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ORIGINAL ARTICLE



Safety and acceptability of intravaginal rings releasing estradiol and progesterone

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ABSTRACT

Objective: This study aimed to evaluate the safety and acceptability of two fixed-dose 28-day vaginal ring formulations of 17 β -estradiol (E2) and progesterone (P4) to treat vasomotor symptoms (VMS) and the genitourinary syndrome of menopause.

Design: DARE HRT1-001 was the first-in-woman study of 28-day exposure to two 28-day intravaginal rings (IVRs) designed to release 80 μ g/day E2 + 4 mg/day P4 (IVR1) or 160 μ g/day E2 + 8 mg/day P4 (IVR2) compared with oral E2 1 mg/day + oral P4 100 mg/day. To assess safety, participants completed a daily diary to record treatment emergent adverse events (TEAEs). To determine acceptability, at the end of treatment IVR users completed a questionnaire assessing tolerability and usability.

Results: Enrolled women ($n = 34$) were randomized to use IVR1 ($n = 10$), IVR2 ($n = 12$) or oral ($n = 12$). Thirty-one participants (IVR1 = 10, IVR2 = 10, oral = 11) completed the study. The TEAE profile of those in the IVR groups were similar to the referent oral regimen. TEAEs related to the study product were more common with IVR2 use. Endometrial biopsies were not performed unless endometrial thickness was >4 mm or for clinically significant postmenopausal bleeding. One IVR1 participant had an endometrial stripe increase from 4 mm at screening to 8 mm at the end of treatment. The biopsy indicated no evidence of plasma cells or endometritis and no evidence of atypia, hyperplasia or malignancy. Two other endometrial biopsies were performed for postmenopausal bleeding with similar findings. There were no clinically meaningful laboratory or vital sign abnormalities or trends identified in observed values or changes from baseline. Pelvic speculum examination identified no clinically significant abnormalities in any participant at any visit. Tolerability and usability data demonstrated that both IVRs were generally highly acceptable.

Conclusions: Both IVR1 and IVR2 were safe and well tolerated in healthy postmenopausal women. TEAE profiles were comparable to the referent oral regimen.

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Introduction

The advent of the menopause is associated with many symptoms, the most common of which are vasomotor symptoms (VMS) such as hot flashes and night sweats. Other significant symptoms include vaginal dryness, dyspareunia, sleep disturbance and arthralgia [1]. Menopause is associated with a reduction in estrogen levels. Lower levels of estrogen cause thinning of the vaginal epithelium, reduced vaginal elasticity and an increase in connective tissue with eventual fibrotic changes. Decreased estrogen levels are also associated with a reduction in vaginal blood flow and lubrication [2]. These physiological changes can lead to vulvovaginal atrophy (VVA) and symptoms of vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity and vaginal bleeding associated with sexual activity.

Hormone therapy (local and systemic) is accepted as an effective treatment for the management of both VMS and symptomatic VVA. The use of estrogen for the treatment of

symptoms of menopause is advocated by several professional medical organizations [3,4].

Although estrogen is the most effective treatment for VMS, unopposed treatment (estrogen alone without a progestogen) is associated with increased risk of endometrial hyperplasia and carcinoma in women with an intact uterus. A meta-analysis of 30 studies showed a relative risk of cancer of 2.3 (95% confidence interval 2.1–2.5) among women using estrogen without a progestogen [5]. 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 [6]. Furthermore, a Cochrane Review noted a greater effect on reducing hot flash severity following treatment with estrogen and progestogens than with estrogen alone [7].

DARE-HRT1 is an ethylene vinyl acetate (EVA) copolymer intravaginal ring (IVR) designed to release bioidentical 17 β -estradiol (E2) and progesterone (P4) over 28 days of use and is being developed for the following indications: treatment of moderate-to-severe VMS associated with menopause in

women with an intact uterus; and reduction in the incidence of symptomatic VVA in women requiring treatment for VMS due to menopause.

