documented as a prior medication. It is recommended that all medications which are taken 1 month prior to screening are documented. Any other important prior medications even if taken before one month prior to screening should be recorded if considered relevant to the study population or the study treatment as determined by the Investigator. COVID-19 vaccines, initial and boosters, for the past year before consent and during the study period, should be recorded in the e-CRF including dates of vaccination and manufacturer.

All previous contraceptive history should be recorded with full details for the year prior to enrollment. Any prior important medications relevant to the indication or the study treatment (e.g., depot contraceptive injection, contraceptive implant) are recommended to be recorded. If relevant, history more than one year also need to be recorded.

Medications taken after first application of study medication will be documented as concomitant medications.

Subjects will abstain from all prohibited medications as described in the exclusion criteria section of this protocol (also see protocol section on Prohibited Therapy During the Study). Use of prohibited medication during the study will be deemed a protocol deviation and such subjects will be assessed by Sponsor or designee regarding potential need for early termination of study drug (for safety reasons – see section 'Criteria for Study Drug Termination, Withdrawal from the Study and Study Termination').

5.9 Recommended Procedure in a Subject Experiencing Adverse Effects Secondary to Excessive Pharmacological Effects of Study Drug

Overdosage may cause nausea and vomiting, and withdrawal bleeding may occur in females. In case of suspected overdose, all patches should be removed and symptomatic treatment given and the sponsor should be contacted.

5.10 Treatment Compliance

The investigator will ensure the drug accountability by maintaining drug dispensing log, IWRS, and e-Diary for each study participant. Treatment compliance will be assessed by the investigator / designee by reviewing the e-Diary.

Due to risks of pregnancy related to non-compliance, subject should be considered for discontinuation due to non-compliance, unless a specific reason is given by the subject that can be corrected in the next cycle as per investigator's discretion.

Investigators may consider subject discontinuation for the following reasons and should contact the medical monitor to discuss the specific case prior to withdrawal of the subject.

- Non-compliance related to sexual activity: Subjects with 2 consecutive cycles with no sexual activity OR with 2 consecutive cycles with use of back-up contraception. The Investigator should discuss the specific circumstances leading to these events with the subject and medical monitor.
- Non-compliance to e-Diary entry: Subjects with repeated failure to enter diary data related to assessments of study drug compliance, sexual activity, and use of back up contraception. The Investigator should discuss the specific circumstances leading to these events with the subject and medical monitor.

6.0 STUDY CONDUCT

This study is designed as a multicenter, open-label, single arm study in healthy, post-menarcheal, premenopausal, heterosexually active women of childbearing potential of at least 16 years of age, who are at risk of pregnancy and are seeking hormonal contraception for at least 12 months (13 cycles).

The study is planned to be conducted in clinical sites (approximately 75) in USA, including Puerto Rico, and Canada. Adequate number of subjects will be screened so that approximately 1,200 women meeting all study criteria will be enrolled.

Subjects eligible for study recruitment will have the nature, purpose, and risks of the study explained to them/guardian (as applicable) by the investigator. They will be provided with a written copy of the informed consent form (ICF)/assent for participating in the study. Subjects will be given sufficient time to consider the study's implications before deciding to participate in the study. Subjects agreeing to participate in the study will sign the ICF/assent and be given a duplicate copy before undergoing any screening or pre-screening (if required) procedures. A unique SID will be issued at the time of consent/assent by IWRS system.

Once a subject enrolls in this trial, the site will make every effort to retain the subject for the planned duration of the trial. Clinical trial site staff are responsible for developing and implementing support and retention plans. Elements of this plan may include the following.

- To ensure that the subjects are adequately educated regarding their responsibilities during the trial:
    - A detailed subject teaching plan with appropriate materials will be developed and implemented.
    - All subjects will be educated regarding the importance of compliance at repeated intervals throughout the study.
- Thorough explanation of the complete clinical trial visit schedule and procedural requirements during the informed consent/assent process and re-emphasis at each clinic visit.
- A simple explanation of the key data and key time points that are critical for the trial's successful analysis, and the importance of the study treatment to the overall success of the trial.
- Discussion at screening, and subsequent regular review of possible barriers to clinic visit attendance and full study participation and compliance.
- Collection of contact information at screening (address, phone numbers, email), which is regularly reviewed at subsequent clinic and telephone visits. The clinic staff may also use publicly available information to assist in locating a subject.
- Use of appropriate and timely study visit reminders.

- Immediate and multifaceted follow-up on missed clinic visits, including the possible use of trained staff to complete in-person contact with subjects.

In cases where a subject misses a scheduled visit (both telephonic and clinic visits), attempts to reschedule the visit should be made within one day. The rescheduled visit should be targeted within the appropriate cycle. In a shortened cycle, the visit should be conducted as soon as possible during the next cycle before removal of the last patch (up to Day 21). After waiting one business day for the subject to respond, site should make additional attempt(s) to contact the subject.

If the subject is not reached within 2 more business days, then a certified letter should be sent to the subject‘s address requesting subject to contact the site to schedule a visit.

If the subject fails to respond within 3 - 4 business days after expected receipt of the certified letter, a second certified letter should be sent. This second letter should request contact for return to the clinic. It should also note that if the subject is choosing to withdraw from the study, it is still requested for her to return the remainder of the study supplies. If still there is no response within 24 hours after receipt of the second letter, she will be considered lost to follow-up. The last date of contact with the subject will be recorded as the date of discontinuation. The certified letter receipt will be filed with the Investigator’s copy of the subject’s source document. If the subject re-contacts the clinical site prior to being discontinued, and extenuating circumstances exist, the subject may be allowed to continue in the study with medical monitor approval.

All contact attempts should be documented in the subject's study record.

For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the CRF. Regardless of site plans to support and retain subjects within the trial, subjects may voluntarily withdraw from the trial for any reason and at any time.

For a subject that completes the study and all procedures it is anticipated that the duration of study would be ~15 months.

For details and timings of assessments, refer to Section ‘Treatment procedures and assessment criteria’.

6.1 Screening Procedures

Each prospective subject must agree to participate in screening procedures by signing the most recent, IRB approved ICF/assent before any study related procedure is initiated. The Principal Investigator or Medical Sub-Investigator will review the inclusion and exclusion criteria to confirm eligibility of each subject prior to enrollment.

For all post-menarcheal adolescent subjects (age <18 years), the Principal Investigator should discuss eligibility with the medical monitor prior to enrollment.

The study will have a screening period of 7 to 60 days and a treatment period of ~12 months (13 cycles). If the screening period exceeds 60 days as a result of unexpected delays, then the subject’s status will need to be discussed with the Sponsor or designee to consider the

subject's potential for re-screening (if re-screening is agreed upon, the subject will need to be re-consented and assigned a new unique SID via IWRS). Re-screening for other reasons may be possible following discussion with the Medical Monitor. If re-screening occurs, it will be clearly documented within the site file.

6.1.1 Screening Visit

Subjects will commence screening procedures within 7-60 days prior to enrollment, to confirm that they meet the selection criteria for the study. All screening assessments should be performed during the screening period. Screening can happen on multiple days across this period.

Assessments: Each subject and their guardian (if applicable) will be informed about the requirements for the participation in the study including the compliance requirements, UPTs at home, prohibited medication, and the requirement to complete an e-Diary in real time with all necessary information. Demographic data including date of birth, age, race, ethnicity, educational status, height, body weight, BMI, alcohol abuse, smoking, & drugs of abuse history and a general medical, contraceptive, obstetric & gynecological history including menstrual and medication history will be documented. Safety laboratory parameters including hematology, chemistry and urinalysis will be assessed at screening as per the study schedule.

e-Diary training: Since the study will utilize an e-Diary, all eligible subjects will be trained to use the e-Diary. The e-Diary will be used to capture data including the use of back-up and/or emergency contraception, sexual activity, vaginal bleeding/spotting (both scheduled & unscheduled), severity of bleeding episodes, patch use information including anatomical sites of application, patch adhesion data, local tolerability, reason for early removal & unscheduled replacement (if any), patch exposure to water, any possible reasons or risk factors for detachment and possible application site reactions.

Subjects should be able to complete the e-Diary to be eligible for enrollment. For this purpose, during screening visit, an e-Diary application will be installed onto the subject's device (mobile or tablet). If subject does not have a device, it may be possible for the sponsor to provide a device to only be used for this study and that will be returned at study completion. Subjects will be asked to enter data on sexual activity, contraception use and vaginal bleeding/spotting during the screening period and for at least 7 days. The screening period should be at least for 7 days before enrollment visit.

Subjects who are not using any hormonal contraception MUST use barrier methods of contraception during the screening period up to first patch placement.

Subjects who are current users of hormonal contraception including combined hormonal contraceptives including oral pills, patches, and rings will continue to use the same method during the screening period. It is highly recommended that all women even if they are current users of hormonal contraception use barrier methods of contraception during the screening period up to first patch placement.

For all subjects for use during screening period and up to first patch placed, condoms and spermicide will be provided at the screening visit. However, subjects may use independently

procured back-up methods of contraception of their choice, either condom and spermicide or diaphragm and spermicide. The use of contraception should be documented as concomitant medication in the source note as well as in e-CRF.

