Clinical Study Protocol

A Phase 1, Open-Label, Parallel Group Study to Evaluate the Pharmacokinetics and Safety of DARE-HRT1 (80µg Estradiol/4mg Progesterone and 160µg Estradiol/8mg Progesterone Intravaginal Rings) in Healthy Post-Menopausal Women

Protocol Number: DARE-HRT1-001

Final Version

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1 PROTOCOL SUMMARY

Protocol Title:	A Phase 1, Open-Label, Parallel Group Study to Evaluate the Pharmacokinetics and Safety of DARE-HRT1 (80 µg Estradiol/4 mg Progesterone and 160 µg Estradiol/8 mg Progesterone Intravaginal Rings) in Healthy Post-Menopausal Women
Study Phase:	1
Objectives:	Primary: • To describe the pharmacokinetic (PK) parameters over 28 days of two different dose combinations of éE-HRT1 intravaginal ring (IVR): o Estradiol 80 µg/progesterone 4 mg/day IVR o Estradiol 160 µg/progesterone 8 mg/day IVR Secondary: • To assess the safety and tolerability of DARE-HRT1 • To compare the systemic exposure of estradiol, estrone, and progesterone over 28 days after administration of DARE-HRT1 IVR and once daily (QD) oral Estrace®/Prometrium® Exploratory: • To assess usability and subject tolerability of the DARE-HRT1 IVR
Hypotheses:	No formal hypotheses will be tested.
Endpoints:	Primary: • Steady-state concentration (C_{ss}) and maximum observed plasma concentration (C_{max}) for estradiol, estrone, and progesterone for each treatment Secondary: • adverse events • clinical laboratory findings • physical examination findings • vital signs • pelvic examination findings • vaginal pH and cytology Exploratory: • responses to Usability and Tolerability questionnaire

<table>
<tr>
<td>Study Design:</td>
<td>This is a randomized, open-label, 3-arm, parallel group study in approximately 30 healthy postmenopausal women with intact uteri. This study is designed to assess the PK of estradiol, estrone, and progesterone from DARE-HRT1 intravaginal rings at two dose strengths. Oral estradiol 1 mg/progesterone 100 mg once-daily for 28 days will serve as an active reference. Upon completion of screening procedures and confirmation of eligibility (including an endometrial biopsy, cervical screening test, and transvaginal ultrasound), eligible subjects will be admitted to the clinical research unit (CRU) on Day -1.

Randomization will occur prior to initiation of treatment and subjects will be randomized in a 1:1:1 ratio to the treatment groups below.
<table>
<tr><th>Treatment Group and Number of Subjects</th><th>Treatment</th></tr>
<tr><td>IVR Dose 1
(n = 10)</td><td>28-day IVR 80/4 (estradiol 80 µg/day + progesterone 4 mg/day)</td></tr>
<tr><td>IVR Dose 2
(n = 10)</td><td>28-day IVR 160/8 (estradiol 160 µg/day + progesterone 8 mg/day)</td></tr>
<tr><td>Oral Reference
(n = 10)</td><td>Oral Estrace®/Prometrium® QD for 29 days (estradiol 1 mg/progesterone 100 mg oral capsule)</td></tr>
</table>
Day 1 is defined as the first day of treatment, i.e., the day the IVR is self-inserted by the subject. The same IVR is to remain intravaginal for 28 days, with removal of IVR in the CRU on the morning of Day 29.

Plasma sampling will occur on Day 1 predose at -1, -0.5, and 0 (immediately; within ± 5 minutes) hours prior to insertion of IVR and at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following insertion. Subjects will be discharged from the CRU after safety assessments have been completed on Day 3.
On the morning of Days 8, 11, 15, and 22 subjects will return to the CRU for a single PK blood draw and safety assessments.
Subjects will return to the CRU on Day 28 for a PK blood draw, safety assessments, confirmation of IVR placement, and to begin confinement. On the morning of Day 29 a PK blood sample will be collected. The IVR will then be removed and PK samples will be collected 0.5, 1, 2, 4, 8, 12, and 24 hours post-removal.

</td>
</tr>
</table>

Study Design (continued):	Those enrolled in the oral arm (Estrace/Prometrium) will also begin dosing on Day 1, concluding with a last dose on Day 29. Subjects enrolled in the oral arm will be directed to self-administer the medication in the morning with a meal and approximately 240 mL of water, starting on Day 2 through Day 27. Doses will be administered in the CRU each of the mornings of Day 1 and Days 28 and 29 with a moderate-fat breakfast. • Plasma sampling will occur on Day 1 predose at -1, -0.5, and 0 (immediately: within ± 5 minutes) hours prior to oral dose administration and 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose. Subjects will be discharged from the CRU and instructed to self-administer the oral treatment each morning, with food and approximately 240 mL of water, at approximately the same time. • On Days 8, 15, and 22, subjects will return to the CRU for a single PK blood draw and safety assessments. • Subjects will return on Day 28 and be admitted to consume their oral dose with breakfast and begin PK sampling prior to (0 hours) dosing on Day 29 and the following timepoints post oral dose: 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours. A follow-up phone call will be made from the CRU to each subject to monitor any ongoing or emergent AEs approximately 7 days after the last dose of study medication or removal of IVR.
Subject Selection Criteria:	Healthy postmenopausal women with body mass index (BMI) between 18 and 38 kg/m^2, inclusive, normal appearing cervix and vagina based upon pelvic examination, intact uterus, acceptable result from endometrial biopsy, normal cervical screening test and mammogram, endometrium lining < 4 mm (upon transvaginal ultrasound at screening), and without a peanut allergy.
Study Drug, Dose, and Route of Administration:	DARE-HRT1 is an intravaginal ring that delivers estradiol and progesterone and is self-administered by intravaginal insertion once and remains in place for 28 days. The oral reference is Estrace/Prometrium given by oral capsule QD for 29 days.
Planned Sample Size:	Approximately 30 subjects are planned to be enrolled, with 10 subjects randomized to each treatment arm. Subjects who terminate early from the trial may be replaced to ensure an adequate number of subjects contributing to the PK for each treatment arm.

Table 1.1 Schedule of Assessments and Procedures - IVR Treatment Arm

Study Procedure	Screening	Pre-Treatment		28-Day Treatment Period					Follow-Up Phone Call
Study Day	Days -28 to -2	Day -1	Day 1 Predose	Days 1, 2, and 3	Days 8, 11, 15, and 22	Day 28	Day 29	Day 30	
Time				0.5, 1, 2, 4, 8, 12, 24, and 48 hours post insertion					
Informed consent[a]	X								
Assign Subject ID	X								
Eligibility assessment	X		X						
Randomization			X[b]						
Admission to CRU		X				X			
Demographics	X								
Medical and surgical history		X							
Physical examination[c]	X	X						X	
Cervical screening test (if needed)	X								
Pelvic exam with speculum & vaginal visual exam[d]	X							X	
Vaginal cytology and pH	X							X	
Endometrial biopsy	X								
Height (cm), weight (kg), and BMI	X	X							
12-lead ECG	X	X							
Vital signs (BP and PR), RR, oral temp	X	X	X		X			X	
Hematology & blood chemistry	X	X			X (excluding Day 11)			X (EOS)	

Table 1.1 Schedule of Assessments and Procedures - IVR Treatment Arm

Study Procedure	Screening	Pre-Treatment		28-Day Treatment Period					Follow-Up Phone Call
Study Day	Days -28 to -2	Day -1	Day 1 Predose	Days 1, 2, and 3	Days 8, 11, 15, and 22	Day 28	Day 29	Day 30	
Time				0.5, 1, 2, 4, 8, 12, 24, and 48 hours post insertion					
FSH	X								
Serology tests[e]	X								
Drug and alcohol urine screen	X	X							
Transvaginal Ultrasound	X							X	
Urine dipstick	X	X						X (EOS)	
Dispense test article(s)			X						
Training on use of IVR	X		X						
Usability and Tolerability questionnaire								X	
Insert Vaginal Ring (after predose PK sample)			X						
Confirm vaginal ring placement				X[f]	X		X		
PK blood samples	X	X	X (-1, -0.5, and 0 hours predose)	X (once)	X (once)	X (once)	X (0, 0.5, 1, 2, 4, 8, and 12 hours postdose)	X (24 hours postdose)	
Remove vaginal ring/Return test article(s)							X		
Review of daily diary				X	X	X	X		
Discharge from CRU				X (Day 3)				X	
Follow-up Phone Call[g]									X
Adverse events				AEs collected beginning at IVR placement and in on-going manner, as appropriate					

