Results of a Phase 1 Pharmacokinetic and Safety Study of DARE-HRT1, a 28-day Intravaginal Ring for Codelivery of Bio-Identical Estradiol and Progesterone

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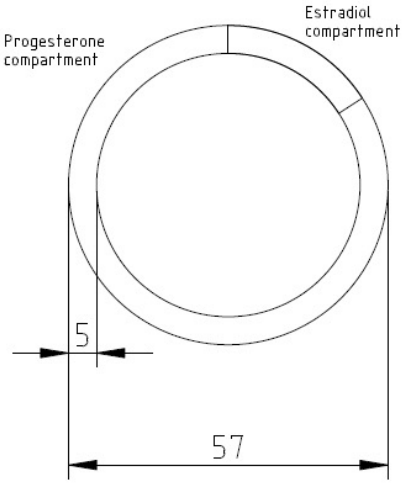
Disclosures

- **Dr Kim Hartman is a paid consultant for Daré Bioscience, Inc.**
- **Dr David Friend and Ms Nadene Zack are paid employees of Daré Bioscience, Inc. and hold stock options or stock in the company**

DARE-HRT1

- DARE-HRT1 is a segmented intravaginal ring (IVR) composed of an elastomer (ethylene vinyl acetate copolymer) designed to release drugs over a 28-day period
- The segments are loaded with bio-identical 17β-estradiol (E2) or progesterone (P4) for the treatment of vasomotor symptoms (VMS) or genitourinary symptoms of menopause
- By varying loading and length of the IVR segments, it is possible to release drugs at a number of desired rates

Dimensions are mm