At Screening Visit , the following will be completed:

- Obtain signed informed consent (or assent as applicable) from subject (or guardian as applicable). Subject (guardian as applicable) will receive a copy of the informed consent form/assent.
- Review and document inclusion/ exclusion criteria
- IWRS registration with allocation of SID.
- Record demographic information
- Record contact information
- Obtain medical, surgical and medication history. Risk of VTE should also be reviewed
- Obtain gynecological, obstetric, menstrual & contraceptive use history
- Obtain alcohol abuse, smoking & drugs of abuse history
- Perform a targeted general physical examination including a gynecological examination
- Measure height, weight and calculate BMI
- Measure vital signs (Blood pressure (BP), Respiratory rate (RR), pulse rate (PR) and temperature)
- Collect blood and urine samples for laboratory investigations (hematology, chemistry and urinalysis); samples should be collected at a fasting state for chemistry
    - Note: Include samples for HIV testing and HbA1C
- Urine drug screen testing
- Obtain sample for Chlamydia trachomatis and Neisseria gonorrhea
- Obtain sample for cervical cancer screening for applicable subjects
    - Cervical cancer screening will be performed for subjects ≥21 years of age and if results from previous exams within 6 months of screening are not available
        - For women aged 21 to 29 years, pap test will be performed, pap test may be followed by reflex HPV if needed
        - For ≥30 years, HPV and cytology will be performed
        - For all subjects, cervical cancer screen test results are acceptable from previous testing if they are available from testing within last 6 months of screening
- Perform UPT

  Note: If subject has a positive UPT at screening, subject will be screen failed; such pregnancy would be designated as a pre-treatment pregnancy and will not be reviewed by Pregnancy Review Committee (PRC)
- Dispense run-in e-Diary with subject training
- Dispense condoms and spermicide for contraception during screening period
- Record AEs
- Review intention to plan for pregnancy
- Schedule the next study visit for eligible subjects such that it is within 14 days before the start of the next menstrual cycle.

6.2 Treatment Phase

6.2.1 Enrollment Visit

Subjects will visit the clinic for the enrollment visit during the period within 14 days before the expected start date of the next cycle.

At this visit, UPT and Serum Pregnancy Test (SPT) will be performed and subjects' e-Diary data will be reviewed and assessed for e-Diary compliance. Subjects who continue to meet all inclusion and no exclusion criteria and who have a negative UPT with a minimum of 70% e-Diary compliance will be enrolled into the study. If the screening period exceeds 28 days, the screening e-Diary compliance will be estimated based on the data entries either in the e-Diary for the entire screening period or initial 28 days from the date of activation of screening e-Diary (specifically if the compliance is less than 70% for a screening period that is longer than 28 days, then the compliance for the first 28 days can be calculated; if this meets the 70% threshold, then the criterion has been met). Serum pregnancy test results may be available later. However, the subject will continue to fill the screening e-Diary untill the first patch placement. SPT results should be reviewed immediately when available. If the enrollment visit SPT is positive, the subject should be immediately contacted to stop/remove the patch application as applicable, be discontinued from the study, and instructed to seek immediate medical help and counselling on pregnancy continuation.

Following procedures will be completed at this visit:

- Review and document inclusion/ exclusion criteria and confirm continued eligibility
- Review gynecological, obstetric, menstrual & contraceptive use history during the screening period
- Review intention to plan for pregnancy
- Measure height*, weight and calculate BMI
    - *Note: Height measurement only for adolescent subjects (i.e. < 18 years of age)
- Measure vital signs (BP, RR, PR, temperature)
- Perform UPT

  Note: If subject has a positive UPT at enrollment, subject will be screen failed; such pregnancy would be designated as a pre-treatment pregnancy and will not be reviewed by PRC
- Collect sample for SPT

  Note: SPT results may only be available later. Subjects with positive SPT results should be discontinued; such pregnancy would be designated as a pre-treatment pregnancy and will not be reviewed by PRC
- Review run-in e-Diary and record compliance

  Note: Subjects must demonstrate at least 70% compliance to be eligible for enrollment; If the screening period exceeds 28 days, the screening e-Diary compliance will be estimated based on the data entries either in the e-Diary for the the entire screening period or intial 28 days from the date of activation of screening e-Diary (specifically if the compliance is less than 70% for a screening period that is longer than 28 days, then the compliance for the first

28 days can be calculated; if this meets the 70% threshold, then the criterion has been met).

- Enroll eligible subjects
- Dispense Study Patches (including reserve patches) with instructions

  Note: Subjects should be adequately trained on all patch use instructions; a demonstration patch should be used to train the subject if subject is going to apply the first patch at home later (demonstration patch is for use only in the clinic and should be removed prior to the subject leaving the clinic visit).
- First patch application at site for applicable subjects

  Note: If the first study patch is applied at the site, this will be the Cycle 1 Day 1 for the subject.
- Dispense study e-Diary with subject training and instructions
- Dispense home urine pregnancy kits with instructions

  Note: If subject is going to apply first study patch at home, subject must first perform an UPT, and ONLY if it is negative, she can go ahead and apply the study patch. If the subject has a positive UPT, she will be withdrawn from the study; such pregnancy would be designated as a pre-treatment pregnancy and will not be reviewed by PRC.

  If the subject applies her first patch later than 7 days after enrollment visit, the subject should contact the site immediately after application of her first patch to schedule a visit to peform a SPT within 7 days from the first patch application.
- Record AEs
- Review contact information
- Schedule next Visit

6.3 Clinic Visits (Cycle 2, Cycle 5, Cycle 8, and Cycle 12)

Clinic visits post enrollment will be performed during Day 1 through Day 15 of Cycle 2, Cycle 5, Cycle 8, and Cycle 12. In unforeseen circumstances where a cycle was ended early before the scheduled visit (shortened cycle) and a new cycle was started with a new Day 1, the Investigator should recalculate the subsequent visit schedule according to the new Day 1.

The following procedures will be completed during these visits.

- Confirm and validate current cycle with e-Diary entry
- Confirm and validate Day 1 of the current cycle with e-Diary entry
- Measure height*, weight and calculate BMI at Cycle 8 visit

  *height only for adolescent subjects (i.e. < 18 years of age)
- Measure vital signs (BP, RR, PR, temperature)
- Perform UPT
- Pregnancy determination

  Note: Pregnancy determination only if UPT is positive or indeterminate; SPT and pelvic examination will be performed at the earliest possible time, preferably on the same day whenever a UPT result is positive or indeterminate. In case of the positive UPT, transvaginal ultrasound will be performed as early as possible, preferably the same day; it is highly recommended that an early transvaginal ultrasound examination is performed

on the same day when UPT is positive (serial quantitative SPTs and transvaginal ultrasound examinations may be needed to determine the date of conception)

- Review and record concomitant medication
- Dispense Study Patches (including reserve patches as required) with instructions
- Dispense home urine pregnancy kits based on availabity with the subject
- Review compliance (including e-Diary use, patch use, back-up contraception, sexual activity) and re-training of subject as necessary and documentation of patch use information in source.
- Investigator's/sub-investigator's evaluation of patch application site
- Investigator's/sub-investigator's evaluation of patch adhesion.
    - Note: Patch adhesion should not be evaluated if the subject is not wearing the patch during clinic visit.
- Record AEs
- Review intention to plan for pregnancy
- Review contact information

At Cycle 12 visit:

- The investigator should discuss and counsel regarding the contraceptive options available after the treamtent completion.
- Subjects should be instructed to use barrier contraceptives after the patch-free week of cycle 13 through the end of study visit irrespective of planned methods or actual start of any contraception including any CHCs
- Dispense condoms and spermicide based on availability with the subject to be used after patch-free week of cycle 13

6.4 Telephonic Follow up

Telephonic Follow-up (TFU) to be performed during Days 1 through 15 of Cycle 1, Cycle 3, Cycle 4, Cycle 6, Cycle 7, Cycle 9, Cycle 10, Cycle 11, and Cycle 13. In unforeseen circumstances where a cycle was ended early before the scheduled visit (shortened cycle) and a new cycle was started with a new Day 1, the Investigator should recalculate the visit schedule according to the new Day 1.

The following procedures will be completed during these visits.

- Confirm and validate current cycle with e-Diary entry
- Confirm and validate Day 1 of the current cycle with e-Diary entry
- Review compliance (including e-Diary use, patch use, back-up contraception, sexual activity) and re-training of subject as necessary and documentation of patch use information in source.
- Review and record concomitant medication
- Record AEs
- At Cycle 1 TFU: review UPT results if subject applied the first ever study patch at home

- Pregnancy determination
  Note: Pregnancy determination only if UPT is positive or indeterminate; SPT and pelvic examination will be performed at the earliest possible time, preferably on the same day whenever a UPT result is positive or indeterminate. In case of positive UPT, transvaginal ultrasound will be be performed as early as possible, preferably the same day; it is highly recommended that an early transvaginal ultrasound examination is performed on the same day when UPT is positive. (serial quantitative SPTs and transvaginal ultrasound examinations may be needed to determine the date of conception)
- Review intention to plan for pregnancy
- Review contact information
- Schedule next visit

6.5 Early Study Drug Termination (ET) Visit

Subjects may request to discontinue use of the study drug or withdraw from the study at any time, or be required to withdraw or discontinue study drug by the investigator or sponsor for reasons as per Section on 'Criteria for study drug termination, withdrawal from the study and study termination'. If study drug is terminated or the subject withdraws or is withdrawn, the reason for termination/withdrawal should be established and recorded. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document the outcome of subject contact attempt, if possible. The investigator will contact the Sponsor or designee in the event that a subject fails to complete the study or violates the protocol.

If the subject withdraws from the study, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. Unless consent is withdrawn, subjects who prematurely terminate study drug will be asked to return to the clinic for an ET visit. However, even if subject withdraws consent, she should be encouraged to return to the clinic for an early termination visit whenever possible to at least have a pregnancy test performed. If the subject refuses to return to the clinic for an ET visit, it will be requested she use a home urine pregancy test and report results to the investigator (either via virtual visit or provision of a photograph of the resulting test). If such test is positive or indeterminate, follow instructions in Section 7.8 unless consent has been withdrawn.