Table 1.1 Schedule of Assessments and Procedures - IVR Treatment Arm

Study Procedure	**Screening**	**Pre-Treatment**		**28-Day Treatment Period**					
Study Day	**Days -28 to -2**	**Day -1**	**Day 1 Predose**	**Days 1, 2, and 3**	**Days 8, 11, 15, and 22**	**Day 28**	**Day 29**	**Day 30**	**Follow-Up Phone Call**
Time				**0.5, 1, 2, 4, 8, 12, 24, and 48 hours post insertion**					
Serious adverse events	SAEs collected beginning at ICF signing and in on-going manner								
Prior/conmeds	X	X	X	Conmeds collected in on-going manner, as appropriate					

Abbreviations: AE = adverse event; BP = blood pressure; conmed = concomitant medication; CRU = clinical research unit; ECG = electrocardiogram; EOS = end of study; FSH = follicle-stimulating hormone; ID = identification; HRT = hormone replacement therapy; IVR = intravaginal ring; PK = pharmacokinetic; PR = pulse rate; RR = respiration rate; SAE = serious adverse event; temp = temperature.

a. Subjects who elect to undergo washout of prior HRT will be asked to sign the informed consent prior to the start of that washout. Washout periods of 8 weeks will require that Screening not commence until 28 days prior to Day 1.

b. Randomization will occur after screening procedures are completed and eligibility is verified.

c. Complete physical examination at Screening and Day 30 visit. Symptom-directed examination at all other visits for subjects exhibiting or reporting symptoms since their last visit.

d. The purpose of the pelvic speculum exam is to identify vaginal irritation or abnormalities at baseline so that AEs related to IVR can be associated with IVR and not baseline abnormalities.

e. Serology tests include HIV-1 and HIV-2 antibodies, hepatitis B surface antigen, and HCV antibodies.

f. Placement of IVR will be confirmed prior to first post-dose PK collection.

g. The purpose of the call is to follow up on any ongoing or emergent AEs since discharge from the CRU after the subject's treatment has been completed (approximately 7 days after the last dose of study medication or removal of the IVR).

Table 1.2 Schedule of Assessments and Procedures - Oral Treatment Arm

Study Procedure	Screening	Pre- Treatment		Treatment Phase							Follow-Up Phone Call
								In-Clinic			
Study Day	Days -28 to -2	Day -1	Day 1 Predose	Days 1 and 2	Day 8	Day 15	Day 22	Day 28	Day 29	Day 30	
Informed consent[a]	X										
Assign Subject ID	X										
Eligibility assessment	X		X								
Randomization			X[b]								
Admission to CRU		X						X			
Demographics	X										
Medical and surgical history	X	X									
Physical examination[c]	X	X								X	
Height (cm), weight (kg), and BMI	X										
Cervical screening test (if needed)	X										
Pelvic exam with speculum & vaginal visual exam[d]	X										
Vaginal cytology and pH	X									X	
Endometrial biopsy	X										
12-lead ECG	X	X									
Vital signs (BP and PR), RR, oral temp	X	X	X		X	X	X			X	
Hematology & blood chemistry	X	X			X	X	X			X (EOS)	
FSH	X										
Serology tests[e]	X										

Table 1.2 Schedule of Assessments and Procedures - Oral Treatment Arm

Study Procedure	Screening	Pre- Treatment		Treatment Phase							Follow-Up Phone Call
								In-Clinic			
Study Day	Days -28 to -2	Day -1	Day 1 Predose	Days 1 and 2	Day 8	Day 15	Day 22	Day 28	Day 29	Day 30	
Drug and alcohol urine screen	X	X									
Transvaginal Ultrasound	X									X	
Urine dipstick	X	X								X (EOS)	
Administer Treatment (Oral HRT)				X	X	X	X	X	X		
Review of daily diary				X	X	X	X	X			
PK blood samples	X	X	X (-1.0, -0.5, and 0 hours)	X[f]	X (once)	X (once)	X (once)		X (0, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12 hours postdose)	X (24 hours postdose)	
Discharge from CRU				X[g]						X	
Follow-up Phone Call[h]											X
Adverse events				AEs collected beginning at first dose and in on-going manner, as appropriate							
Serious adverse events	SAEs collected beginning at ICF signing and in on-going manner										
Prior/conmeds	X	X	X	Conmeds collected in on-going manner, as appropriate							

Abbreviations: AE = adverse events; BP = blood pressure; conmed = concomitant medication; CRU = clinical research unit; ECG = electrocardiogram; EOS = end of study; FSH = follicle stimulating hormone; HRT = hormone replacement therapy; ID = identification; IVR = intravaginal ring; PK = pharmacokinetic; PR = pulse rate; RR = respiration rate; SAE = serious adverse events; temp = temperature.

a. Subjects who elect to undergo washout of prior HRT will be asked to sign the informed consent prior to the start of that washout. Washout periods of 8 weeks will require that Screening not commence until 28 days prior to Day 1.

b. Randomization will occur after screening procedures are completed and eligibility is verified.

c. Complete physical examination at Screening and Day 30 visit. Symptom-directed examination at all other visits for subjects exhibiting or reporting symptoms since their last visit.

d. The purpose of the pelvic speculum exam is to identify vaginal irritation or abnormalities at baseline.

e. Serology tests include HIV-1 and HIV-2 antibodies, hepatitis B surface antigen, and HCV antibodies
f. Day 1 only at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose
g. Discharge on Day 2 following Day 1, 24-hour PK collection
h. The purpose of the call is to follow up on any ongoing or emergent AEs since discharge from the CRU after the subject's treatment has been completed (approximately 7 days after the last dose of study medication or removal of the IVR).

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to 24 hour; calculated using the linear/log trapezoid rule (oral dosing only)
AUC_{D1-D30}	area under the plasma concentration-time curve from time 0 (Day 1) to the time of the last quantifiable concentration on Day 30; calculated using the linear/log trapezoid rule (IVR dosing only)
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CFR	Code of Federal Regulations
C_{avg}	time-weighted average observed plasma concentration over 24 hours (Day 29 PK profile for oral dosing only)
C_{max}	maximum observed plasma concentration
C_{ss}	steady-state concentration (IVR dosing only)
C_{tau}	concentration at the end of the dosing interval (tau) (oral dosing only)
conmed	concomitant medication
CRU	clinical research unit
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HPV	human papillomavirus
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IEC	independent ethics committee
IRB	institutional review board

Abbreviation	Definition
IVR	intravaginal ring
LC/MS/MS	liquid chromatography/tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
Pap	Papanicolaou
PK	pharmacokinetic(s)
PR	pulse rate
QD	once daily
RR	respiration rate
SAE	serious adverse event
SOP	standard operating procedure
SRM	study reference manual
SSP	study-specific procedure
$t_{½,\ eff}$	effective half-life; calculated using AUC_{0-24} on Days 1 and 29 (oral dosing only)
t_{max}	time at which the maximum plasma concentration was observed
temp	temperature
ULN	upper limit of normal
VMS	vasomotor symptoms
VVA	vulvovaginal atrophy

STUDY ADMINISTRATIVE STRUCTURE

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2 INTRODUCTION AND BACKGROUND

2.1 Introduction

Menopause is defined by the Endocrine Society as the "clinical status after the final menstrual period, diagnosed retrospectively after cessation of menses for 12 months in a previously cycling woman and reflecting complete or nearly complete permanent cessation of ovarian function and fertility" (Stuenkel CA, et al., 2015), and occurs at a median age of 51 years in North America (American College of Obstetricians and Gynecologists, 2014). Vasomotor symptoms (VMS), including hot flushes and night sweats are the most frequently observed symptoms during menopause, although these are not experienced by all women. Additional symptoms may include vaginal symptoms such as dryness and dyspareunia, sleep disturbances, and arthralgia (Stuenkel CA, et al., 2015).

The pathophysiology of genitourinary symptoms is caused by a reduction in estrogen levels. Lower levels of estrogen cause a thinning of the vaginal epithelium, the elasticity of the vagina is reduced, and there is an increase in connective tissue with eventual fibrotic change in some women. Decreased estrogen levels are also associated with a reduction in vaginal blood flow and in vaginal lubrication (Mac Bride MB, et al., 2010). These physiological changes lead to "vulvovaginal atrophy" (VVA) and are responsible for the range of symptoms observed in many menopausal women, including vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity, and vaginal bleeding associated with sexual activity.