To understand the safety, tolerability and usability of these IVRs, a phase 1 clinical study (DARE-HRT1-001) was conducted in Australia. The primary objectives of the study were to describe the pharmacokinetic (PK) parameters over 28 days of two different dose combinations of the IVRs: E2 at an average daily release rate of 80 µg/day and P4 at a daily release rate of 4 mg/day (IVR1); and E2 at a daily release rate of 160 µg/day and P4 at 8 mg/day (IVR2). The results of the PK assessment have been published elsewhere [8]. A referent arm of oral E2 1 mg/day + oral P4 100 mg/day (oral) was also evaluated. The secondary objectives of the study were to assess the safety and acceptability (tolerability and usability) of each IVR, and the results of these objectives are reported herein.

Materials and methods

Study design

This was a randomized, open-label, three-arm, parallel group study in approximately 30 healthy postmenopausal women with an intact uterus conducted at two sites in Australia (PARC Clinical Research, Adelaide, South Australia and Keogh Institute for Medical Research, Nedlands, Western Australia). The primary objective of the study was to assess the PK of E2, E1 and P4 from DARE-HRT1 IVRs at two dose strengths (IVR1 and IVR2, respectively) over 28 days. The rings were composed of EVA copolymers. Oral E2 1 mg (Estrifem®)/P4 100 mg (Prometrium®) once daily for 29 days served as the active reference. The results of the PK analysis are reported elsewhere [8]. The secondary objective was to assess the safety and tolerability of the IVRs, while the exploratory objective was to assess usability and participant tolerability of the IVRs.

The main inclusion criteria admitted healthy postmenopausal female participants (postmenopausal was defined as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum follicle stimulating hormone [FSH] levels >40 mIU/ml, or 6 weeks post-surgical bilateral oophorectomy without hysterectomy), with body mass index ≥ 18 and ≤ 38 kg/m², normal cervix and vagina, intact uterus, up to date with all Australian screening requirements for cervical cancer, normal mammogram within 24 months of screening and no known hypersensitivity to E2 or P4, or the components of the IVR. The main exclusionary criteria were: endometrial thickness >4 mm on transvaginal ultrasound at screening; history of endometrial hyperplasia or cervical or uterine carcinoma; hysterectomy; use of any estrogen and/or progestogen not meeting washout requirements; and clinically significant uterine fibroids identified at screening.

At the screening visit, serology (HIV, hepatitis B and C), FSH, drug/alcohol screening, transvaginal ultrasound, urine dipstick and PK blood samples were performed, and information about prior and concomitant medications was collected. A similar schedule of visits occurred in the oral arm although there was one less visit compared to the IVR arms. Two

women had endometrial biopsies collected during the study for postmenopausal bleeding and one at the end of the study when the endometrial thickness increased from 4 to 8 mm.

Safety was assessed by the following endpoints: adverse events, clinical laboratory findings, physical examination findings, vital signs, pelvic examination findings and vaginal pH. IVR acceptability (usability and tolerability) was an exploratory endpoint and was assessed by questionnaires from participants in the IVR groups only.

Collection of data

Safety analyses were conducted on the Safety Population (SP), which was defined as all screened participants who received active treatment, that is, had inserted an IVR (and thus were exposed to one of the IVRs), or who took at least one dose of the oral reference. The SP was used for all listings, and for all safety variables. All adverse events were coded by primary system organ class and preferred term according to Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 and presented by participant in data listings. A treatment emergent adverse event (TEAE) was defined as any adverse event that began or worsened after the first dose of the study drug.

The overall incidence of TEAEs (number and percentage of participants) as well as the number of events were summarized for each treatment arm. They were subcategorized as mild TEAE, moderate TEAE, severe TEAE, TEAE assessed as at least possibly related, serious adverse event (SAE), TEAE leading to study or drug discontinuation, SAE related to study drug, life-threatening SAE and SAE resulting in death.