Whenever possible, it is recommended that ET visits be performed at 14 (+5) days after removal of last study patch. However, this can be performed at the earliest possible time before this timepoint based on subject's convenience in visiting the site, subject's decision to become pregnant and hence refusal to use contraception anymore and/or at the investigator's clinical decision. However, subjects should be instructed to use back-up contraception (condom and spermicide or diaphragm and spermicide) until completion of the early termination visit.

If subject telephonically communicates for a premature termination, the subject can be immediately withdrawn through an unscheduled telephonic visit and can be called later for an ET visit.

At the ET visit the following procedures will be completed:

- Perform a targeted general physical Examination including a gynecological examination
- Measure height, weight and calculate BMI
    - Note: Height ONLY for adolescent subjects (i.e., < 18 years of age).
- Measure vital signs (BP, RR, PR, temperature)
- Collect blood and urine samples for laboratory investigations
- Perform UPT
- Collect sample for SPT
- Pregnancy determination

    Note: Pregnancy determination only if UPT is positive or indeterminate; SPT and pelvic examination will be performed at the earliest possible time, preferably on the same day whenever a UPT result is positive or indeterminate; in case of positive UPT , transvaginal ultrasound will be performed as early as possible, preferably the same day; it is highly recommended that an early transvaginal ultrasound examination is performed on the same day when UPT is positive
- Investigator's evaluation of previous patch application site
- Review compliance (including e-Diary use, patch use, back-up contraception, sexual activity) and re-training of subject as necessary and documentation of patch use information in source.
- Collect unused condoms
- Review and record concomitant medication
- Record AEs
- Review contact information
- The investigator should reiterate and instruct regarding the contraceptive options available after the study

Subjects may be sent home from the clinic at the discretion of the investigator following completion of all ET assessments.

6.6 End of Treatment

This will be the day of removal of the last patch in the study.

6.7 End of Study (EOS) Visit

For subjects who continue until the end of the study, EOS Visit to be performed 14 (+5) days after removal of last study patch (the end of treatment). At this visit, safety assessments including hematology, chemistry and urinalysis will be performed. The investigator should also reiterate the contraceptive options available after the study. If other therapy is needed, the subjects should receive treatment at the investigators' discretion according to current local medical practice.

At this visit the following procedures will be completed.

- Perform a targeted general physical examination including a gynecological examination
- Measure height, weight and calculate BMI
  - Note: Height ONLY for adolescent subjects (i.e., < 18 years of age).
- Measure vital signs (BP, RR, PR, temperature)
- Collect blood and urine samples for laboratory investigations
- Perform UPT
- Collect sample for SPT
- Pregnancy determination
  Note: Pregnancy determination only if UPT is positive or indeterminate; SPT and pelvic examination will be performed on the same day whenever a UPT result is positive or indeterminate. In case of positive UPT, transvaginal ultrasound will. be performed as early as possible, preferably the same day; it is highly recommended that an early transvaginal ultrasound examination is performed on the same day when UPT is positive.
- Investigator's evaluation of previous patch application site
- Review compliance (including e-Diary use, patch use, back-up contraception, sexual activity) and re-training of subject as necessary and documentation of patch use information in source.
- Review and record concomitant medication
- Record AEs
- Review contact information
- Collection of unused condoms
- The investigator should reiterate and instruct regarding the contraceptive options available after the study.

Subjects who decide to discontinue from treatment, should be discontinued at the same time from the study, i.e., no further assessments or procedures are required unless required for other reasons, e.g., follow-up of AEs or a pregnancy.

6.8 Unscheduled Visit

At any time of the study, an unscheduled visit could occur in case of suspicion of pregnancy based on a positive pregnancy test performed at home by the subject or in case the Investigator judges it necessary to examine a subject who would present a potential significant AE or to evaluate any safety or compliance concerns or to collect or distribute any clinical supplies. Additional assessments can be performed at the Investigator's discretion.

6.9 Delayed and Missed Visits

Every attempt should be made to complete the visits within the given window period for each scheduled visit (clinic and telephonic visits).

A visit will be considered as delayed if it was not performed within the protocol specified window period, but during the protocol specified cycle.

A visit will be considered as missed, if it was not performed before the end of that cycle.

- When a clinic visit could not be conducted because of a shortened cycle, the visit should be conducted as soon as possible during the next cycle before removal of the last patch (up to Day 21).
  Note: Whenever a clinic visit moves to the next cycle because of a shortened cycle, the telephonic visit planned for that next cycle can be skipped (For example, if Cycle 2 clinic visit was planned for Day 12 and if at Cycle 2 Day 10, the Cycle was advanced to Cycle 3, the subject should have a clinic visit during Cycle 3 following the clinic visit assessments for Cycle 2 and a Cycle 3 phone visit can be skipped).
- When a telephonic visit could not be conducted because of a shortened cycle, the visit will be considered as missed. The subsequent visits should happen as per protocol schedule.

All delayed and missed visits should be recorded as protocol deviations. The reasons for the delayed or missed visits must be documented in the patient's study records and appropriate section of the eCRF.

6.10 COVID-19 Pandemic Specific Precautionary Measures

As stated above, patients with active COVID-19 infections or subjects with an increased risk of serious COVID-19 related morbidity as determined by the investigator at the time of screening and/enrollment are excluded from enrolling in the study. However, patients who are successfully enrolled into the study are subject to the following ongoing COVID-19 precautionary measures. The following measures in addition to the study site's internal policies and procedures for COVID-19 must be followed for the duration of the COVID-19 pandemic. If any of the following precautionary measures conflict with the study site's COVID-19 policies, the study site's policies should govern. Any additional COVID-19 screening procedures that may be mandated by the study site do not need to be the subject of protocol deviation, even if performed during clinical study visits. However, any such additional COVID-19 screening procedures mandated by the study site should be reported to the sponsor.

Patients who are currently in quarantine or have active COVID-19 infection at the time of a study visit, may not visit the site for the study. Subjects having any one of the following conditions (COVID-19 Risks) within fourteen (14) days of any study visit, must be evaluated by the investigator prior to a study visit:

- Symptom(s) of COVID-19 including for example fever, cough, muscle aches, difficulty breathing, fatigue, and loss of sense of taste/smell;
- Travel outside of the US, or travel within the US to/from a high-risk area;
- Contact with any COVID-19 positive individual; or
- Subject to isolation or quarantine by a government or local authority.

COVID-19 Risks also include conditions specific to the study site that create a heightened risk of COVID-19 infection/exposure or heightened risk to the safety or health of a study subject attending a study visit, including for example:

- The study site has reached or exceeded its maximum capacity due to an influx of COVID-19 patients;
- The study site has a shortage of the supplies or materials necessary for a subject's study visit, as a result of COVID-19; or
- COVID-19 is spreading throughout the study site at a heightened rate.

If the investigator becomes aware of any COVID-19 Risks, the investigator shall determine, within his/her discretion and pursuant to the site's standard clinical practice, if the subject may attend the study visit. The investigator should make this determination by weighing the risk of COVID-19 infection/exposure to all people at the study site (e.g., the study subject, the Investigator, other physicians and staff, other patients) against the risk or harm caused by cancelling or postponing the study visit. This determination may vary by region and and can change over time based on the current local prevalence of infection.

Any visit modification due to COVID-19 should be documented as protocol deviations with reference to COVID-19 in the deviation description. Changes in study visit schedules, including cancelled or postponed visits may lead to missing information (i.e., for protocol-specified procedures). The investigator should capture specific information in the case report form that explains the basis for any missing data, including the relationship to COVID-19, for the missing protocol-specified information. Although any such modification is considered a deviation from the protocol, prior IRB and sponsor approval is not required as long as the sponsor is informed afterwards.

Subjects must be informed of the above policies upon enrollment into the study, and must be required to report any COVID-19 Risks prior to visiting the study site.

7.0 TREATMENT PROCEDURES AND ASSESSMENT CRITERIA

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator or designated representative will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the investigator or designated representative will document the reason and also a protocol deviation for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The Sponsor's study team will be informed of these incidents in a timely fashion.

Activities specific to this protocol are explained below:

7.1 Efficacy Assessment

Contraceptive efficacy will be evaluated by calculation of pregnancy rates using the PI. Cycle-wise and gross cumulative probability of pregnancy will also be measured using a life table analysis.

All pregnancies with an estimated date of conception (EDC) between the date of the first patch application of the study and 7 days (inclusive) of the removal of the last patch of the study will be considered as 'on-treatment' pregnancies.

7.2 Safety Assessment

Subjects who have received at least one dose of the study medication will be evaluable for safety assessment.

Safety monitoring will be performed by monitoring of vital signs (BP, PR, RR, and body temperature), targeted physical examination and gynaecological examination, assessment of AEs, concomitant medications, and clinical laboratory tests for safety assessments.

All AEs, whether previously known with the individual drugs or not, will be recorded on the CRF with their description, intensity, action taken, duration, outcome and opinion about causal relationship to the study drug.

Any adverse experiences of a serious nature, whether or not considered to be drug related, must be communicated to the sponsor immediately upon discovery of the events.

Blood samples will be obtained at visits as explained in schedule of events for laboratory test during the trial period.

SAE/AE observed during the study will be reported as mentioned in the protocol AE section.

In addition contraceptive safety will be evaluated as described below:

Cycle control will be evaluated by assessing incidence of bleeding and/or spotting episodes. The e-Diary will be used to determine the number of days of scheduled bleeding/spotting and

unscheduled bleeding/spotting. Bleeding and spotting will be defined as per Mishell et al. (Mishell, 2007b).