Hormone therapy (HT) is accepted as an effective treatment for the management of both VMS and symptomatic VVA, with both local and systemic treatments widely used. The use of estrogen for the treatment of symptoms of menopause is advocated by professional medical organizations (American College of Obstetricians and Gynecologists, 2014).

Although estrogen is the most effective treatment for VMS, unopposed treatment (estrogen alone without progesterone) is associated with an increased risk of endometrial hyperplasia and carcinoma in women with an intact uterus, with a meta-analysis of 30 studies showing a relative risk of 2.3 (95% confidence interval [CI]: 2.1-2.5) among women using estrogen and those not using it (Grady D, et al., 1995).

This risk is reduced by the addition of progestogens, with the incidence of endometrial cancer under combined treatment being no different from that in untreated women (Anderson GL, et al., 2003). Furthermore, a Cochrane Review noted a greater effect on reducing hot flash severity following treatment with estrogen and progestogens than with estrogen alone (MacLennan AH, et al., 2004).

DARE-HRT1 is an ethylene vinyl acetate (EVA) copolymer intravaginal ring (IVR) containing 17β-estradiol and progesterone and is being developed for use in the treatment of menopause, with the following indications:

- Treatment of moderate-to-severe VMS associated with menopause in women with an intact uterus.
- Reduction in the incidence of symptomatic VVA in women requiring treatment for VMS due to menopause.

2.2 Investigational Product Background

The DARE-HRT1 IVR is being developed to release 17β-estradiol at an average rate of 80 µg or 160 µg/day, and progesterone at an average rate of 4 mg or 8 mg/day, for a period of up to 28 days, as long as the ring is present intravaginally.

Estradiol and progesterone are the two major steroid reproductive hormones in females and are produced by the ovaries. Estradiol is approved for a range of indications, including the treatment of VMS of menopause, VVA, postmenopausal osteoporosis prevention, hypoestrogenism, and the palliative treatment of breast cancer and androgen-dependent carcinoma of the prostate. Dose formulations include oral tablets (10 µg to 2 mg), vaginal cream (0.01%), vaginal inserts (0.004 mg to 0.01 mg), transdermal film release (0.025 to 0.1 mg/24 hr), and transdermal spray (1.53 mg). Progesterone is also approved for a wide range of indications, including amenorrhea, HRT, and infertility as part of assisted reproductive technology treatment. Dose formulations include oral capsules (100 mg to 200 mg), vaginal gels (4% to 8%) and inserts (100 mg), and injections (50 mg/mL).

2.3 Summary of Findings to Date

The IVR component of DARE-HRT1 is an EVA copolymer ring. Subject exposure to vinyl acetate (VA) monomer within the EVA is not expected given the nature of irreversible cross-linking of the monomers. The product's specification for residual VA monomer (100 ppm) falls below the qualification limit as detailed in the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidance Q3B(R2). The safety of the EVA copolymer has been established from nonclinical and clinical investigations described in the literature, and IVRs made from EVA have been widely approved for use as a vaginal insert for drug delivery, including approvals in the US, the EU, and Australia.

The DARE-HRT1 IVR has been evaluated in a nonclinical study conducted in ovariectomized sheep to evaluate the pharmacokinetics (PK) of the 17β-estradiol and progesterone and the safety and tolerability of the ring. In this study, IVRs were placed in sheep on Day 1 and remained in place through Day 29. The IVRs were well retained over the 28-day period. Pharmacokinetic analysis showed sustained release of 17β-estradiol and progesterone over a 28-day period. Results of histological assessments of the vagina and cervix showed minimal to mild irritation consistent with the expected pharmacodynamic response and a foreign object placement.

No clinical data are currently available for DARE-HRT1, which has yet to be evaluated in humans. A Phase 1 human factors study was conducted with 4 mm and 6 mm cross sectional

diameter placebo IVRs. These rings had the same EVA composition as the DARE-HRT1 IVR but did not include any active hormone components. In addition to evaluating subjects' comprehension of the instructions for use, subjects were also evaluated on their ability to properly insert and remove the rings and were asked to report on the acceptability and tolerability of the IVR. The study demonstrated that the placebo IVRs were safe and well tolerated, in terms of reported adverse events (AEs) and physicians' assessments and evaluation of the vaginal mucosa, vaginal sections, epithelial integrity, epithelial surface thickness, and vaginal color. The most frequently reported AE was vulvovaginal discomfort in 8 of 44 (18.2%) treated subjects. Subjects generally found the instructions provided for the IVR easy to understand, and 32 of 44 (73.7%) subjects were able to successfully insert and remove the IVR. The IVRs were reported to be comfortable by the majority of subjects, with most subjects reporting that the IVR was convenient to use and worked with their lifestyle.

2.4 Study Rationale

Daré Biosciences Inc. is developing an intravaginal ring (IVR) to provide local administration of 17β-estradiol and natural progesterone to treat VMS in women with an intact uterus, while aiming to reduce the likelihood of the development of genitourinary symptoms. Non-oral routes such as vaginal administration should bypass the first-pass hepatic effect, although this has not been demonstrated conclusively. Among the various vaginal dosing treatment modalities, evidence suggests a patient preference for the use of IVRs over cream or tablets, with an improvement in adherence to treatment (Suckling J, et al., 2006). With low-dose estradiol IVRs already approved in the United States for the treatment of VMS due to menopause, and vaginal progesterone products also on the market, coadministration of the two hormones together in the same IVR is an attractive patient convenience proposition for the treatment of VMS and urogenital symptoms of menopause.

2.4.1 Dose Rationale

Estradiol and progesterone have been administered via IVR in previous studies (Hamada et al, 2003) however, the DARE-HRT1 17β-estradiol and progesterone IVR has not yet been tested in human subjects.

Estradiol – Pharmacokinetics of Vaginal Route

In a randomized clinical study with a novel vaginal capsule containing solubilised 17β-estradiol, the bioavailability and PK of the vaginal capsule in healthy postmenopausal women were compared to those of an approved vaginal estradiol tablet (Vagifem®) (Pickar JH, et al., 2016). A crossover design was used, with subjects randomized to receive single doses of novel capsule then the Vagifem tablet, or the Vagifem tablet followed by the novel capsule. Treatments were administered by an investigator. Blood samples were collected at intervals over 24 hours after treatment. Two separate studies investigated 10 µg and 25 µg doses.

Mean values of PK parameters observed for both estradiol doses following single administration of the two treatments are provided in Table 2.1. The C_{max} values for estradiol differed significantly between the two different formulations, with greater C_{max} values observed with the Vagifem tablets than the novel capsule. Similarly, AUC_{0-24} values were greater with the Vagifem tablet. This study also showed that the time to reach the highest observed (peak) concentration in plasma following administration (t_{max}) for vaginally administered estradiol is greatly dependent on the formulation.

Table 2.1 Mean Pharmacokinetic Values for Estradiol

Dose (µg)	AUC_{0-24} (pg•h/mL)			C_{max} (pg/mL)			t_{max} (h)	
	Test	Vagifem®	p	Test	Vagifem®	p	Test	Vagifem®
10	49.62	132.92	<0.0001	14.38	20.38	0.0194	1.75	9.28
25	89.21	292.1	<0.0001	23.08	42.70	<0.0001	1.85	11.18

p-values indicate statistical significance at <0.05 between the test products and the Vagifem products.
Source: Pickar JH, et al., 2016

Prescribing information for the FDA-approved IVR Femring reports PK data for estradiol (FEMRING Package Insert, 2018). Femring is a cured silicone elastomer IVR that releases estradiol acetate at two strengths: 0.05 mg/day and 0.10 mg/day, for 3 months. With the 0.05 mg/day IVR, the reported C_{max} was 1129 pg/mL, C_{avg} was 40.6 pg/mL, and the t_{max} was 0.9 hours. With the 0.10 mg/day IVR, the reported C_{max} was 1665 pg/mL, C_{avg} was 76.0 pg/mL, and the t_{max} was 0.7 hours.

Since the DARE-HRT1 IVR comprises an EVA polymer compared to Femring's silicone elastomer, predictions of PK that might be expected with the DARE-HRT1 based on the Femring data should be considered cautiously. Furthermore, the doses of estradiol in the Femring (50 and 100 µg/day) are not the same as those in the DARE-HRT1 IVR (80 and 160 µg/day). However, the estradiol PK results from DARE-HRT1 are expected within the same order of magnitude as those reported for Femring.