Acceptability was assessed with a usability and tolerability questionnaire administered to all IVR participants at the end of the study. Responses to the questions were summarized using the count and percentage. Usability and tolerability questionnaire data were collected. Questions covered ease of use, comfort and convenience.

The study followed the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and was reviewed and approved by each institution's Ethics Committee. The National Clinical Trial number for this study is NCT05418426.

Results

Safety

Overall, 34 women were screened and randomized, and 31 women (91.2%) completed the study. All 34 screened women (100%) were included in the Screened Population and the Randomized Population. Thirty-three women (97.1%) were included in the SP. Table 1 presents their age, weight, height, body mass index, vaginal pH and cervical screening results. Three women were withdrawn from the study: two IVR2 users for unrelated TEAEs (mild upper respiratory infection, headache) and one oral user for exclusionary pretreatment laboratory criteria (elevated alanine transferase), thus

Table 1. Summary of demographic data and baseline characteristics (Safety Population) at screening.

Parameter	Treatment group ^a			
	IVR1	IVR2	Oral	Overall
Age				
Number (n)	10	12	11	33
Mean (SD)	58.8 (6.66)	56.0 (3.72)	57.2 (4.42)	57.2 (4.97)
Median (min, max)	58.0 (47, 69)	55.5 (50, 63)	57.0 (51, 64)	57.0 (47, 69)
Weight				
Number (n)	10	12	11	33
Mean (SD)	72.1 (10.0)	80.1 (15.5)	77.0 (10.9)	76.6 (12.6)
Median (min, max)	71.6 (58.1, 84.6)	73.5 (64.4, 106)	73.5 (65.4, 98.2)	73.5 (58.1, 106)
Height (cm)				
Number (n)	10	12	11	33
Mean (SD)	160 (3.97)	165 (5.73)	165 (3.52)	163 (5.06)
Median (min, max)	160 (151, 164)	165 (153, 174)	164 (158, 171)	164 (151, 174)
Body mass index (kg/m ²)				
Number (n)	10	12	11	33
Mean (SD)	28.2 (3.20)	29.3 (4.98)	28.2 (3.18)	28.6 (3.86)
Median (min, max)	27.3 (24.1, 32.8)	27.3 (23.5, 37.9)	27.8 (24.4, 34.0)	27.5 (23.5, 37.9)
Vaginal pH				
Number (n)	10	12	11	33
Mean (SD)	5.16 (0.75)	5.32 (0.63)	5.61 (0.94)	5.37 (0.78)
Median (min, max)	4.85 (4.4, 6.0)	5.00 (4.4, 6.0)	5.70 (4.0, 7.0)	5.30 (4.0, 7.0)
Cervical screening test, n (%)				
Normal	9 (90.0)	11 (91.7)	11 (100)	31 (93.9)
Abnormal	0	0	0	0
Not collected	1 (10.0)	1 (8.3)	0	2 (6.1)

E2, 17 β -estradiol; IVR, intravaginal ring; max, maximum; min, minimum; P4, progesterone; SD, standard deviation.

^aIVR1, 28-day IVR (E2 80 μ g/day + P4 4 mg/day). IVR2, 28-day IVR (E2 160 μ g/day + P4 8 mg/day). Oral, oral reference arm administered once-daily for 29 days (E2 1 mg tablet/P4 100 mg capsule).

Table 2. Overall summary of treatment-related adverse events (Safety Population).