DARE-HRT1-001

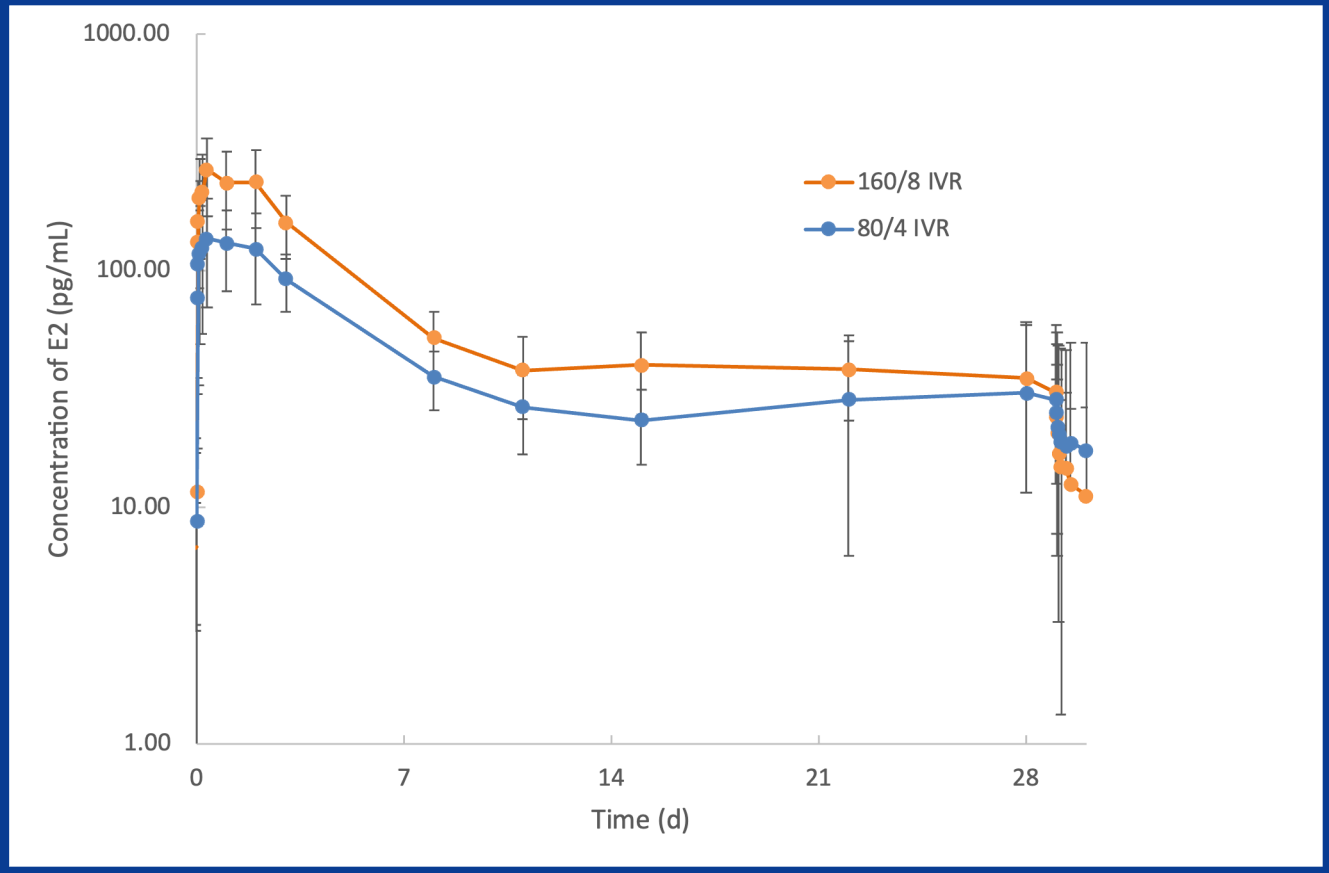
- A study entitled 'A Phase 1, Open-Label, Parallel Group Study to Evaluate the Pharmacokinetics and Safety of DARE-HRT1 (80 µg Estradiol/4 mg Progesterone and 160 µg Estradiol/8 mg Progesterone Intravaginal Rings) in Healthy Post-Menopausal Women' was conducted at two sites in Australia
  - Robinson Research Institute, University of Adelaide, Adelaide
  - Keogh Institute for Medical Research, Sir Charles Gairdner Hospital, Nedlands
- Primary Objective
  - To describe the PK parameters over 28 days of two different dose combinations of DARE-HRT1 intravaginal ring (IVR):
    - Estradiol (E2) 80 µg/day and progesterone (P4) 4 mg/day (80/4) IVR
    - E2 160 µg/P4 8 mg/day (160/8) IVR
- 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® (1 mg E2)/Prometrium® (100 mg P4)
- Exploratory Objective
  - To assess usability and subject tolerability of the DARE-HRT1 IVR