For this study, the duration of the reference period for cycle control will be 28 days. The e-Diary will be used to collect data on bleeding and spotting on a daily real-time basis. Subjects will be asked to document responses to the questions every 24 hours in a consistent manner. All efforts should be made to encourage data recording at approximately the same time within each 24-hour period.

The e-Diary will also collect data on the severity of bleeding episode (light, normal, or heavy) if any (Appendix 7).

Assessment of Local Tolerability:

Local tolerability will be evaluated by self-reported irritation scores rated as none, mild, moderate or severe (Appendix 3). Self-reported irritation will be evaluated by the subject for all days the patch is on and will be entered in the e-Diary.

At all clinic visits, the investigator/sub-investigtor will perform assessment of skin irritation, with irritation rated as none, mild, moderate or severe as per Appendix 4.

Assessment of Patch Adhesion:

Patch adhesion will be evaluated by subjects' daily self-assessment and investigator's assessment at all the clinic visits.

Self-reported adhesion will be evaluated by the subject for all days the patch is on and will be entered in the e-Diary. Adhesion will be evaluated at around the same time of the day but not following a recent attempt to re-adhere their TDS. Self-reported adhesion will be performed using Appendix 1.

Investigator/sub-investigator will evaluate the patch adhesion as per FDA draft guidance on Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs, during the clinic visits using Appendix 2. Adhesion performance should not be evaluated if the subject is not wearing the patch during clinic visit.

Safety will be evaluated in the study by monitoring subjects for AEs.

7.2.1 Adverse Event Assessment

If a subject reports any symptoms before drug application, she will be evaluated by medical staff and necessary measurements will be performed. The Principal Investigator or Medical Sub-Investigator will be notified before drug application to determine the course of action.

Findings from screening procedures, e.g., laboratory tests or physical examinations will be recorded as medical history. Clinically significant worsening from the screening procedures will be recorded as AEs.

Subjects will be routinely queried in regard to the presence or absence of AEs using open ended questions. The clinic will provide documentation of any AEs in the subject's CRF. The

AE source documentation will minimally include the following information: AE term, investigator's causality, onset/end date, action taken, severity, date and time of assessment, the outcome of the response, and identification of the clinic staff member collecting the information.

An independent committee of experts will evaluate the causality assessment for all the VTEs.

7.2.2 Laboratory Safety

The following safety laboratory tests will be performed at times defined in the study schedule of events.

Table 3: Laboratory Safety Tests

Hematology	***Chemistry***	***Urinalysis***	***Others*** *(as specified in the schedule of events)*
Hemoglobin *Hematocrit* *RBC count* *Platelet count* *WBC count* Differential count	*Blood urea nitrogen (BUN)* *HbA_1C (ONLY at screening visit)* *Total bilirubin* *Serum glutamic-pyruvic, transaminase (SGPT/ALT)* *Serum glutamic-oxaloacetic, transaminase (SGOT/AST)* *Alkaline phosphatase* *Gamma-GT* *Total protein* *Albumin* *Globulin* *Creatinine* *Triglycerides* *Cholesterol* *HDL* *LDL*	*Specific gravity* *pH* *Glucose* *Protein* *RBC* *WBC*	*Urine pregnancy test (UPT)* *Serum qualitiative pregnancy test with reflux quantification (SPT)* *ONLY at screening visit:* - *Chlamydia and gonorrhea screening tests* - *Urine drug screen* - *HIV testing* - *Cervical cancer screening:* o *For 21 to 29 years old: Pap test followed by reflex HPV (if required)* o *For ≥30 years old: HPV & cytology*

Hematology, chemistry, SPT, chlamydia and gonorrhea screening, HIV testing, cervical cancer screening and urine drug screen will be analyzed by central laboratory. Urinalysis will be conducted by dipstick at site. Local laboratories may be used for SPT.

Blood volumes to be collected and blood and urine sample handling instructions will be provided in the central vendor laboratory manual. The central laboratory will provide collection materials and directions for packaging and shipment of samples.

Any clinically significant findings in laboratory safety data should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

7.2.3 Vital Signs

BP, PR, RR, and body temperature will be measured at times specified in the schedule of events. Additional collection times, or changes to collection times of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data.

Sitting BP will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg after 5 minutes of rest. Two readings will be taken 1 to 2 minutes apart and the average of the two readings will be considered. (Muntner P et al, 2019) The average reading will be entered in e-CRF. Where possible, the same arm (preferably the dominant arm) will be used throughout the study.

The same size BP cuff, which has been properly sized and calibrated, will be used to measure BP each time. The use of automated devices for measuring BP and PR are acceptable, although, when done manually, PR will be measured in the brachial/radial artery for at least 30 seconds. Any clinically significant changes in BP and PR should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

7.2.4 Targeted Physical Examination and Gynecological Examination

A targeted physical examination and a gynecological examination will be performed as per the schedule of events. The targeted physical examination will consist of an examination of the abdomen, cardiovascular system, lungs, neurological systems, skin, extremities, and thyroid gland by trained medical personnel at the site.

The gynecological examination will include an evaluation of the following: breast examination (performed by palpation) and assessment of the adnexa, cervix, uterus, vagina, and external genitalia.

Height will be assessed at screening and only for adolescent girls at other visits as per schedule thereof. Weight will be assessed at Visits as specified in the schedule of events. Physical examination results will not be recorded in the CRFs, but any clinical significant finding at Screening Visit should be recorded under medical history and changes between Screening Visit and subsequent examinations should be recorded as an AE. Determination of clinical significance and seriousness will be based on the investigator's medical judgment.

7.3 Pharmacokinetic Assessment

PK sampling will be done for subjects reporting any suspected or confirmed arterial or venous thromboembolic event. All possible attempts should be made to collect PK samples as soon as possible in the event of any suspected or confirmed arterial or venous thromboembolic events.

The blood samples will be analyzed for ethinyl estradiol and norelgestromin concentrations using fully validated analytical methods.

7.4 Subject Diary

Since the study will utilize an e-Diary, all eligible subjects should be adequately trained to use the e-Diary. Subjects will be asked to enter data on sexual activity, contraception use and vaginal bleeding/spotting during the screening period and for at least 7 days. Subjects should demonstrate ability (at least 70% complaince during diary run-in) to complete the e-Diary to be eligible for enrollment. If the screening period exceeds 28 days, the screening e-Diary

compliance will be estimated based on the data entries either in the e-Diary for the entire screening period or the intial 28 days from the date of activation of screening e-Diary (specifically if the compliance is less than 70% for a screening period that is longer than 28 days, then the compliance for the first 28 days can be calculated; if this meets the 70% threshold, then the criterion has been met). At first patch application, the subject will start completing the treatment daily e-Diary. The e-Diary will be used to capture data including the use of back-up and/or emergency contraception, sexual activity, vaginal bleeding/spotting (both scheduled & unscheduled), severity of bleeding episodes, patch use information including anatomical sites of application, patch adhesion data, local tolerability, reason for early removal & unscheduled replacement (if any), patch exposure to water, any possible reasons or risk factors for detachment and possible application site reactions. Data entered in the e-Diary should be reviewed by the investigator/ designee. Treatment compliance will be assessed by the investigator / designee by reviewing e-Diary and subject re-training must be carried out as required.

7.5 Contraception

The instructions related to contraceptive use are described in inclusion/exclusion criteria and respective sections of Study Conduct.

Contraception during screening period and up to first study patch application:

Subjects who are not using any hormonal contraception MUST use barrier methods of contraception during the screening period until the first study patch application.

Subjects who are current users of hormonal contraception including combined hormonal contraceptives including oral pills, patches, and rings will continue to use the same method during the screening period. It is highly recommended that the current users also should use barrier methods of contraception during the screening period until the first study patch application.

For all subjects for use during screening period and up to the first study patch application, condoms and spermicide will be provided at the screening visit. However, subjects may use independently procured back-up methods of contraception of their choice, either condom and spermicide or diaphragm and spermicide.

Contraception during period between patch-free week of cycle 13 and end of study:

Irrespective of the future plans for pregnancy or planned/actual methods of contraception used, all women will be instructed to use barrier contraceptives after the patch-free week of cycle 13 through the end of study. For this purpose, condoms and spermicide will be dispensed during the Cycle 12 visit. However, subjects may use independently procured back-up methods of contraception of their choice, either condom and spermicide or diaphragm and spermicide.

In cases of early termination, subjects should be instructed to use such back-up contraception after the last patch removal until conduct of the early termination visit.

7.6 Back-Up Contraception

The study will include only subjects who agree to not use other contraceptives or other methodology to prevent pregnancy during the study (Cycle 1 through Cycle 13) and willing to use study patch as only method of contraception throughout the study.

However, a back-up contraception using barrier methods are permitted ONLY during the following instances:

1. Situations where there arises a necessity to avoid sexually transmitted infections (STIs)
2. Subject notices a partial or complete detachment of the patch late (≥24 hours)
3. Delayed patch applications (anytime during week 1 or by ≥48 hours during week 2 or week 3)

Emergency contraception (ie Morning After Pill/Plan B) can be used ONLY in rare circumstances as described below AND had intercourse

1. Subject notices a partial or complete detachment of the patch late (≥24 hours)
2. Delayed patch applications (anytime during week 1 or by ≥48 hours during week 2 or week 3)

The details of the back-up contraception should be appropriately entered into the e-Diary.

7.7 Post-trial Contraceptive Counselling

At the cycle 12 clinic visit or during an early termination, the investigator should discuss with the subject if there is a plan for preganncy after the study. If subject desires to continue contraception even after the trial, the investigator should initiate post-trial contraceptive counselling and discuss contraceptive options available after the study at this visit. The same needs to be instructed during EOS visit for applicable subjects.