Adverse event category ^b	Treatment group ^a					
	IVR1 (N = 10)		IVR2 (N = 12)		Oral (N = 11)	
	No. of participants (%) ^c	No. of events ^d	No. of participants (%) ^c	No. of events ^d	No. of participants (%) ^c	No. of events ^d
Any TEAE	8 (80.0)	30	9 (75.0)	47 ^e	8 (72.7)	17
Severity						
Mild (Grade 1) TEAE	7 (70.0)	29	9 (75.0)	38	8 (72.7)	17
Moderate (Grade 2) TEAE	1 (10.0)	1	2 (16.7)	9	0	0
Severe (Grade 3) TEAE	0	0	0	0	0	0
TEAE related to study drug ^f	7 (70.0)	18	7 (58.3)	37	5 (45.5)	8
Mild (Grade 1) TEAE	7 (70.0)	18	7 (58.3)	29	5 (45.5)	8
Moderate (Grade 2) TEAE	0	0	2 (16.7)	8	0	0
TEAE leading to study drug and study discontinuation	0	0	1 (8.3)	1	0	0
Any SAE	0	0	0	0	0	0
SAE related to study drug	0	0	0	0	0	0
Life-threatening SAE	0	0	0	0	0	0
SAE resulting in death	0	0	0	0	0	0

E2, 17 β -estradiol; IVR, intravaginal ring; N, number of participants in the safety set; P4, progesterone; SAE, serious adverse event; TEAE, treatment emergent adverse event.

^aIVR1, 28-day IVR (E2 80 μ g/day + P4 4 mg/day). IVR2, 28-day IVR (E2 160 μ g/day + P4 8 mg/day). Oral, oral reference administered once-daily for 29 days (E2 1 mg tablet/P4 100 mg capsule).

^bParticipants with multiple events in the same category were counted only once in that category for each treatment. Participants with events in more than one category were counted once in each of those categories for each treatment.

^cNumber of participants reporting at least one event of the type specified. For participants with 'Any TEAE', the number of participants reporting at least one event of any type is represented.

^dThe total number of events of the type specified. Participants could be represented more than once. For 'Any Event', the number represents the total number of TEAEs.

^eOne participant accounted for 26 of the 47 total number of TEAEs in the IVR2 treatment group.

^fA drug-related TEAE was one whose relationship to study drug was noted as 'Possibly Related' or 'Related'.

31 participants (IVR1 = 10, IVR2 = 10, oral = 11) completed the study.

The overall summary of TEAEs in the SP is presented in Table 2. Overall, 8/10 participants (80.0%) reported 30 TEAEs in the IVR1 arm, 9/12 participants (75.0%) reported 47 TEAEs in the IVR2 arm and 8/11 participants (72.7%)

reported 17 TEAEs in the oral reference arm. In the IVR1 arm, 7/10 participants (70.0%) reported 18 drug-related TEAEs; in the IVR2 arm, 7/12 participants (58.3%) reported 37 drug-related TEAEs; and in the oral reference arm, 5/11 participants (45.5%) reported eight drug-related TEAEs.

Mild (Grade 1) TEAEs were experienced by 7/10 participants (70.0%) in the IVR1 group (29 events), 9/12 participants (75.0%) in the IVR2 group (38 events) and 8/11 participants (72.7%) in the oral reference group (17 events). Moderate (Grade 2) TEAEs were experienced by 1/10 participants (10.0%) in the IVR1 group (one event), 2/12 participants (16.7%) in the IVR2 group (nine events) and zero participants in the oral reference group. No severe, life-threatening or deadly TEAEs or SAEs were reported.

Endometrial biopsies were performed only if the endometrial thickness on ultrasound was >4 mm or if clinically significant postmenopausal bleeding was reported. One IVR1 woman's endometrial thickness increased from 4 mm at screening to 8 mm at the end of treatment. A biopsy indicated no evidence of plasma cells or endometritis and no evidence of atypia, hyperplasia or malignancy. Two other endometrial biopsies were performed during the study for postmenopausal bleeding and with no evidence of plasma cells or endometritis and no evidence of atypia, hyperplasia or malignancy. There were no clinically meaningful laboratory or vital sign abnormalities or trends identified in observed values or changes from baseline. Pelvic speculum examination identified no clinically significant abnormalities in any woman at any visit.

Table 3 presents a summary of the TEAEs of the reproductive system and breast disorders and vascular disorders in the SP. Overall, the most frequently experienced TEAE (>10% of participants in at least one dose group, in order of decreasing frequency) was vaginal bleeding: 2/10 participants (20.0%) in

the IVR1 group, 3/12 participants (25.0%) in the IVR2 group and 1/11 participants (9.1%) in the oral reference group.