DARE-HRT1-001 Demographics

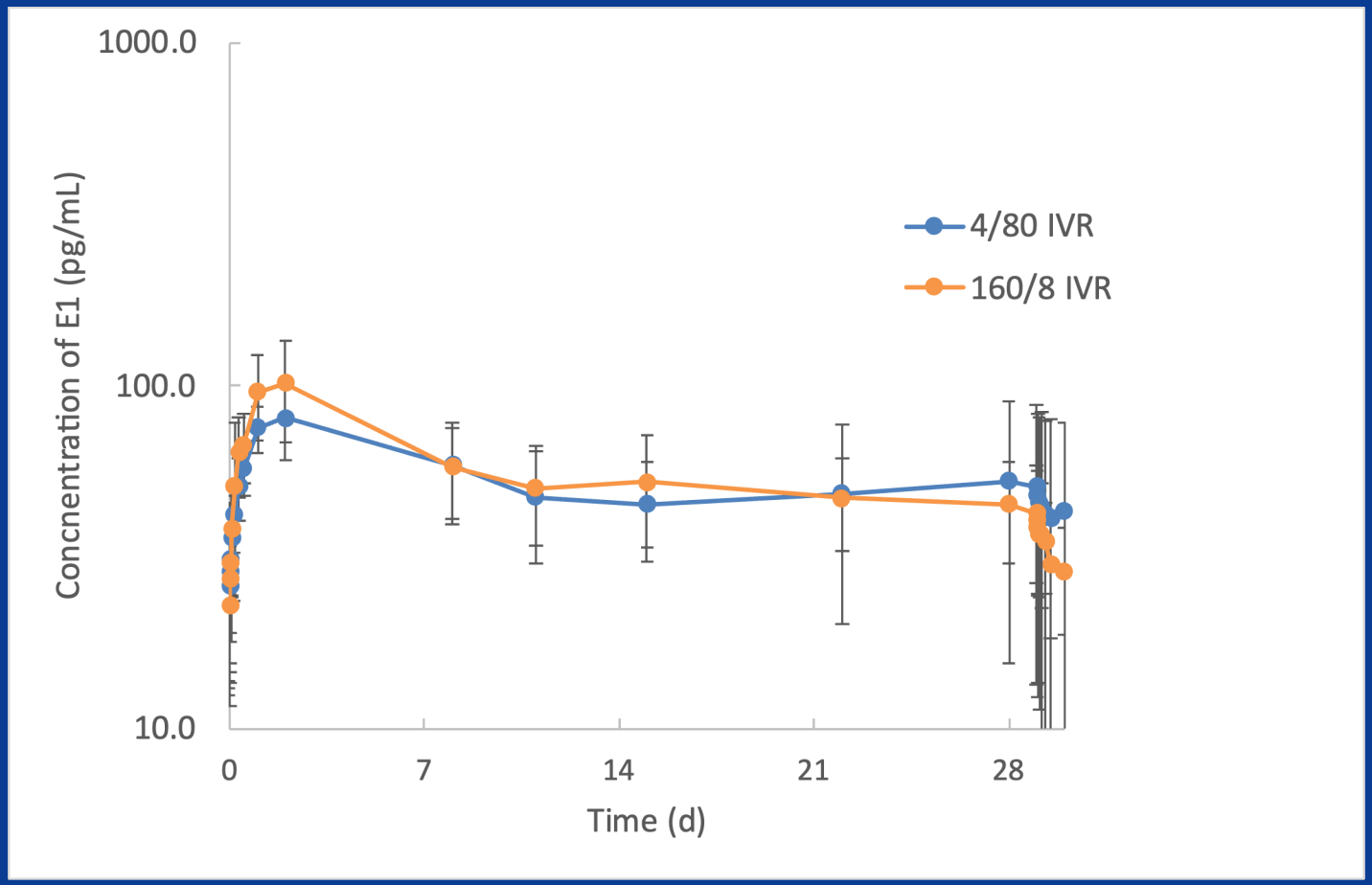
Parameter	Treatment group			
	80/4 IVR	160/8 IVR	Oral Comparator[a]	Overall
Number (n)	10	12	11	33
Mean age (± SD)	58.8 (6.66)	56.0 (3.72)	57.2 (4.42)	57.0 (4.97)
Sex (n [%])	10 (100)	12 (100)	11 (100)	33 (100)
Race (n [%])				
White	10 (100)	11 (91.7)	11 (100)	32 (97.0)
Other	0	1 (8.3)	0	1 (3.0)
Body Mass Index (kg/m^2)	28.2	29.3	28.2	28.6
Vaginal pH (mean)	5.16	5.32	5.61	5.37