Progesterone – Pharmacokinetics of Vaginal Route

In a study comparing the PK of progesterone from a vaginal progesterone gel (Crinone 8%, 90 mg) with that of orally administered progesterone (Prometrium 100 mg), 12 healthy postmenopausal women were randomized in a 1:1 fashion to receive a single dose of the allocated progesterone treatment. The vaginally-administered progesterone had greater bioavailability than the oral progesterone in terms of AUC_{0-24} (1.48 ng•h/mL per mg versus 0.035 ng•h/mL per mg), with a correspondingly greater C_{max} (10.51 ng/mL versus 2.20 ng/mL). However, t_{max} was observed earlier with oral progesterone (1.00 hours) than with the vaginal gel (7.67 hours) (Levine H, et al., 2000).

The PK of vaginally administered progesterone has also been compared to that of intramuscular progesterone administration (Miles RA, et al., 1994) in a study with functionally agonadal women aged 25 to 54 years. Subjects were randomized to receive a cycle of estrogen and

progesterone replacement, comprising oral ethinyl estradiol with either vaginally administered micronized progesterone capsules (200 mg every 6 hours) or intramuscular progesterone (50 mg twice daily) from Day 15 of the cycle. For the PK assessments, samples were collected for 6 hours after the first progesterone dose, with samples for steady-state PK collected on Day 21. Single-dose exposure was significantly greater with the intramuscular treatment (C_{max} 16.06 ng/mL) than with the vaginal capsule (C_{max} 6.64 ng/mL), with a similar difference observed in steady-state concentrations (69.80 versus 11.90 ng/mL). Serum concentrations increased more rapidly with the intramuscular treatment than with the vaginal treatment. As expected, evaluation of progesterone levels in endometrial samples collected on Day 21 showed higher progesterone concentrations with vaginal treatment (11.50 ng/mL) than with intramuscular treatment (1.40 ng/mL).

An alternative vaginal progesterone formulation, using an effervescent delivery system rather than micronized progesterone capsules, showed similar results. Treatment with the effervescent delivery system was able to produce greater endometrial progesterone concentrations than the intramuscular treatment, while measured systemic exposure was lower (Paulson RJ, et al., 2014).

Another study compared progesterone PK following vaginal administration of two different formulations, both of which contained 100 mg progesterone. Single administrations of vaginal tablets (Endometrin®) and vaginal capsules (Utrogestan®) in postmenopausal women showed largely similar results for the two formulations. The AUC was 379.99 nmol/h/L with the tablet and 325.89 nmol/h/L with the capsule. A significant difference was observed for C_{max} of the two formulations, with values of 31.53 nmol/L reported for the tablet and 23.85 nmol/L for the capsule. The authors also reported an increase in systemic progesterone levels when subjects were “primed” with estrogen (3 mg/day ethinyl estradiol for 2 weeks) before receiving the progesterone treatment (Levy T, et al., 2000).

It is not clear how the PK of progesterone from the treatment modalities described here will compare with PK of progesterone released from the EVA ring of DARE-HRT1. It is clear though, that administration via the vaginal route should avoid a first-pass effect of liver metabolism, (Levy T, et al., 2000), which is supported by the comparison of the oral and vaginal routes described by Levine H, et al (2000).

2.4.2 Study Design Rationale

A parallel group study of DARE-HRT1 in healthy postmenopausal women is an appropriate design to assess PK and safety.

2.5 Hypotheses

No formal hypotheses will be tested.

3 OBJECTIVES

3.1 Primary Objective

- To describe the PK parameters over 28 days of two different dose combinations of DARE-HRT1 intravaginal ring (IVR):
  - Estradiol 80 µg/progesterone 4 mg/day IVR
  - Estradiol 160 µg/progesterone 8 mg/day IVR

3.2 Secondary Objectives

- To assess the safety and tolerability of DARE-HRT1
- To compare the systemic exposure of estradiol, estrone, and progesterone over 28 days after administration of DARE-HRT1 IVR and once daily oral Estrace®/Prometrium®

3.3 Exploratory Objective

- To assess usability and subject tolerability of the DARE-HRT1 IVR

4 STUDY DESIGN

4.1 Study Design and Overview

This is a randomized, open-label, 3-arm, parallel group study in approximately 30 healthy postmenopausal women with intact uteri.

This study is designed to assess the PK of estradiol, estrone, and progesterone from DARE-HRT1 intravaginal rings at two dose strengths. Oral estradiol 1 mg/progesterone 100 mg once-daily for 28 days will serve as an active reference.

Three treatment groups will be assessed in this study as shown in Table 4.1.

Table 4.1 Treatment Allocations

Treatment Group and Number of Subjects	Treatment
IVR Dose 1 (n=10)	28-day intravaginal ring 80/4 (estradiol 80 µg/day + progesterone 4 mg/day)
IVR Dose 2 (n=10)	28-day intravaginal ring 160/8 (estradiol 160 µg/day + progesterone 8 mg/day)
Oral Reference (n=10)	Oral Estrace/Prometrium QD for 29 days (estradiol 1 mg/progesterone 100 mg oral capsule)

Subjects who have been on prior hormone replacement therapy (HRT) therapy will be required to have the following washout period prior to randomization (for subjects actively using HRT, washout may begin after their informed consent):

- 4 weeks or longer for prior transdermal estrogen alone or estrogen/progestogen products
- 8 weeks or longer for prior oral estrogen, oral estrogen/progestogen, or intrauterine progestogen therapy
- 3 months or longer for prior progestogen implants and estrogen alone injectable drug therapy
- 6 months or longer for prior estrogen pellet therapy or progestogen injectable drug therapy

Due to study enrollment goals and the length of the required washout period outlined above, patients who are currently on either injectable or pellet therapy at the time of presentation for screening consideration will not be enrolled.

Washout periods of 8 weeks will require that Screening not commence until 28 days prior to Day 1.

Upon completion of their screening procedures and confirmation of their eligibility (including an endometrial biopsy, cervical screening test [if needed], and transvaginal ultrasound), eligible subjects will be admitted to the clinical research unit (CRU) on Day -1. Randomization will

occur prior to initiation of treatment. Subjects will be randomized in a 1:1:1 ratio to the treatment groups.

Day 1 is defined as the first day of treatment, i.e., the day the IVR is self-inserted by the subject. The same IVR is to remain intravaginal for 28 days, with removal of IVR in the CRU on the morning of Day 29. For those randomized to the oral arm (Estrace/Prometrium), dosing will also begin on Day 1, concluding with a last dose on Day 29. Subjects in the oral arm will be directed to self-administer the medication in the morning with a meal and approximately 240 mL of water, starting on Day 2 through Day 27. Doses will be administered in the CRU each of the mornings of Day 1 and Days 28 and 29 with a moderate-fat breakfast.

Safety and tolerability assessments will include monitoring of adverse events and concomitant medications, clinical laboratory findings, physical examinations, vital signs, pelvic examinations, completion of a Usability and Tolerability questionnaire, and vaginal pH and cytology. Refer to the Schedule of Assessments for each treatment arm in Table 1.1 and Table 1.2 for specific details.

IVR Treatment Groups:

- A single predose blood draw for estradiol, estrone, and progesterone will be obtained at screening and Day -1, and -1, -0.5, and 0 (immediately prior to insertion of IVR $\pm$ 5 min) hours on Day 1. Plasma samples for estradiol, estrone, and progesterone will then be obtained at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following administration/insertion. Subjects will then be discharged from the CRU after safety assessments have been completed on Day 3.
- Subjects will return on the morning of Days 8, 11, 15, and 22 for a single blood draw as well as safety assessments.
- Subjects will return to the CRU on Day 28 for a PK blood draw, safety assessments, confirmation of IVR placement, and to begin confinement. On the morning of Day 29 a PK blood sample will be collected. The IVR will then be removed and PK samples will be collected 0.5, 1, 2, 4, 8, 12, and 24 hours post-removal.

Additional details of sampling and safety assessment procedures are presented in the Schedule of Assessments and Procedures - IVR Treatment Arm in Table 1.1.

Oral Treatment Group:

- A single predose blood draw for estradiol, estrone, and progesterone will be obtained at screening and Day -1, and -1.0, -0.5, and 0.0 hours immediately prior to and at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours after the first dose on Day 1. Following the 24-hour PK, subjects will be discharged and instructed to self-administer oral estradiol and progesterone treatments each morning, with food and approximately 240 mL of water, at approximately the same time.

- Subjects will return on Days 8, 15, and 22 for a single blood draw as well as safety assessments.
- Subjects will return to the clinic and be admitted on Day 28 to consume their oral dose with breakfast. A PK sample will be collected just prior to the last oral dose on the morning of Day 29, with additional PK sampling performed at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose.