Irrespective of the plans for pregnancy and planned methods or actual start of any contraception including any CHCs, all women will be instructed to use barrier contraceptives after the patch-free week of cycle 13 through the end of study visit.

For this purpose, condoms and spermicide will be dispensed at Cycle 12 visit. However, subjects may use independently procured back-up methods of contraception of their choice, either condom and spermicide or diaphragm and spermicide.

7.8 Pregnancy Testing and Adjudication

An UPT will be performed at the screening visit and enrollment visit and a serum pregnacy test (SPT) at the enrollment visit and EOS/ET.

At each study visit, the subject will be asked if she has a desire to become pregnant. In case of a positive answer, the subject will be discontinued from the study.

During the study, pregnancy will be monitored using UPT. UPT will be performed before first ever study patch application (Cycle 1 Day 1), at all clinic visits and whenever a subject is

at risk of pregnancy or when pregnancy is suspected (e.g., any symptoms/signs suggestive of pregnancy, delayed/missed patch application during a cycle without use of a back-up contraception as per requirements).

A UPT and SPT will also be conducted at 14 (+5) days after removal of the last patch.

All subjects with an indeterminate or a positive UPT result at any of the post first patch placement visits will undergo a SPT, pelvic examination. In case UPT is positive, transvaginal ultrasonography at the earliest possible time, preferably on the same day. Serial quantitative SPTs may be needed to help determine the date of conception, timing of subsequent transvaginal ultrasounds, or other obstetric reasons. The pelvic examination is performed for assessment of uterine size (weeks).

A transvaginal ultrasound should be performed preferably on the same day for determination of the EDC. Repeat assessments may be performed (e.g., a repeat ultrasound if the earlier initial ultrasound was performed prior to presence of gestational sac or for crown rump length for dating) as necessary for accurate determination of EDC. First trimester transvaginal ultrasound will be considered the most accurate method for estimating the EDC. Subsequent ultrasounds, ie second and third trimester, will not be used to amend the EDC, if an adequate first trimester ultrasound has been obtained.

EDC will be separately estimated by the investigator, medical monitor (MM) and an independent PRC.

An accurate and timely adjudication will be done for every confirmed, positive pregnancy test obtained after first patch placment. For this purpose, an independent PRC comprising of experts in early antenatal ultrasonography will review all confirmed, positive pregnancy tests obtained after first patch placment.

For all confirmed pregnancy events reported after enrollment (i.e., excluding subjects with positive UPTs or SPTs at enrollment), the MM and the PRC will review all the applicable data including those that are available from the below list to determine the date of conception.

First trimester transvaginal ultrasound results will be considered the most accurate; images and reports will be submitted. The following will be supportive:

- Date of the last patch worn (date of application and date of removal); the subject will be queried whether the information in the e-Diary is accurate; if not, the verbally reported dates will be used and recorded in CRF
- Uterine size from clinical examination
- Date of start and duration of last bleeding episode (scheduled/unscheduled)
- Dates of the sexual activity during the last cycle
- Quantitative serum beta-hCG levels
- Dates of the last negative and first positive UPTs, including home pregnancy test if performed
- Any other relevant supportive information related to pregnancy
- Any other reports including those related to termination of pregnancy

Based on this review, the MM and the PRC will adjudicate all the confirmed pregnancy events as pre-treatment, on-treatment, or post-treatment based on following guideline:

- Pre–treatment: EDC is prior to the first ever patch application of the study
- On–treatment: EDC is between the date that the first patch application of the study and 7 days (inclusive) of the removal of the last patch of the study
- Post–treatment: EDC is after 7 days from the last patch removal of the study

Any positive pregnancy testing occurring after enrollment visit will be followed up and reported to the sponsor as per protocol Section on 'Reporting of SAEs and Pregnancy Exposures'.

7.9 Prohibited Therapy During the Study

- Use of any contraceptive method* other than the investigational product

  *However, a back-up contraception using barrier methods such as condoms and spermicide or a diaphragm and spermicide should be used during instances when subject notices a partial or complete detachment of the patch late (≥24 hours) or delayed patch applications (anytime during week 1 or by ≥48 hours during week 2 or week 3). Barrier methods are permitted to be used when there arises a necessity to avoid sexually transmitted infections (STIs).
- Treatment with hCG supplements or exogenous sex steroids/gonadocorticoids other than study medication. Emergency contraception (ie Morning After Pill/Plan B) can be used only in rare circumstances when the subject has had a late patch application or partial or complete detachment as described above AND has had intercourse.
- Use of systemic corticosteroids (topical and inhaled corticosteroids are allowed)
- Use of drugs or herbal products that induce or inhibit (moderate/strong inducers and inhibitors) certain enzymes such as cytochrome P450 3A4 (CYP3A4) including, but not limited to the following:
  - Anticonvulsant therapy with phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, felbamate, rufinamide or lamotrigine
  - Use of antibiotics rifampin or rifabutin, systemic antifungal agents griseofulvin, ketoconazole, voriconazole, itraconazole or fluconazole, and antiviral agents (fos)amprenavir, nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, tipranavir/ritonavir, indinavir or atazanavir/ritonavir; use of hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir; non-nucleoside reverse transcriptase inhibitors nevirapine or etravirine.
  - Use of bosentan
  - Use of aprepitant
  - Any product that contain St. John's wort

Note: This is not an exhaustive list. Please refer to prescribing information of the specific product for guidance or contact the medical monitor.

- Any other drug, the prescribing information of which has a warning or contraindication for concomitant use with an estrogen-progestin combined hormonal contraceptive agent

7.10 Restrictions

Study restrictions are as listed and explained in this protocol sections, Lifestyle Guidelines, Prohibited Therapy During the Study and the Concomitant Medications and will be prohibited throughout the duration of the study. If concomitant medications change during the study, Principal Investigator or a Medical Sub-Investigator at his/her discretion can discuss with medical monitor, and a decision to continue or discontinue the subject can be made based on the risk of potential safety concern posed by use of such medications.

8.0 STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

8.1 Sample Size Determination

Approximately 1,200 eligible women enrolled and treated for up to 13 cycles are expected to provide at least 10,000 evaluable cycles for safety.

The study population will be selected such that:

- The proportion of non-white study participants will be at least 30% of the total study population to reflect the general population in the US
- The proportion of women over the age of 35 years will represent approximately 10% of the total study population
- The proportion of women with higher BMI ($\geq$30 kg/m^2) will be capped to a maximum of 10% of the total study population

Based on the asumptions above, it is expected that approximately 1,000 enrolled women aged 16 to $\leq$35 years and with BMI <30 kg/m^2 will provide at least 5000 evaluable cycles (after excluding cycles with back-up contraception and abstinent cycles) for efficacy. [redacted]

At least 200 subjects will complete the study.

8.2 Populations for Analyses

Definitions of analysis populations:

1. All-enrolled population: All subjects who were enrolled into the study (i.e. subjects who had a non-missing enrollment date on the enrollment page of the CRF)
2. Safety population: All subjects who had at least one patch application after enrollment
3. Contraceptive efficacy population (CEP): All subjects in the safety population who have a negative serum β-hCG at enrollment visit. If the test was missed to be performed due to unforeseen reasons, results if available from UPT found to be negative at enrollment visit, can be considered for inclusion in the CEP.

4. Cycle control population: All subjects in CEP who provide information on bleeding and patch application.
5. Efficacy evaluable (EE) population: All subjects in CEP aged 16 to 35 years (inclusive) at enrollment who have a baseline BMI <30 kg/m^2 and have at least one efficacy evaluable cycle that meets the following criteria:
    - Cycles in which vaginal intercourse occurred
    - Cycles in which no backup or emergency contraception was used based on e-Diary data, unless a pregnancy occurred in such a cycle

8.3 Statistical Analyses

8.3.1 Definition of the Primary Efficacy Endpoint

The primary contraceptive efficacy endpoint used in this study will be Pearl Index (PI). PI is defined as the number of pregnancies per 100 women-years and will be calculated by multiplying number of on-treatment pregnancies by 1,300 (for 13 cycles in a year) and divided by the number of 28-day evaluable cycles.

$$Pearl\ Index = \frac{number\ of\ on\text{-}treatment\ \ pregnancies \times 13}{number\ of\ evaluable\ cycles} \times 100$$

where,

- On-treatment pregnancy is defined as the pregnancy with an estimated date of conception between the date of application of the first patch through 7 days after the removal of the last patch in the study
- Evaluable cycles are defined as the complete or incomplete 28-day cycles in which vaginal intercourse occurred and in which no back-up contraception was used based on the e-Diary data, unless a pregnancy occurred in such a cycle.

8.3.2 Analysis of Primary Endpoint

The PI and corresponding 95% CI will be calculated. The CI will be calculated using a Poisson distribution. The CI limits will be calculated by the following equations:

$$CL_{lower} = \frac{\frac{1}{2}\chi^2_{0.025,2x}}{number\ of\ evaluable\ cycles} \times 1300$$

$$CL_{upper} = \frac{\frac{1}{2}\chi^2_{0.975,2(x+1)}}{number\ of\ evaluable\ cycles} \times 1300$$

where x is the number of on-treatment pregnancies and $\chi^2_{alpha,df}$ is the alpha quantile from chi-square distribution with df degrees of freedom.

The primary efficacy analysis will be performed on the EE population.

For the primary efficacy analysis, PI will be calculated utilizing the number of on-treatment pregnancies adjudicated by the PRC.

An additional analysis will be performed based on the medical monitor's determination of EDC. The calculations will be also done for all women in CEP.

8.3.3 Missing Data

Handling of missing data will be described in the SAP.

8.3.4 Sub-Group Analyses

Sub-group analyses will be performed based on baseline BMI, body weight, age, race, ethnicity, and previous hormonal contraceptive use as defined below for the EE.