Vaginal discharge was experienced by 2/10 participants (20.0%) in the IVR1 group, 1/12 participants (8.3%) in the IVR2 group and 1/11 participants (9.1%) in the oral treatment group. Vulvovaginal candidiasis was experienced by 2/10 participants (20.0%) in the IVR1 group and 1/12 participants (8.3%) in the IVR2 group.

Vaginal pH

Vaginal pH results are presented in Table 4. The mean (standard deviation) vaginal pH results at day 30 were decreased from screening for treatment groups.

Table 4. Summary of vaginal pH findings (Safety Population).

Visit	Summary statistic	Treatment, n (%) ^a		
		IVR1 (N = 10)	IVR2 (N = 10)	Oral (N = 11)
Screening	<i>n</i>	10	12	11
	Mean (SD)	5.16 (0.75)	5.32 (0.63)	5.61 (0.94)
	Min, max	4.4, 6.0	4.4, 6.0	4.0, 6.0
Day 30	<i>n</i>	10	10	11
	Mean (SD)	4.86 (0.69)	4.98 (0.80)	5.02 (0.69)
	Min, max	4.0, 6.0	4.0, 6.0	4.0, 6.0

Test strips included pH range of 4–6. Percentages calculated as $100 \times (\text{number of women } [n] / N)$. E2, 17 β -estradiol; IVR, intravaginal ring; max, maximum; min, minimum; N, number of women in the respective category; *n*, number of non-missing data points; P4, progesterone; SD, standard deviation.

^aIVR1, 28-day IVR (E2 80 μ g/day + P4 4 mg/day). IVR2, 28-day IVR (E2 160 μ g/day + P4 8 mg/day). Oral, oral reference administered once-daily for 29 days (E2 1 mg tablet/P4 100 mg capsule).

Table 3. TEAEs of the reproductive system and breast disorders and vascular disorders, preferred term and treatment (Safety Population).

System organ class preferred term ^b	Treatment group ^a					
	IVR1 (N = 10)		IVR2 (N = 12)		Oral (N = 11)	
	No. of participants (%) ^c	No. of events ^d	No. of participants (%) ^c	No. of events ^d	No. of participants (%) ^c	No. of events ^d
Reproductive system and breast disorders	6 (60.0)	14	7 (58.3)	24	5 (45.5)	6
Breast pain	0	0	0	0	1 (9.1)	1
Breast tenderness	1 (10.0)	1	2 (16.7)	3	0	0
Dysmenorrhea	0	0	0	0	1 (9.1)	1
Dyspareunia	0	0	1 (8.3)	1	0	0
Intermenstrual bleeding	0	0	1 (8.3)	1	0	0
Nipple pain	0	0	1 (8.3)	1	0	0
Pelvic discomfort	1 (10.0)	1	2 (16.7)	2	2 (18.2)	2
Pelvic pain	1 (10.0)	1	1 (8.3)	1	0	0
Sexual dysfunction	0	0	1 (8.3)	1	0	0
Vaginal discharge	2 (20.0)	2	1 (8.3)	1	1 (9.1)	1
Vaginal bleeding/spotting	2 (20.0)	2	3 (25.0)	3	1 (9.1)	1
Vulvovaginal burning sensation ^e	2 (20.0)	2	3 (25.0)	4	0	0
Vulvovaginal dryness	1 (10.0)	1	0	0	0	0
Vulvovaginal pain	1 (10.0)	1	1 (8.3)	3	0	0
Vulvovaginal pruritus ^e	2 (20.0)	2	2 (16.7)	3	0	0
Vulvovaginal swelling	1 (10.0)	1	0	0	0	0
Vascular disorders	1 (10.0)	1	1 (8.3)	1	0	0
Hemorrhage	1 (10.0)	1	0	0	0	0
Hot flush	0	0	1 (8.3)	1	0	0

E2, 17 β -estradiol; IVR, intravaginal ring; N, number of women in the Safety Population; P4, progesterone; TEAE, treatment emergent adverse event.