Additional details of sampling and safety assessment procedures are presented in the Schedule of Assessments and Procedures - Oral Treatment Arm in Table 1.2.

4.1.1 Duration of Study

Subject participation is expected to last up to 65 days, including a 28-day screening period, a 30-day on-study period (consisting of a 29-day treatment period and additional sample collections), and the follow-up phone call 7 days after the last dose of the investigational product [IP]).

4.1.2 Definition of Study Completion

End-of-study procedures will be performed as specified in the schedule of assessments (Table 1.1 and Table 1.2). Subjects who terminate from the study early will have EOS procedures performed at the time of discontinuation. Subjects with ongoing significant clinical or laboratory findings will be followed until the finding is resolved or medically stable. All reasonable attempts will be made to follow-up with subjects. The subject's participation in the study will end once all study assessments and follow-up have been completed.

4.1.3 End of Study

The end of the study is defined as the date when the last subject has completed all study procedures up to and including the EOS/early termination visit as specified in the schedule of assessments (Table 1.1 and Table 1.2).

5 SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects must meet all the following criteria in order to be enrolled in the study.

5.1 Inclusion Criteria

Subjects must meet all inclusion criteria to be eligible for study participation.

1. Postmenopausal women with a body mass index (BMI) ≥ 18 and ≤ 38 kg/m^2.

   $$BMI = \text{weight (kg)}/(\text{height [m]})^2$$

   Postmenopausal is defined as 12-months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy (although subjects who have had a hysterectomy are not eligible for this study).
2. Normal cervix and vagina based on pelvic examination with speculum
3. An intact uterus
4. An acceptable result from an evaluable screening endometrial biopsy, evaluated by a pathologist. Tissue must be read as benign, inactive, or atrophic endometrium by at least one pathologist. If no tissue is obtained from the biopsy, the subject will be excluded.
5. Current on all Australian screening requirements for cervical cancer
6. Able and willing to correctly and independently complete all study procedures
7. Able to read, understand, and provide written informed consent after the nature of the study has been fully explained and must be willing to comply with all study requirements and procedures
8. Normal mammogram report within 24 months of screening

5.2 Exclusion Criteria

Subjects will not be eligible for study participation if they meet any of the exclusion criteria, or will be discontinued at the discretion of the investigator in consultation with the medical monitor if they develop any of the exclusion criteria during the study.

1. Prior abnormal cervical screening test (CST) or Pap result within 2 years of screening. Subject can have atypical squamous cells of undetermined significance (ASCUS), if HPV negative.
2. Subjects with any self-reported active sexually transmitted disease and/or evidence of infection based on visual vaginal exam by the investigator
3. Subjects with a UTI during screening as assessed by urine dipstick test with abnormal test findings (any positive result for leukocytes AND any positive result for nitrites)
4. Subjects with > 4 mm endometrium lining at screening (on the transvaginal ultrasound)

5. Have a history of endometrial hyperplasia or cervical or uterine carcinoma
6. Subjects with indwelling catheters or requiring intermittent catheterization
7. Subjects with multiple or unsuccessful (e.g., still having symptoms) pelvic reconstructive surgery, or suffers from pelvic relaxation
8. Subjects who have had a hysterectomy
9. Subjects taking any estrogen and/or progesterone products (see Section 4.1 for washout requirements)
10. Subjects with concomitant use of personal lubricants (water-based lubricants are allowed) or any intravaginal product or medication, either by prescription or over-the-counter (e.g., Femring [estradiol acetate vaginal ring], ESTRING® [estradiol vaginal ring]) with the exception of those who agree not to use these products during the IVR use period
11. Self-reported or observed vaginal irritation; vaginal, vulvar, or cervical lesions, undiagnosed vaginal bleeding; or tenderness
12. Subjects with a finding of clinically significant uterine fibroids at screening
13. Subjects with a known hypersensitivity to progesterone, estradiol, Femring, or the components of the IVR (e.g., ethylene vinyl acetate)
14. Subjects with known hypersensitivity to peanuts (Prometrium capsules contain peanut oil)
15. Subjects with prior pelvic malignancies
16. Subjects with a history of any severe acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with trial participation or study treatment administration or could interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into the trial. This includes but is not limited to the following:
    a. Human immunodeficiency virus (HIV) infection (confirmed by medical history/ serology testing)
    b. Active chronic hepatitis B or hepatitis C infection including hepatitis B surface antigen and hepatitis C antigen positive subjects with or without abnormal liver enzymes (confirmed by medical history/serology testing)
    c. Concurrent neurodegenerative disease
    d. Cardiovascular: uncontrolled hypertension, unstable angina, myocardial infarction or symptomatic congestive heart failure within the past 6 months, serious uncontrolled cardiac arrhythmia, use of Class 1 antiarrhythmic medications, or history of venous thromboembolism or stroke
    e. Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of the protocol
    f. History of gallbladder disease unless gallbladder removed

g. Symptomatic bacterial vaginosis

17. Have fasting triglyceride of > 300 mg/dL and/or total cholesterol of > 300 mg/dL
18. AST or ALT > 1.5 times the upper limit of normal
19. Fasting glucose > 125 mg/dL
20. Evidence of current alcohol or drug abuse in the past 60 days including a positive result from the urine drugs of abuse or alcohol screen, or history of drug or alcohol dependence in the last two years, as assessed by principal investigator. Alcohol abuse is defined as greater than 14 standard units/week for females and drug abuse is defined as known psychiatric or substance abuse disorder that would interfere with participation with the requirements of this study, including current use of any illicit drugs.
21. Participation in any other investigational drug or device trial in which administration of an investigational study drug/device occurred within 30 days or placement of a non-drug eluting medical device within 15 days prior to screening.

5.3 Subject Re-enrollment

Subjects who screen fail from the study prior to randomization and study drug administration may be re-screened and re-enrolled as long as the subject was not screen failed due to noncompliance with the protocol (i.e., positive urine drugs of abuse screen, etc.). The Medical Monitor must be consulted prior to re-screening any subject. If the subject is re-screened, the subject must be re-consented and the same subject number must be used.

Screen failure data (date of consent, demographics, reason for screen failure, and adverse events, if applicable) will be recorded in the eCRF.

5.4 Subject Withdrawal

Subjects are free to discontinue the study at any time, for any reason, and without prejudice to further treatment. The investigator may remove a subject if, in the investigator's judgment, continued participation would pose unacceptable risk to the subject or to the integrity of the study data. All procedures for early termination must be completed. Reasons for removal or withdrawal may include:

- Withdrawal of consent
- Administrative decision by the investigator or sponsor
- Ineligibility
- Significant protocol deviation
- Subject noncompliance
- Safety concern by the investigator or sponsor

- Lost to follow-up

Subjects who are withdrawn prior to completing all study visits may be replaced.

In the event of a subject's withdrawal, the investigator will promptly notify the sponsor and medical monitor and will make every effort to complete the EOS assessments. All withdrawn subjects with ongoing clinically significant clinical or laboratory findings will be followed until the finding is resolved or medically stable; reasonable attempts will be made to follow-up with subjects.

5.5 Early Termination of Study

The study may be terminated at any time by the sponsor if serious side effects occur, if potential risks to study participants are identified, if the investigator does not adhere to the protocol, or if, in the sponsor's judgment, there are no further benefits to be achieved from the study. In the event that the clinical development of the study drug is discontinued, the sponsor shall inform all investigators/institutions and regulatory authorities.

6 TREATMENT OF SUBJECTS

6.1 Identity of Study Drugs

A description of the study drugs is presented in Table 6.1.

Table 6.1 Study Drugs

Treatment Group and Number of Subjects	Treatment
IVR Dose 1 (n=10)	28-day IVR 80/4 (estradiol 80 µg/day + progesterone 4 mg/day)
IVR Dose 2 (n=10)	28-day IVR160/8 (estradiol 160 µg/day + progesterone 8 mg/day)
Oral Reference (n=10)	Oral Estrace/Prometrium QD for 29 days (Estradiol 1 mg/progesterone 100 mg oral capsule)

DARE-HRT1 IVRs will be sourced by Daré Bioscience Australia Pty LTD; oral Estrace/Prometrium will be sourced by the CRU.

6.2 Treatments Administered

Each subject will receive either an IVR or daily oral capsule for 28 days.

The IVR is self-inserted by the subject and is to remain intravaginal for 28 days, with removal of IVR in the CRU on the morning of Day 29. If a subject cannot self-insert the IVR, the site physician will insert the IVR.