BMI and weight:

- Normal: BMI < 25 kg/m^2 and overweight: BMI ≥25 to <30 kg/m^2.
- Weight categories defined by median and/or quartiles.

Age: ≥18 to ≤35 years at enrollment

Race: White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian and Other Pacific Islander

Ethnicity: Hispanic or Latino, Not Hispanic or Latino

Previous hormonal contraceptive use status:

- Naïve Users: women who have not previously used any hormonal contraceptive
- Prior Users: women with previous use of hormonal contraceptives but not in the 6 months prior to enrollment
- Recent Users: women who are not currently using a hormonal contraceptive, but have used a hormonal contraceptive within 6 months prior to enrollment
- Current Users: women who are currently using a hormonal contraceptive

8.3.5 Definition and Analysis of the Secondary Endpoint(S)

The method failure PI and corresponding 95% CI will be calculated in the EE population.

The method failure PI is defined as PI among all complete or incomplete on therapy cycles in which intercourse occurred and excluding the following:

1) Cycles with reported patch detachment and not followed protocol guidelines (see section - Patch Replacement Guidelines)
2) Cycles with reported missed patch application and not followed protocol guidelines (see section 'Procedures for Delayed/Missed Patch Application/Change/Removal')
3) Cycles immediately following points 1) and/or 2) started as a new cycle after an incomplete cycle
4) Cycles with reported major protocol deviations potential to have impact on contraceptive efficacy of the patch

A life-table analysis of cycle-wise and cumulative pregnancy rates up to 13 cycles will be performed on the EE population. The analysis will be done for all pregnancies and for all method failure pregnancies.

8.3.6 Safety Analyses

Analysis of all safety data will be performed on the Safety Population.

8.3.6.1 Adverse Events

AEs will be coded using latest version of Medical Dictionary for Regulatory Activities (MedDRA). The occurrence of AEs, and SAEs will be summarized in terms of incidence, as well as in terms of total number of AEs. Analysis of AEs in terms of incidence by severity and by relatedness will also be provided.

8.3.6.2 Cycle Control and Patch Adhesion

An analysis of cycle control data will be performed as follows:

- All available data will be analyzed
    - Incomplete cycles (i.e., those with < 100% method utilization) or cycles with incomplete bleeding data will not be excluded from the initial analyses
- Incidences (percentage of subjects) of *unscheduled bleeding and/or spotting episodes* within each 28-day cycle will be reported; incidence will be calculated as number (n) of subjects with unscheduled bleeding and/or spotting among the number (N) of subjects in the cycle control population
- The mean, median, and range of *number of observed days of bleeding and/or spotting* within each cycle will be reported. This will be presented for total days, unscheduled days (patch-on), and scheduled days (patch free) for bleeding and/or spotting, bleeding only and spotting only. Incidences (percentage of subjects) of *complete absence of bleeding or spotting* during the cycle will be reported.
- A tabular presentation of statistical data (mean, median, range) for the *incidence of unscheduled bleeding and/or spotting episodes* and the observed number of days of bleeding and/or spotting will be made.
- A *graphical* presentation of the *incidence of unscheduled bleeding and/or spotting episodes* for all the cycles will be reported as per recommendations by Mishell et al., 2007a.
- For evaluation of *bleeding patterns over time*, an analysis including only subjects who completed the study as well as an analysis of the cycle control population will be conducted.
- A separate subgroup analysis of cycle control profile will be conducted and reported *for subjects who discontinued the* study *prematurely due to unacceptable bleeding.*

- Analysis of cycle control will also be performed for the subgroups based on the variables BMI, weight, age, parity, history of prior hormonal contraceptive use.

Adhesion performance data will be reported descriptively.

8.3.6.3 Vital Signs

BP, PR, RR, and body temperature will be listed and descriptively summarized (N, mean, standard deviation, minimum and maximum) by visit. Baseline (defined as the pre-dose value collected before first study patch application) and changes from baseline will be similarly summarized.

8.3.6.4 Laboratory Data

Descriptive summaries of observed values and change from baseline will be presented for clinical laboratory evaluations (Serum chemistry and hematology). Assessments of laboratory variables according to clinical relevance will be tabulated by visit for each clinical laboratory parameter in frequency tables. Additionally, for each laboratory parameter, shifts in value from baseline to all post-baseline visits will be presented in shift tables.

The assessment of categorical urinalysis variables will be tabulated by visit for each urine parameter in frequency tables. Additionally, for each of the urine parameters, shifts in assessments from baseline visits will be presented in shift tables.

8.3.6.5 Other

Prior and concomitant medications will be coded by the latest version of WHO Drug Dictionary Enhanced and will be summarized. Medical history will be listed by subject and coded using the latest version of MedDRA and will be summarized.

Application site reactions data will be reported descriptively.

8.3.7 Planned Interim Analyses

No interim analysis is planned for this study.

8.3.8 Evaluable Cycles Monitoring

This study requires at least a minimum of 5,000 evaluable cycles for efficacy and 10,000 cycles for safety as per the definitions for efficacy evaluable cycles and safety cycles. For effiacy, evaluable cycles are defined as the complete or incomplete 28-day cycles in which vaginal intercourse occurred and in which no back-up contraception was used based on the e-Diary data, unless a pregnancy occurred in such a cycle. Safety population will include all subjects who had at least one patch application after enrollment and will be used for safety evaluation.

[redacted]

[redacted]

9.0 ADMINISTRATIVE PROCEDURES

9.1 Source Documentation Forms

All clinical data will be recorded by the clinical staff on raw data sheets and/or recorded electronically using validated software. If computerized systems are used to create, modify, maintain, archive, retrieve or transmit source data, they must comply with the applicable regulatory regulations and/or guidance.

The nature and location of all source documents will be documented separately. Source data may be directly captured from devices, transferred from 3rd parties (e.g., laboratory data) or entered manually into CRF/database.

9.2 Access to Data/Source Documentation

The Investigator or authorized designee will permit full access to data and source documentation for the purpose of clinical monitoring, audits, IRB/IEC review and regulatory inspections.

9.3 Final Clinical Study Report and Case Report Forms (CRFs)

A written clinical study report will be provided in accordance with the International Conference on Harmonization (ICH) E-3 guidelines including Annex I (Synopsis) documenting the clinical execution of the study. This report will include a description of any protocol deviations. The final report will also include reasons for withdrawals and any necessary treatment(s). The reports will include any potential changes in study conduct and contingency measures implemented during the restrictions related to the COVID-19 pandemic. A listing of all participants affected by the COVID-19 related study disruption will be included in the CSR. Analyses and corresponding discussions that address the impact of implemented contingency measures on the safety and efficacy results will also be reported in the CSRs. The report will also include tables presenting demographics (separate summary tables for enrolled and completed subjects), and AEs recorded during the study. In addition, the clinical study report will include a Quality Assurance statement, documenting that the report has been reviewed for completeness, accuracy, and compliance with the protocol and applicable local and federal regulations. For final clinical reporting purposes only, AEs deemed “definite”, “probable” or “possible” will be included in the treatment-related summaries/listings.

Case Report Forms (CRFs) containing data transcribed from subject source documents (as appropriate) and copies of other source documents will be supplied by the clinical site. The Principal Investigator must sign each subject’s CRF after completion of data entry, signifying that the data entered in the CRF is complete and accurate. Electronic CRFs may be provided.

9.4 Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety and wellbeing of the study subjects requires medical treatment, the study will be conducted as described in the approved protocol (and amendments, if applicable), GCP and applicable

SOPs. In addition, the study will be conducted in accordance with the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted. Any deviation(s) from the protocol will be recorded and presented in the final report. Principal investigator should document protocol deviations for all disruptions due to COVID-19 pandemic by referring to COVID-19 in the deviation description.

9.5 Data Handling and Record Retention

All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the study subjects remains protected.

A CRF is required to be completed for each subject receiving study medication. The CRF is property of the sponsor and the Investigator must review all CRFs prior to submission to the sponsor.

The CRF may be considered as the source document. The investigator must seek prospective agreement to the sponsor in writing to use the CRF as source document prior the start of the study. In addition, items directly recorded in the CRF must be documented that they will be considered as source.

All records pertaining to the receipt and return of study supplies (particularly study medication) and copies of final CRFs , worksheets, and other pertinent source documents must be retained in accordance with ICH-GCP and the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

The investigator must obtain in writing the sponsor’s agreement to dispose of any records, even if the retention period has been reached.

9.6 Confidentiality

Information furnished to Clinical Investigators and IRBs/Ethics Committees will be maintained in confidence by the Clinical Investigator and IRB/Ethics Committee. By signing this protocol, the Investigator affirms to the Sponsor that he/she will maintain, in confidence, information furnished to the IRB/Ethics Committee relevant to this study under appropriate understanding of confidentiality with such IRB/Ethics Committee.

By signing the protocol, the Investigator agrees that within local regulatory restrictions and institutional and ethical considerations, the Sponsor may consult and/or copy source documents (e.g., laboratory/X-ray reports, ECG tracings, workbooks, medical records) in order to verify CRF data.

9.7 Ethics and Regulatory Authorities

Guidelines will be followed with regard to the treatment of human subjects in the study, in accordance with the requirements of the Declaration of Helsinki and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human

Use (ICH-E6) in addition to the regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

9.7.1 Institutional Review Board/Ethics Committee

The Investigator is responsible for obtaining initial and continuing review (at least once per year) of the study by an IRB/Ethics Committee, or in accordance with applicable government regulations of the country where the study is being conducted as well as the country where the study will be submitted. This study will not enroll any subjects until the IRB/Ethics Committee provides written approval of the protocol and the informed consent/assent (as applicable) to the investigator. In addition, a copy of the IRB/Ethics Committee approval documents must be provided to the sponsor prior to enrolling any subjects into the study.