^aIVR1, 28-day IVR (E2 80 μ g/day + P4 4 mg/day). IVR2, 28-day IVR (E2 160 μ g/day + P4 8 mg/day). Oral, oral reference administered once-daily for 29 days (E2 1 mg tablet/P4 100 mg capsule).

^bParticipants with multiple events in the same category were counted only once in that category for each treatment. Participants with events in more than one category were counted once in each of those categories for each treatment.

^cNumber of participants reporting at least one event of the type specified. For participants with 'Any TEAE', the number of participants reporting at least one event of any type is represented.

^dThe total number of events of the type specified. Participants could be represented more than once.

^eParticipants 102–129 (IVR2) experienced vulvovaginal candidiasis on days 16–24 and associated adverse events of vulvovaginal pruritus on days 16–24 and vulvovaginal burning sensation on days 18–20.

Table 5. Acceptability (usability and tolerability) of the IVRs.

Category/subcategory question	Response	IVR1 (N = 10), ^a n (%)	IVR2 (N = 12), ^b n (%)
Ease of use			
Ease of insertion	Very easy	8 (80)	7 (58)
	Somewhat easy	1 (10)	4 (33)
	Neutral, not easy or difficult	0	0
	Somewhat difficult	0	0
	Very difficult	1 (10)	0
Ease of removal	Very easy	8 (80)	7 (58)
	Somewhat easy	0	2 (17)
	Neutral, not easy or difficult	1 (10)	0
	Somewhat difficult	1 (10)	1 (8)
	Very difficult	0	1 (8)
Comfort and convenience			
IVR is comfortable to wear	Strongly agree	8 (80)	9 (75)
	Agree	1 (10)	1 (8)
	Neither agree nor disagree	1 (10)	0
	Disagree	0	1 (8)
	Strongly disagree	0	0
IVR is convenient to use	Strongly agree	8 (80)	8 (67)
	Agree	2 (20)	2 (17)
	Neither agree nor disagree	0	0
	Disagree	0	0
	Strongly disagree	0	1 (8)
IVR works with my lifestyle	Strongly agree	8 (80)	8 (67)
	Agree	1 (10)	2 (17)
	Neither agree nor disagree	1 (10)	0
	Disagree	0	0
	Strongly disagree	0	1 (8)

Percentages calculated as $100 \times (\text{number of participants } [n] / N)$. E2, 17 β -estradiol; IVR, intravaginal ring; N, number of women in the respective category; n, number of non-missing data points; P4, progesterone.

^aIVR1, 28-day IVR (E2 80 μ g/day + P4 4 mg/day). IVR2, 28-day IVR (E2 160 μ g/day + P4 8 mg/day).

^bOne woman in the IVR2 group did not provide usability or tolerability data.

Table 6. Additional usability and tolerability of the IVRs.

Category/subcategory question	Response	IVR1 (N = 10), ^a n (%)	IVR2 (N = 12), ^b n (%)
Please rate overall comfort of the IVR	Very comfortable	6 (60)	7 (58)
	Comfortable	2 (20)	3 (25)
	Neither comfortable nor uncomfortable	1 (10)	0
	Uncomfortable	1 (10)	1 (8)
	Very uncomfortable	0	0
How likely would you be to use the IVR for a condition or disease that is related to women's health (e.g. hormone therapy, overactive bladder, uterine fibroids)	Very likely	6 (60)	10 (83)
	Somewhat likely	2 (20)	0
	Neither likely nor unlikely	1 (10)	0
	Somewhat unlikely	0	0
	Very unlikely	1 (10)	1 (8)
How likely would you be to use the IVR for a condition or disease that is not related to women's health (e.g. high blood pressure, diabetes)	Very likely	4 (40)	10 (83)
	Somewhat likely	3 (30)	0
	Neither likely nor unlikely	1 (10)	0
	Somewhat unlikely	0	0
	Very unlikely	1 (10)	1 (8)

Percentages calculated as $100 \times (\text{number of participants } [n] / N)$. E2, 17 β -estradiol; IVR, intravaginal ring; N, number of women in the respective category; n, number of non-missing data points; P4, progesterone.