Those enrolled in the oral arm (Estrace/Prometrium) will also begin dosing on Day 1, with a last dose on Day 29. Subjects enrolled in the oral arm will be directed to self-administer the medication in the morning with a meal and approximately 240 mL of water, starting on Day 2 through Day 27. Doses will be administered in the CRU each of the mornings of Days 1, 28, and 29 with a moderate-fat breakfast.

6.3 Method of Assigning Subjects to Treatment Groups

ICON will prepare the randomization scheme in accordance with its SOPs and the randomization plan, which reflect GCP standards. Refer to Section 9.3 for a description of randomization methods. Eligible subjects will be assigned to a treatment group according to the list of subject randomization assignments.

6.4 Measurements of Treatment Compliance

Treatment compliance of study drug administered by IVR will be confirmed by PK evaluation and subject daily diary. Treatment compliance of study drug administered by oral capsule will be confirmed during periods of subject confinement to the CRU, and Day 1, as IP will be administered by licensed healthcare professionals. Treatment compliance while oral capsule IP is self-administered will be confirmed by subject daily diary. Details regarding dosing, including the dose administered and the date and time of dosing, will be recorded. Additionally, meal

compliance will be confirmed during periods of subject confinement to the CRU (% of meal completed, etc. will be recorded).

6.5 Investigational Product Storage, Accountability, and Retention

6.5.1 Storage Conditions

The IP is to be stored at refrigerated temperature (2°C to 8°C). The product does not need protection from light. Additional information can be found in the Investigator's Brochure.

The investigator will ensure that all the study drugs are stored and dispensed in accordance with local regulations concerning the storage and administration of investigational drugs.

6.5.2 Drug Accountability and Retention

The investigator must ensure that all study drug supplies are kept in a secure locked area with access limited to those authorized by the investigator. The investigator must maintain accurate records of the receipt of all study drug shipped by Daré Bioscience Australia Pty LTD or their representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all study drug. Current dispensing records will also be maintained including the date and amount of study drug dispensed and the subject receiving the drug. All remaining study drug not required by regulations to be held by the CRU must be returned to Daré Bioscience Australia Pty LTD or their representative immediately after the study is completed.

It is the responsibility of Daré Bioscience Australia Pty LTD to ship a sufficient number of dosage units to allow the CRU to maintain an appropriate sampling on-site as per applicable regulatory requirements. Each reserve sample shall consist of a sufficient quantity to permit the local regulatory agency to perform 5 times all of the release tests required in the application or supplemental application.

6.6 Packaging and Labeling

6.6.1 Investigational Product

Details regarding IP packaging, labeling, and use instructions will be provided in the study reference manual.

6.6.2 Blinding of Treatment Assignment

Not applicable. This is an open-label study.

6.7 Concomitant Medications and Procedures and Other Restrictions

6.7.1 Concomitant Medications and Procedures

No concomitant medications and personal lubricants (water-based lubricants are allowed) or any intravaginal product or medications (prescription, OTC, and herbal), with the exception of paracetamol 650 mg/day (not to exceed 2000 mg total in the 7 days prior to administration of the study drugs), or vaccinations may be administered during the study unless they are prescribed by

the investigator for treatment of specific clinical events. No concomitant procedures will be performed during the study unless approved by the investigator. All medications (prescription and OTC), vitamin and mineral supplements, and herbs taken during the study will be documented on the concomitant medication eCRF. Information recorded will include: start and stop dates and times, dose and route of administration, and indication. Medications taken for a procedure will also be included, as well as the procedure itself.

6.7.2 Other Restrictions

Subjects will be instructed to adhere to the following restrictions:

- Strenuous activity (as assessed by the investigator) is prohibited from 48 hours prior to admission until final discharge from the CRU.
- Subjects are not permitted to consume alcohol for 3 days prior to admission to the CRU and should refrain from consumption of alcohol until EOS.
- Subjects are not permitted to consume any food and drink from outside of the CRU while residing at the CRU.
- Subjects must comply with the CRU smoking policy, if applicable.
- Subjects are not permitted to participate in any other clinical trial or donate blood or plasma while participating in this clinical trial.

7 STUDY ASSESSMENTS AND PROCEDURES

Subjects will undergo study procedures and assessments at time points specified in the schedule of assessments (Table 1.1 and Table 1.2).

7.1 Medical and Surgical History

The investigator or designee will collect a complete medical and surgical history at screening. Medical and surgical history will be collected at CRU admission to determine if any changes have occurred since screening.

7.2 Demographic Characteristics

Demographic characteristics including sex, age, race, and ethnicity will be recorded.

7.3 Physical Measurements

Height (cm) and body weight (kg) without shoes will be recorded.

7.4 Pharmacokinetic Assessments

7.4.1 Drug Concentration Measurements

Plasma PK samples will be collected at time points specified in the PK sampling schedule within the schedule of assessments (Table 1.1 and Table 1.2). Blood sample collection, processing, and shipping details will be outlined in a separate SRM.

Plasma concentrations of estradiol, estrone, and progesterone will be determined at using a validated method.

7.4.2 Pharmacokinetic Parameters

Pharmacokinetic variables will be calculated from the plasma concentration data using noncompartmental methods (Phoenix™ WinNonlin®, Version 6.4 or later; Certara LP, Princeton, New Jersey, USA) and actual sampling times.

The following PK parameters will be determined:

C_{avg}	Time-weighted average observed plasma concentration over 24 hours (Day 29 PK profile for oral dosing only)
C_{ss}	Steady-state concentration (IVR dosing only)
C_{max}	Maximum observed plasma concentration
C_{tau}	Concentration at the end of the dosing interval (tau) (oral dosing only)
t_{max}	The time that C_{max} was observed

AUC_{0-24}	Area under the plasma concentration-time curve from time 0 to 24 hours; calculated using the linear/log trapezoid rule (oral dosing only)
AUC_{D1-D30}	Area under the plasma concentration-time curve from time 0 (Day 1) to the time of the last quantifiable concentration on Day 30; calculated using the linear/log trapezoid rule (IVR dosing only)
$t_{½,eff}$	Effective half-life; calculated using AUC_{0-24} on Days 1 and 29 (oral dosing only)

Baseline correction, using the average of the three predose concentrations on Day 1, may be performed prior to the calculation of PK parameters by noncompartmental methods. C_{max} (and t_{max}) will be computed over each 24-hour PK profile (Days 1 and 29) and, for IVR administration, over the entire 28-day treatment interval. Additional PK parameters may be calculated as appropriate.

7.5 Safety Assessments

7.5.1 Adverse Events

Subjects will be monitored for AEs from administration of the first dose (insertion of IVR or first oral dose, as applicable) of study drug through the follow-up phone call. Refer to Section 8 for additional details.

7.5.2 Laboratory Tests

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests listed in Table 7.1. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the first dose of study drug.

Subjects will fast a minimum of 8 hours prior to clinical laboratory sample collection at screening.

During screening, if a subject has an out-of-range value for a clinical laboratory parameter that the investigator believes is not clinically significant or the investigator does not believe is correct (e.g., lab or specimen processing error), but the investigator wants to confirm with a repeat laboratory test, a single repeat is allowed to confirm the initial result.

Additional safety laboratory tests may be conducted as needed by the investigator to evaluate subject safety.

Table 7.1 Clinical Laboratory Tests

Hematology	Chemistry	Urine Dipstick
Hematocrit	Albumin	Specific gravity
Hemoglobin	Alkaline phosphatase	Ketones
Red blood cell count	Alanine aminotransferase	pH
White blood cell count	Aspartate aminotransferase	Protein
Neutrophils (absolute)	Gamma glutamyl transferase	Blood
Lymphocytes (absolute)	Direct bilirubin	Glucose
Monocytes (absolute)	Total bilirubin	Leukocyte esterase
Basophils (absolute)	Lactate dehydrogenase	Microscopic analysis (performed if blood, leukocytes, or protein are present)
Eosinophils (absolute)	Total protein	
Platelet count (estimate not acceptable)	Blood urea nitrogen	
	Creatinine	
	Calcium	
	Phosphate	
	Sodium	
	Potassium	
	Carbon dioxide	
	Chloride	
	Glucose [a]	
	Total cholesterol	
	Triglycerides [a]	

a. Fasting

For any laboratory test value outside the reference range that the investigator considers clinically significant during the on-study period (i.e., following dose administration), the investigator will:

- Repeat the test to verify the out-of-range value and clinical significance.
- Follow the out-of-range value until the value returns to normal or baseline, or until the value is deemed stable and not clinically significant by the investigator.
- Record as an AE any laboratory test value that is confirmed by repeat and the investigator considers clinically significant, requires a subject to be discontinued from the study, requires a subject to receive treatment, or requires a change or discontinuation of the study drug (if applicable).