9.7.2 Regulatory Authority

This clinical study protocol, IEC(s)/IRB(s) approvals, and other relevant documentation will be submitted to the local Regulatory Authorities for review and approval. Upon completion, the Regulatory Authorities will be notified the study has ended. The study will only be undertaken in compliance with the local regulatory requirements.

9.8 Informed Consent/Assent

A properly executed, written informed consent (and assent as applicable) in compliance with current GCP guidelines and ICH guidelines shall be obtained from each volunteer prior to entering the study. A copy of the informed consent document/assent to be used will be submitted by the investigator to an independent institutional review board (e.g., IRB or ethics committee) and the Sponsor and/or its agent for review and approval prior to the start of the study. The investigator shall provide a copy of the signed and dated informed consent/assent to the subject and guardian as applicable, and a signed and dated copy shall be maintained in the volunteer's medical record.

9.9 Disclosure and Publication of Clinical Study Data

The disclosure and publication of clinical study data will be detailed in the clinical trial agreement with the Investigators.

9.10 End of Trial

The end of trial is considered to be the date of last subject last visit or the date of early termination of the study whichever is the later.

10.0 ADVERSE EVENTS AND SAFETY REPORTING

The AE collection period begins at signing of informed consent/assent and continues until 14 (+5) days after removal of the last patch. AEs occurring during this period need to be reported to the sponsor according to Section 'Collection and Recording of Adverse Events' The investigator is also responsible for notifying the sponsor if he/she becomes aware of any AE after the study period has ended and it is considered related to the study medication (i.e., an adverse drug reaction). Once an AE is detected, it should be followed until its resolution or until it is judged by the principal investigator to be stable or permanent.

10.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physical findings, symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

Clinically significant changes from baseline in laboratory assessments, vital signs, and physical examination are to be recorded as AEs. Clinically significant abnormalities include:

- a result associated with accompanying signs/symptoms
- a result that requires additional diagnostic testing or medical/surgical intervention
- a result that leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- a result considered to be an AE by the investigator or sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

An abnormal safety assessment (e.g., laboratory, vital signs) associated with a clinical diagnosis that has been recorded as an AE does not require a separate AE entry.

Events meeting the definition of an AE also include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug or drug-food interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication.
- A symptom or medical complication related to a protocol-mandated intervention, including screening procedures

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** (SAE) is any AE that is:

- fatal
- life-threatening

  NOTE: The term **"life-threatening"** in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires in-patient hospitalization or prolongation of existing hospitalisation

  Note: In-patient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the study drug or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization or accommodation problems and without medical background does not need to be considered an SAE.

Events NOT to be reported as SAEs are hospitalizations for the following:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
- Admission to a hospital or other institution for general care due to social or economic reasons (e.g., no access to local ambulatory medical care)
- Treatment on an emergency, out-patient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

Hospitalization also does not include the following: Rehabilitation facilities, Hospice facilities, Respite care (e.g., caregiver relief), Skilled nursing facilities, Nursing homes

- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event.
  - Note: medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject and / or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
  - The seriousness criterion of "medically significant" should **only** be selected when none of the other seriousness criteria apply to the event but the investigator still considers the event as serious.

All AEs that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Drug Reaction

All noxious and unintended responses to an investigational product ***related*** to any dose of the investigational product should be considered adverse drug reactions (ADRs). The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an AE is at least a reasonable possibility. All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to an investigational product will be designated as ADRs.

All AEs, with the causal relationship to the study drug reported as "possible", "probable" or "definite" will be considered ADRs. If the relationship to the study drug is not given, then the AE must be treated as if the relationship were "possible."

Expected/Unexpected Adverse Event

An expected AE is defined as one whose nature, severity or outcome is consistent with the applicable reference safety information described of the study drug.

An AE is to be considered unexpected if the nature, severity or outcome is not consistent with the applicable product reference safety information.

Pre-existing Condition

Any medical condition that is present at the time that the participant is screened will be considered as baseline medical history and not reported as an AE. A baseline or preexisting condition should be recorded as an AE only if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

Any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

Post-study Adverse Event/Serious Adverse Event

The investigator should notify the study sponsor of any death or SAE occurring at any time after a subject has discontinued or terminated study participation that may reasonably be ***related*** to this study. The sponsor should also be notified if the investigator becomes aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Reporting COVID-19 as an Adverse Event/Serious Adverse Event

If subject has a diagnosis of COVID-19 infection during the study, it should be recorded as AE or SAE if the event meets seriousness criteria.

10.2 Special Situations

The following situations may by associated with a serious outcome and should be evaluated for expedited reporting to the sponsor.

- Any diagnosis of **Cancer** or **Neoplasm** is to be reported as a SAE.
- **Emergency Room Visits:** Events that result in emergency room visits that do not result in admission to the hospital are not routinely considered to be serious events; however, these events should be evaluated for one of the other serious outcomes (e.g., life-threatening, other serious [medically significant] events).
- **Overdose:** Overdose *per se* will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent; this should be reported regardless of sequelae. Signs and symptoms associated with accidental overdose are to be recorded as AEs or as serious AEs. If AEs associated with overdose fulfil any of the serious criteria (as defined in section 'Serious Adverse Event'), a completed SAE report form is required to be submitted.
- Reports of **Drug-drug interaction and Drug Abuse and Medication Errors**: drug interactions or abuse of the study medication must be recorded as AEs. Medication errors will be captured as protocol deviations while any associated signs or symptoms must be recorded as AEs on the CRF. In addition, any serious consequence of drug interactions, drug abuse, or medication error must be reported immediately if these fulfil any of the SAE criteria.

10.3 Collection and Recording of Adverse Events

During the AE Reporting Period, the investigator will record all AEs. At each contact with the subject, the investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source document, and in the appropriate AE module of the CRF. Information to be collected includes AE name or term (in standard medical terminology) and final diagnosis, event description, time and date of onset, clinician's assessment of severity, seriousness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), action taken with the study drug, treatment for the event and time (if available) and date of resolution/stabilization of the event.

All clearly related signs, symptoms, and abnormal results of diagnostic procedures should be grouped under one diagnosis on the CRF where possible and appropriate.

The clinical course of each event should be followed until resolution or stabilisation. AEs that are still ongoing at the end of the study period must be followed up to determine the outcome. Any AE that occurs after the study period and is related to the study treatment or study participation should be recorded; and if serious, the investigator should also immediately report it to the Sponsor.

10.4 Classification of an Adverse Event

10.4.1 Severity

The Investigator will assign a severity rating to each AE. For purposes of consistency, the following scale is to be used:

Grade 1 - MILD	Does not interfere with subject's usual function.
Grade 2 - MODERATE	Interferes to some extent with subject's usual function.
Grade 3 – SEVERE	Interferes significantly with subject's usual function.

It is important to distinguish between severe AEs and Serious AEs. Severity is a classification of intensity, whereas an SAE is an AE that meets any of the regulatory specified criteria (see Definitions Serious Adverse Event).

10.4.2 Causality

For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality of each AE.

An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. The Investigator must assess the relationship of each AE (serious and non-serious) to the study treatment(s) and record this relationship in the CRF.

Factors that need to be considered when making a causality assessment include: Temporal relationship, Clinical and pathological characteristics of the event(s), Pharmacological plausibility, Exclusion of confounding factors (medical and medication history), Drug interactions, De-challenge/re-challenge, Dose relationship.

A suspected relationship (definite, probable, possible) between the events and the study medication means, in general, that there are facts (evidence) or arguments to suggest a causal relationship. Receipt of additional or clarifying information may warrant reassessment of causality. The Investigator is responsible for assessing relationship of AEs to study treatment in accordance with the following definitions:

Category	Causality	Description
DEFINITE	Causal relationship is certain	For example: the temporal relationship between drug exposure and the adverse event (AE) onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated; the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
PROBABLE	High degree of certainty for causal relationship	For example: the temporal relationship between drug exposure and AE onset/course is reasonable, there is a clinically compatible response to de-challenge (re-challenge is not required), and other causes have been eliminated or are unlikely.

POSSIBLE	Causal relationship is uncertain	For example: the temporal relationship between study treatment exposure and the AE onset/course is reasonable or unknown, de-challenge information is either unknown or equivocal; could also be explained by disease or other drugs.
UNLIKELY	Causal relationship is improbable	Another explanation is more likely such as disease, environment, or other medication. Does not represent a known reaction to study drug.
UNRELATED/NOT RELATED	No possible relationship	The temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study drug is impossible

For SAEs, if the relationship to the study treatment(s) is considered to be unlikely or not related, an alternative suspected etiology should be provided when possible (e.g., concomitant medications, intercurrent illness/events, study-related procedure).

10.4.3 Expectedness

The Sponsor or its designated representative will be responsible for determining whether an AE is expected or unexpected based on the reference safety information. The reference safety information mentioned in the IB will be used in this study for the expectedness assessment of SAEs.

10.4.4 Outcome

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to Sponsor or its designated representative.

The outcome at the time of last observation will be classified as:

RECOVERED/RESOLVED where the subject recuperated and is free of any pathological conditions resulting from the prior disease or injury.

RECOVERED WITH SEQUELAE where the subject recuperated but retained pathological conditions resulting from the prior disease or injury.

NOT RECOVERED/NOT RESOLVED (i.e. ongoing) where the subject has not recuperated from the condition or injury and the event is still considered ongoing

RECOVERING where the subject has begun to recuperate from the condition or injury but the event is considered ongoing at a reduced intensity

FATAL the condition or injury results in the subject's death. The investigator should identify the principal cause of death and assign Fatal outcome to that event. Other concurrent ongoing AE/SAEs present at the time of death would remain Not recovered/Not resolved.