^aIVR1, 28-day IVR (E2 80 μ g/day + P4 4 mg/day). IVR2, 28-day IVR (E2 160 μ g/day + P4 8 mg/day).

^bOne woman in the IVR2 group did not provide usability or tolerability data.

IVR acceptability

Responses from the IVR acceptability based on a usability and tolerability questionnaire are presented in Tables 5 and 6. Tolerability of the IVRs were reported by the categories of ease of use and of comfort and convenience. The majority of women in both IVR treatment groups responded favorably for each category related to ease of insertion/removal, comfort when wearing, convenience to use, fit with lifestyle and likelihood to use IVR for future health conditions. At least 80% of participants in both IVR treatment groups (80% in the IVR1 group and 83.3% in the IVR2 group) reported the IVR as comfortable or very comfortable. Similarly, at least

80% of participants in both IVR groups (80% in the IVR1 group and 83.3% in the IVR2 group) stated that they were either somewhat or very likely to use the IVR for a condition or disease related to women's health. Additionally, 100% of participants in the IVR1 group and 83.4% of participants in the IVR2 group agreed or strongly agreed that the IVR was convenient to use.

Discussion

This study examined the safety and acceptability of two different IVRs in a small group of women. Vaginal rings have

been evaluated as treatments for VMS or vaginal symptoms associated with menopause (i.e. VVA) [9–22]. The rings used in this study were segmented so that release of each active ingredient occurs from separate regions of the ring. They were designed to be similar in mechanical properties to those of NuvaRing® (Organon, Jersey City, NJ, USA). Both IVRs are composed with the same EVA thermoplastic material and have similar dimensions.

The majority of women (25/33, 75.8%) experienced at least one TEAE. It was more common for the TEAEs to be attributed to the study product in the IVR2 group. However, one of the 12 IVR2 women accounted for 26 of the 47 reported TEAEs in that group. Overall, the IVR1 and IVR2 safety results related to the levels of exposure to the two active ingredients, E2 and P4. Both hormones have a long history of postmenopausal use administered by several routes. Bleeding/spotting and breast tenderness are common adverse events when E2 and P4 were administered by vaginal rings [15]. These complaints occurred early in the trial (the first 1–2 months). In this study, there were reports of vaginal bleeding and spotting in all three groups with a slightly higher number in the IVR groups (see Table 4). This is a common occurrence on the initiation of combined E2/P4 therapy as noted earlier. Breast tenderness was noted in the IVR1 (1/10 participants) and IVR2 (2/12 participants) groups but neither group reported breast pain.

The decrease in vaginal pH following administration of the IVRs and orally administered E2 and P4 was consistent with the use of E2 in a postmenopausal population [23].

In general, vaginal rings composed of EVA are well tolerated [24–27]. The women using IVR1 and IVR2 reported good tolerability, as summarized in Tables 5 and 6. This finding is important in that IVR1 and IVR2 are segmented rings. Each segment has somewhat different mechanical properties as opposed to NuvaRing®, which is a uniform coaxially extruded, single welded IVR [28].

In conclusion, both IVR1 (E2 80 µg/day + P4 4 mg/day) and IVR2 (E2 160 µg/day + P4 8 mg/day) were safe and well tolerated in healthy postmenopausal women. TEAE profiles were comparable to the referent oral regimen. IVR1 and IVR2 rings have shown good safety and tolerability (acceptability/useability) profiles in this phase 1 trial. Since the number of women in this study was small, additional studies in larger groups need to be undertaken to prove their usefulness in clinical practice. These vaginal rings may prove to be another tool in the treatment repertoire for women with postmenopausal symptoms.

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