7.5.3 Other Tests

The following tests will be performed:

- Urine drugs of abuse (at a minimum, cocaine, tetrahydrocannabinol, amphetamines, opiates, and phencyclidine), and alcohol screens
  - During the screening period, urine drugs of abuse, and alcohol screens may not be repeated for eligibility
- Serology tests (i.e., HIV-1 and HIV-2 antibodies, hepatitis B surface antigen, and HCV antibody, and any confirmatory tests performed at the discretion of the investigator)
- FSH (screening only; as needed to confirm postmenopausal status)
- Transvaginal ultrasound
- Cervical screening test (if needed)
- Pelvic examination with speculum and vaginal visual examination
- Vaginal cytology and pH
- Endometrial biopsy

7.5.4 Usability and Tolerability Questionnaire

A Usability and Tolerability questionnaire will be administered to all IVR subjects at the end of the study.

7.5.5 Vital Signs

Vital signs assessments will include oral temperature (C°), respiratory rate (breaths per minute), systolic and diastolic blood pressure (mmHg) and pulse rate (bpm). Blood pressure and pulse rate will be measured after the subject has been resting quietly in a supine position or in the most recumbent position possible for at least 5 minutes. Any clinically significant abnormal vital sign assessment requires at least one repeat measurement.

Vital signs abnormalities that are considered clinically significant initially and on confirmation, require a subject to be discontinued from the study, require a subject to receive treatment, or require a change or discontinuation from the study drug (if applicable) will be recorded as AEs.

7.5.6 Physical Examination

Comprehensive physical examinations (excluding rectal and breast examinations [unless indicated]) will be performed, and abnormal findings will be documented in the subject's eCRF. Pelvic speculum and visual examinations will be conducted to identify vaginal irritation or abnormalities at baseline (screening) and for IVR treatment arm subjects on Day 30.

An abnormal physical examination finding that is considered clinically significant and requires the subject to be discontinued from the study, requires the subject to receive treatment, or requires a change or discontinuation of the study drug (if applicable) will be recorded as an AE.

7.5.7 Electrocardiograms

Electrocardiogram assessments will be conducted at screening and Day -1 only for subject inclusion/exclusion purposes.

7.5.8 Appropriateness of Safety Assessments

Safety evaluations selected for this study are typical of those for this subject population and utilize widely accepted measures.

8 ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not thought to be related to the study drug.

Subjects will be monitored throughout the study for AEs, from IVR placement or first oral dose, as applicable, through the follow-up phone call. Adverse events that are identified at the last assessment visit (or the early termination visit) as specified in the protocol must be recorded on the AE eCRF with the status of the AE noted. All events that are ongoing at this time will be recorded as ongoing on the eCRF. All (both serious and nonserious) AEs must be followed until they are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted. The investigator should use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

The procedures specified in Section 8.4 are to be followed for reporting SAEs.

8.1 Recording Adverse Events

Adverse events are to be recorded on the AE page of the eCRF. The following information will be recorded:

- Assessment of whether or not the AE is an SAE (Section 8.2.1)
- Assessment of AE intensity (Section 8.2.2)
- Assessment of AE relationship to study drug (Section 8.2.3)
- Action taken - categorized as dose increased, dose not changed, drug interrupted, drug withdrawn, not applicable, or unknown, as applicable
- Outcome - recorded as fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, or unknown, as applicable

8.2 Assessment of Adverse Events

The investigator will assess each AE for seriousness, intensity, and relationship to study drug.

8.2.1 Serious Adverse Events

The investigator is responsible for determining whether an AE meets the definition of an SAE. An SAE is any AE occurring from ICF signing through the follow-up phone call that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- An important medical event*

*Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment. They may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: SAEs require immediate reporting to the sponsor and medical monitor. Refer to Section 8.4 for details.

8.2.2 Intensity

The intensity of an AE will be graded according to the following definitions:

- Grade 1: Mild; the subject experiences awareness of signs or symptoms but these are easily tolerated or managed without specific treatment.
- Grade 2: Moderate; the subject experiences discomfort enough to cause interference with usual activity, and/or the condition requires specific treatment.
- Grade 3: Severe; the subject is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures.
- Grade 4: Disabling or with life threatening consequences, urgent intervention indicated
- Grade 5: Death

8.2.3 Relationship to Study Drug

The relationship of an AE to the study drug should be determined by the investigator according to the following criteria:

- Not related: The event is most likely produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs, and does not follow a known response pattern to the study drug, or the temporal relationship of the event to study drug administration makes a causal relationship unlikely
- Unlikely related: The event is most likely produced by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject and it does not follow a known response pattern to the study drug
- Possibly related: The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs
- Related: The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, and cannot be reasonably explained by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs

8.3 Discontinuation due to Adverse Events

Any subject who experiences an AE may be withdrawn at any time from the study at the discretion of the investigator. Subjects withdrawn from the study due to an AE, whether serious or nonserious, may be followed by the investigator until the clinical outcome of the AE is determined. The AE(s) should be noted on the appropriate eCRFs and the subject's progress should be followed until the AE is resolved or stabilized as determined by the investigator. The sponsor and medical monitor must be notified. If the AE relates to overdose of study treatment, the Investigator's Brochure should be consulted for details of any specific actions to be taken.

8.4 Reporting Serious Adverse Events

In the event of any SAE reported or observed during the study, whether or not attributable to the study drug, site personnel will report it immediately by telephone to the sponsor, medical monitor, and SAE hotline at ICON (ICON plc Pharmacovigilance) in accordance with procedures described in the SRM and/or SAE SSP. Site personnel will follow up with a written report to the sponsor on the next working day.

SAE Report Forms will be provided to the CRU to assist in collecting, organizing, and reporting SAEs and follow-up information.

All SAEs should be followed to their resolution, with documentation provided to the sponsor, medical monitor, and ICON on a follow-up SAE Report Form.

9 STATISTICAL CONSIDERATIONS

The statistical analysis will be conducted following the principles as specified in ICH Topic E9 (CPMP/ICH/363/96).

All statistical analyses will be described in a separate statistical analysis plan.

9.1 Sample Size Calculation

A total of 30 healthy, postmenopausal female subjects (n = 10 per arm) are planned for inclusion in this study. The sample size for this study is based on the desire to accurately assess the PK of estrogens and progesterone from the DARE-HRT1 IVR, is empirically derived, and supported by the PK data obtained from ovarectomized sheep. Descriptive analyses compared to oral estrogen/progesterone therapy will also be performed.

The sample sizes provided are deemed sufficient to allow for adequate assessment of the PK of the IVR (test) formulations. Dropouts may be replaced. Subjects who terminate early from the trial may be replaced to ensure an adequate number of subjects contributing to the PK for each treatment arm.

9.2 Analysis Populations

Pharmacokinetic Population: all subjects who received a full course of study treatment for their dispensed treatment and who have sufficient concentration data for determination of PK parameters (primary endpoints); data will be analyzed according to the actual study treatment received.

Safety Population: all enrolled subjects who received active treatment, i.e., inserted an IVR (and thus who were exposed to one of the IVRs) or who took at least one dose of the oral reference.

9.3 Randomization

Upon completion of their screening procedures and confirmation of their eligibility (including an endometrial biopsy, cervical screening test, and transvaginal ultrasound), eligible subjects will be admitted to the CRU on Day -1 and will be randomized. Randomization will occur prior to initiation of treatment. Subjects will be randomized in a 1:1:1 ratio to the treatment groups.

9.4 Endpoints

9.4.1 Primary Endpoints

- C_{ss} and C_{max} for estradiol, estrone, and progesterone for each treatment

9.4.2 Secondary Endpoints

- adverse events
- clinical laboratory findings
- physical examination findings
- vital signs

- pelvic examination findings
- vaginal pH and cytology

9.4.3 Exploratory Endpoint

- responses to Usability and Tolerability questionnaire

9.5 Pharmacokinetic Statistical Analysis

The DARE-HRT1 IVR is the test (investigational) product of interest, with two dose combinations of estradiol and progesterone being assessed. Thus, comparisons of the estrogen and progesterone concentrations will be made for each dose combination as DARE-HRT1 IVR versus oral therapy.