UNKNOWN can be selected if none of the other situations apply or are known. Follow-up should be conducted to obtain one of the preceding outcomes.

10.4.5 Action Taken with the Study Treatment

Action	Description
Treatment interrupted	The treatment was temporarily discontinued
Treatment withdrawn	The treatment was permanently discontinued
Unknown	Not known, not observed, not recorded, or refused
No action taken	The AE did not result in any modification of dose or frequency of dosing
Not applicable	The AE occurred prior to first dose or following last scheduled dose

10.5 Reporting of Serious Adverse Events and Pregnancy Exposures

Investigators and the Sponsor or designated representative must conform to the SAE reporting timelines, formats and requirements of the various entities to which they are responsible.

10.5.1 Investigator Reporting: Notifying the Study Sponsor

Immediate notification of SAEs by the investigator to Sponsor PSRM is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

SAEs must be reported to the study sponsor within 24 hours of awareness. To report such events, a Serious Adverse Event (SAE) Report form must be completed and signed by the investigator or designee and forwarded to:

Sponsor's Global Product Safety and Risk Management (PSRM)

Email: [redacted] (primary; preferred)

Fax: [redacted] (secondary)

If the initial notification using the completed 'SAE report form' is not possible, the notification may be made via email/fax or over telephone with the following minimum necessary information

- Study identifier
- Study center
- Subject number
- A description of the event
- Current status (outcome of event-if known and whether study medication is continuing)
- The reason why the event is classified as serious
- Investigator assessment of the causality between the event and study treatment

The investigator should provide further information on the as soon as possible, preferably within 48 hours of awareness. This should include a copy of the completed SAE Report form,

and any other diagnostic information and medical records that will assist in the understanding of the event.

Subject identifying information must not be visible on SAE forms or any supporting documentation provided by the Investigator. Any information that could be used to identify the subject (e.g. name, address, medical record number) must be de-identified before submission to Sponsor or its designee. The subject's study specific ID number should be recorded on every page of documentation forwarded to the sponsor.

The Principal Investigator should provide the final diagnosis as the SAE term whenever possible in the SAE report form and CRF. The signs and symptoms should be provided in the narrative only, not as SAE terms. The investigator should only list all signs and symptoms as SAE terms if no diagnosis is available at the time of report.

10.5.2 Follow-up

New information and any important missing information from prior reports on a SAE must be provided promptly to the study sponsor. In addition, the Investigator may be requested by Sponsor/designee to obtain specific additional follow-up information in an expedited fashion. The investigator should respond to targeted follow-up requests as soon as possible and preferably within 48 hours from receipt of the request.

10.5.3 Investigator Reporting: Notification of Ethics Committee

Investigators are responsible for safety reporting to their Local Ethics Committee (LEC) and complying with their LEC's reporting requirements. Copies of each report and documentation of LEC notification and receipt will be kept in the investigator's study file.

10.5.4 Investigator Reporting of Pregnancy - Notifying the Study Sponsor

No other birth control measures are required apart from the study medication for all subjects who participate in the study unless during circumstances when use of back-up contraception is required by the protocol (see section 7.6). Pregnancy testing will be conducted during the study, as detailed in the schedule of assessments.

A subject who is found to be pregnant (positive UPT) at the screening/enrollment visit will be excluded from the study and will be a screening failure.

Subjects who have been enrolled in the study should be instructed to contact the Investigator or study staff immediately if a positive pregnancy test occurs or is suspected after first patch placement. Early termination visit assessments are required as soon as possible after learning of the pregnancy. Pregnant females will be discontinued from study treatment by the Investigator.

Details of the pregnancy should be recorded on the Pregnancy Report form and reported to Sponsor's PSRM within 24 hours of awareness by email to [redacted] (primary) or facsimile +1.304.285.6409 from the time of initial awareness, even if beyond the closure of the clinical database. The pregnancy must also be reported to the pregnancy review comittee via email to [redacted]

The Investigator is also responsible for following the pregnancy every 3 months or until delivery or termination and informing the Sponsor about its outcome. Reports where the embryo or foetus may have been exposed to the study drug(s), should be followed-up in order to collect information on the:

- outcome of the pregnancy
- outcome for both mother and foetus (malformation/anomalies diagnosed since initial report)
- development of the child after birth (developmental assessment, infant illnesses, hospitalizations, drug therapies, breastfeeding)

Healthy newborns should be followed-up at 1 month after birth to confirm no congenital anomalies were subsequently detected (if possible).

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or termination of a pregnancy for medical reasons will be recorded as an AE or an SAE. A spontaneous abortion is always considered to be a SAE and will be reported to the Sponsor.

Elective termination (i.e., without medical reasons) of an uncomplicated pregnancy is considered an elective procedure and not an AE; nevertheless, Sponsor requests the outcome (e.g., elective termination) be reported within 24 hours of awareness and sent as a follow-up on the Delivery and Infant Follow-up Form).

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as at least possibly related to the study treatment, must be promptly reported to Sponsor's PSRM.

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12.0 APPENDICES

Appendix 1

Self-Reported Scoring System of Patch Adhesion Assessment

Score	Definition
0	The patch has essentially no lift off the skin (≥90% adhered)
1	Only some edges of the patch lift off the skin (≥75% to <90% adhered)
2	Less than half of the patch lifts off the skin (≥50% to <75% adhered)
3	The patch is not detached, but more than half of it lifts off the skin without falling off (>0% to <50% adhered)
4	The patch is detached and is completely off the skin (0% adhered)

Appendix 2

Investigator's Scoring System of Patch Adhesion Assessment during Clinic Visits

Score	Definition
0	≥90% adhered (i.e., the TDS has essentially no lift off the skin)
1	≥75% adhered but <90% (e.g., only some edges of the TDS lift off the skin)
2	≥50% adhered but <75% (i.e., less than half of the TDS lifts off the skin)
3	>0% to <50% (i.e., the TDS is not detached, but more than half of it lifts off the skin without falling off)
4	0% adhered (i.e., the TDS is detached and is completely off the skin)

(Note: Adhesion performance should not be evaluated if the visit happens on a patch-free week)

Appendix 3

Self-Reported Scoring System of Application Site Irritation Assessment

Score	Definition
None	No irritation or barely seen/very minimal skin redness
Mild	Minimal skin redness covering most of the application site
Moderate	More than minimal skin redness, possible minimal swelling
Severe	Intense skin redness, possible swelling, rashes, blisters, and/or broken skin

Appendix 4

Assessment of Skin Irritation - Investigator's Scoring System

Score	Definition
None	No irritation or barely perceptible/spotty erythema
Mild	Mild erythema covering most of the application site
Moderate	Moderate erythema, possible mild edema
Severe	Severe erythema, possible edema, vesiculation, bullae and/or ulceration

Appendix 5

Definition of the Terms

Pre-treatment pregnancy	Pre–treatment: EDC is prior to the first ever patch application of the study
On-treatment pregnancy	EDC is between the date that the first patch application of the study and 7 days (inclusive) of the removal of the last patch of the study
Post-treatment pregnancy	EDC is after 7 days from the last patch removal of the study
Pearl Index	PI is defined as the number of pregnancies per 100 women-years and will be calculated as follows: $Pearl\ Index = \frac{number\ of on\text{-}treatment\ \ pregnancies \times 13}{number\ of\ evaluable\ cycles} \times 100$
Evaluable cycles	Evaluable cycles are defined as the complete or incomplete 28-day cycles in which vaginal intercourse occurred and in which no back-up contraception was used based on the electronic diary (e-Diary) data, unless a pregnancy occurred in such a cycle
Naive users	Women who have not previously used any hormonal contraceptive
Prior Users	Women with previous use of hormonal contraceptives but not in the 6 months prior to enrollment
Recent Users	Women who are not currently using a hormonal contraceptive, but have used a hormonal contraceptive within 6 months prior to enrollment
Current Users	Women who are currently using a hormonal contraceptive

Appendix 6

Cycle Control Terminologies

Cycle Control Terminologies	Definitions
Bleeding	Evidence of blood loss that requires use of sanitary protection with a tampon, pad, or pantyliner
Spotting	Evidence of minimal blood loss that does not require new use of any type of sanitary protection, including pantyliners
Episode of bleeding/spotting	Bleeding/spotting days bound on either end by 2 days of no bleeding/spotting
Scheduled bleeding or withdrawal bleeding	Any bleeding/spotting that occurs during the patch-free interval and may continue into the first 4 days (Days 1-4) of the subsequent cycle
Unscheduled bleeding and Unscheduled spotting	Any bleeding or spotting episode that occurs when the subject is wearing the contraceptive transdermal patch with the following exceptions: • Bleeding/spotting episode that begins during a patch-free interval and continues through Days 1-4 of the subsequent active cycle will not be considered unscheduled • Any bleeding/spotting episode that is reported during Days 1-7 of the first cycle will not be considered unscheduled

Appendix 7

Definitions of Subjects' Assessment of Bleeding Intensity

Intensity of Bleeding	Definitions
Light	Less than associated with normal menstruation relative to subject's experience, with need for sanitary protection
Normal	Like normal menstruation relative to subject's experience
Heavy	More than normal menstruation relative to the subject's experience

Appendix 8

Instructions For Use

Attached as a separate signed document

Document Name : Protocol Amendment - MR-100A-01-TD-3001 - 002974148

Title : MR-100A-01-TD-3001 Protocol [redacted]

Status : Approved

Electronic Signatures

[redacted]	Justification
	Approver
	Approver