The PK analysis will be performed for each IVR dose and assessed versus the oral reference. Graphics will be provided to allow for visual inspection of the mean and individual subject concentration-time profiles.

The PK parameters C_{avg}, C_{ss}, C_{max}, C_{tau}, t_{max}, AUC_{0-24}, AUC_{D1-D30}, and $t_{½,\,eff}$ will be determined from the plasma concentration-time profiles, where possible. Geometric mean values and coefficients of variation (CV%) will be estimated and reported.

If possible, the dose proportionality for the DARE-HRT1 IVR estradiol and progesterone doses will be assessed.

Other details of the PK analysis will be described in a separate Statistical Analysis Plan.

9.6 Safety Analysis

Adverse events, concomitant medications, clinical laboratory findings, physical examinations, pelvic examination with speculum examination and visual vaginal examination findings, endometrial biopsy findings, cervical screening test results, and vital signs for each subject will be tabulated or summarized descriptively, where appropriate.

Vital signs data (observed and change from baseline) will be summarized by time point and treatment using appropriate descriptive statistics. For the safety population, changes from baseline at each post-randomization visit and end of treatment will be compared among treatment arms. Qualitative analysis of laboratory tests in terms of abnormality will be performed. Findings on physical examination will be reported and compared at the screening and end of treatment.

The number and percentage of subjects reporting any treatment-emergent AE will be tabulated by system organ class and preferred term for each treatment (coded using MedDRA). Treatment-emergent AEs will be further classified by severity and relationship to treatment.

10 ACCESS TO SOURCE DATA/DOCUMENTS

The investigator will provide direct access to source data and documents for individuals conducting study-related monitoring, audits, IRB/IEC review, and regulatory review. The investigator must inform the study subject that his/her study-related records may be reviewed by the above individuals without violating the subject's privacy of personal health information in compliance with HIPAA regulations.

By signing this protocol, the investigator affirms to the sponsor that the investigator will maintain, in confidence, information furnished to him or her by the sponsor and will divulge such information to the IRB/IEC under an appropriate understanding of confidentiality with such board.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Daré Bioscience Australia Pty LTD / ICON will implement and maintain quality control and quality assurance procedures with written SOPs to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

11.1 Conduct of Study

This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof (Tokyo 2004), and in accordance with the ICH E6 Guidelines on GCPs (CPMP/ICH/135/95). Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed by an IRB or IEC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject will give his or her written, informed consent before any protocol-driven tests or evaluations are performed.

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB/IEC, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study and are approved by the medical monitor and/or Daré Bioscience Australia Pty LTD. Any deviation may result in the subject having to be withdrawn from the study, and may render that subject nonevaluable.

11.1.1 Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the subject, investigator, or site staff. Examples of deviations include, but are not limited to:

- Failure to adhere to study exclusion and inclusion criteria
- Failure to comply with dispensing or dosing requirements
- Use of medications, food, drink, herbal remedies, or supplements that are specifically prohibited in the protocol
- Missed or out-of-window visits
- Drug dosing not administered within the time frame specified in the protocol

- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, PK blood draws, medical history, etc. – either tests not done, incorrect tests done, or not done within the time frame specified in the protocol
- Procedural deviations such as incorrect storage of investigational product, failure to update the ICF when new risks become known, failure to obtain IRB approvals for the protocol and ICF revisions

At the outset of the study, a process for defining and handling protocol deviations will be established. This will include determining which violations will be designated "key," requiring immediate notification to the medical monitor and Daré Bioscience Australia Pty LTD. The investigator is responsible for seeing that any known protocol deviations are recorded and handled as agreed.

11.2 Protocol Amendments

Only Daré Bioscience Australia Pty LTD may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between Daré Bioscience Australia Pty LTD, the medical monitor, and the investigator. All amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/IEC prior to their implementation.

11.3 Monitoring of Study

The investigator will permit the site monitor to review study data as frequently as is deemed necessary to ensure data are being recorded in an adequate manner and protocol adherence is satisfactory.

The investigator will provide access to medical records for the monitor to verify eCRF entries. The investigator is expected to cooperate with Daré Bioscience Australia Pty LTD/designee in ensuring the study adheres to GCP requirements.

The investigator may not recruit subjects into the study until Daré Bioscience Australia Pty LTD or a designee has conducted a visit at the site to conduct a detailed review of the protocol and eCRF. With agreement of Daré Bioscience Australia Pty LTD, attendance at an investigator meeting may fulfil this requirement.

12 ETHICS

12.1 Institutional Review Board/Independent Ethics Committee Approval

12.1.1 Ethics Review Prior to Study

The investigator will ensure that the protocol and consent form are reviewed and approved by the appropriate IRB/IEC prior to the start of any study procedures. The IRB/IEC will be appropriately constituted and will perform its functions in accordance with ICH GCP guidelines and local requirements as applicable.

12.1.2 Ethics Review of Other Documents

In addition, the IRB will approve all protocol amendments (except for Daré Bioscience Australia Pty LTD-approved logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures, written information to be provided to the subjects, available safety information, information about payment and compensation available to subjects, the investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB/IEC and regulatory authority as applicable.

12.2 Written Informed Consent

The nature and purpose of the study will be fully explained to each subject (or the subject's legally responsible guardian). The subjects must be given ample time and opportunity to inquire about details of the study, to have questions answered to their satisfaction, and to decide whether to participate. Written informed consent must be obtained from each subject (or guardian) prior to any study procedures being performed.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Reporting and Case Report Forms

13.1.1 Case Report Forms

The investigator will be provided with eCRFs, and will ensure all data from subject visits are promptly entered into the eCRFs in accordance with the specific instructions given. The investigator must sign the eCRFs to verify the integrity of the data recorded.

13.1.2 Laboratory Data

All safety samples will be analyzed by the CRU and all bioanalytical samples will be analyzed by Agilex Biolabs Pty Ltd, Adelaide, South Australia. A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. The investigator must maintain source documents such as laboratory reports and complete history and physical examination reports.

13.1.3 Retention of Source Documents

The investigator must maintain source documents such as laboratory reports, x-rays, ECGs, consultation reports, and complete history and physical examination reports.

13.2 Retention of Essential Documents

The study essential documents must be maintained as specified in the ICH guidelines for GCP and the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

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

14 ADMINISTRATIVE INFORMATION

14.1 Financing and Insurance

Financing and insurance will be addressed in a separate agreement between Daré Bioscience Australia Pty LTD and the investigator.

14.2 Publication Policy

Daré Bioscience Australia Pty LTD will retain ownership of all data. All proposed publications based on this study will be subject to Daré Bioscience Australia Pty LTD's approval requirements.

15 REFERENCES

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APPENDIX A Usability and Tolerability Questionnaire

APPENDIX B Subject Daily Diary

16 SIGNATURES

Protocol Number: DARE-HRT1-001

Protocol Title: A Phase 1, Open-Label, Parallel Group Study to Evaluate the Pharmacokinetics and Safety of DARE-HRT1 (80 µg Estradiol/4 mg Progesterone and 160 µg Estradiol/8 mg Progesterone Intravaginal Rings) in Healthy Post-Menopausal Women

Daré Bioscience Australia Pty LTD Signatures

This clinical study protocol has been reviewed and approved by Daré Bioscience Australia Pty LTD.

March 6, 2019

Nadene Zack, MS
Senior Director, Clinical Operations

Date

Protocol Number: DARE-HRT1-001

Protocol Title: A Phase 1, Open-Label, Parallel Group Study to Evaluate the Pharmacokinetics and Safety of DARE-HRT1 (80 μg Estradiol/4 mg Progesterone and 160 μg Estradiol/8 mg Progesterone Intravaginal Rings) in Healthy Post-Menopausal Women

Daré Bioscience Australia Pty LTD Signatures

This clinical study protocol has been reviewed and approved by Daré Bioscience Australia Pty LTD.

David Friend

03/06/2019

David Friend, PhD
Chief Scientific Officer

Date

Protocol Number: DARE-HRT1-001

Protocol Title: A Phase 1, Open-Label, Parallel Group Study to Evaluate the Pharmacokinetics and Safety of DARE-HRT1 (80 μg Estradiol/4 mg Progesterone and 160 μg Estradiol/8 mg Progesterone Intravaginal Rings) in Healthy Post-Menopausal Women

Investigator Signature

I agree to conduct the aforementioned study according to the terms and conditions of the protocol, GCP guidelines, and all other applicable local and regulatory requirements. All information pertaining to the study will be treated in a confidential manner.

_____
Site Name

_____
Print Name

_____ _____
Signature Date