[a]Estrace (1 mg E2)/Prometrium (100 mg P4) each qd for 29 days

Plasma Concentrations of E2 from 80/4 and 160/8 IVRs

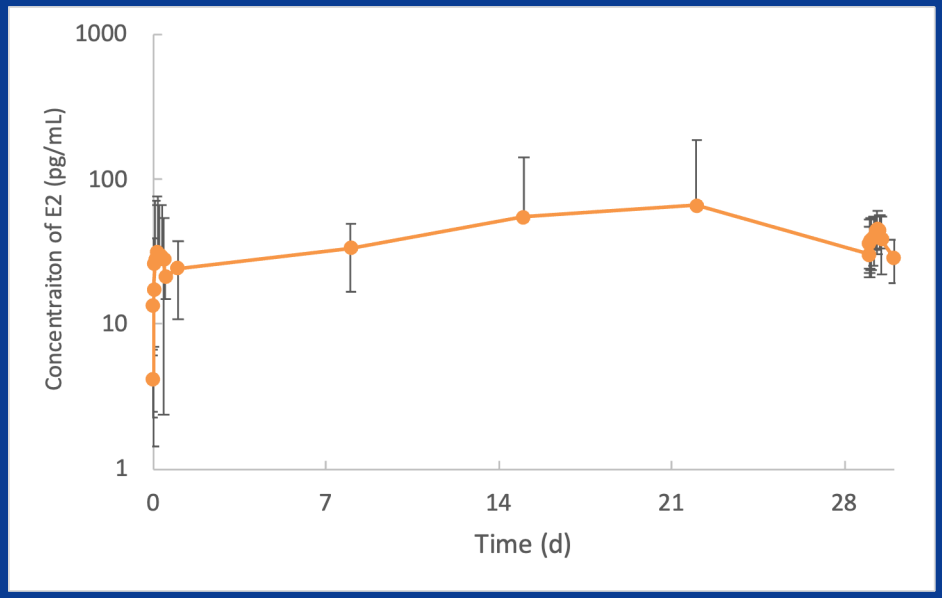


Plasma Concentrations of E1 from 80/4 and 160/8 IVRs

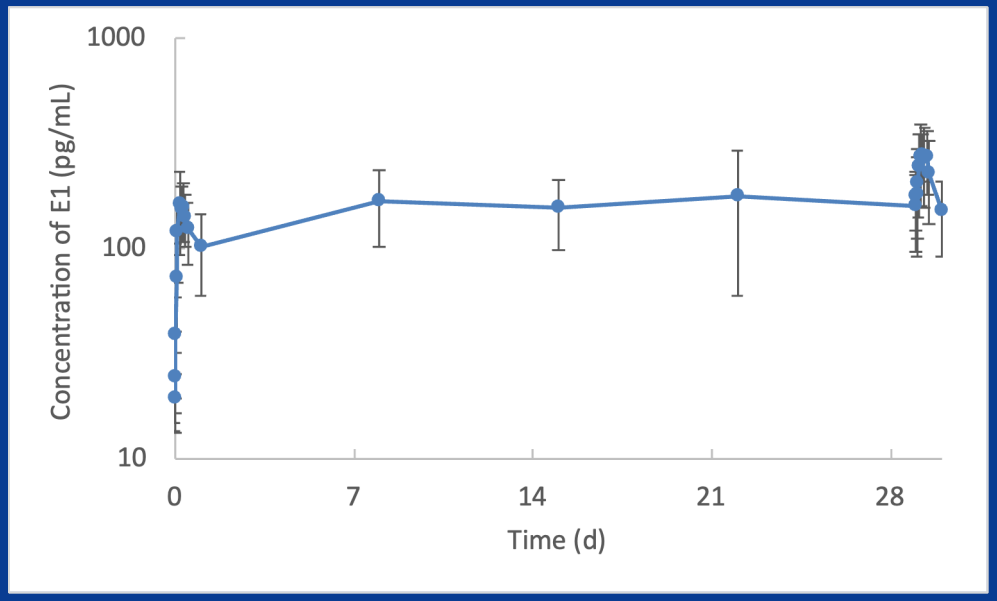


Plasma Concentrations of E2 and E1 from Oral Estrace (1 mg E2)

E2

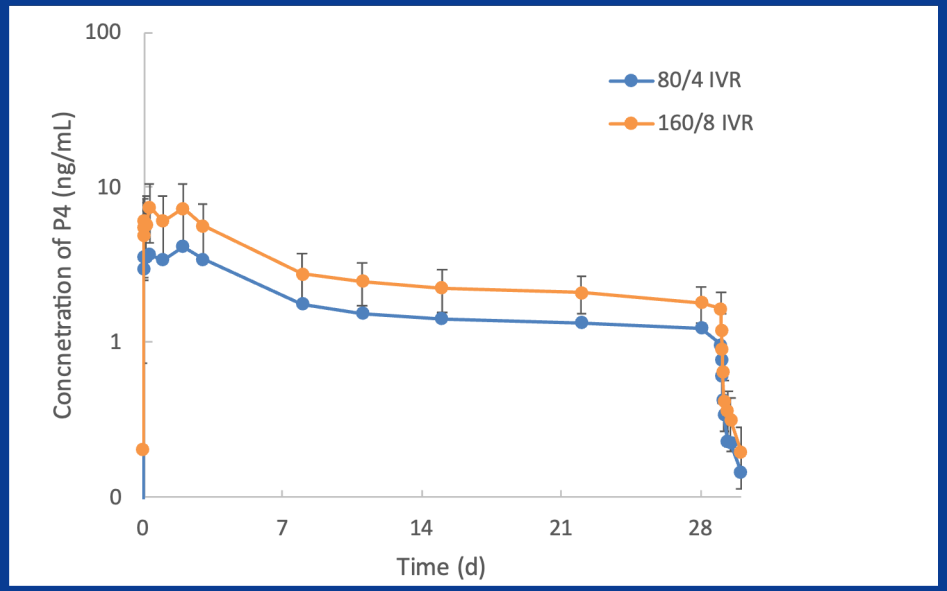


E1

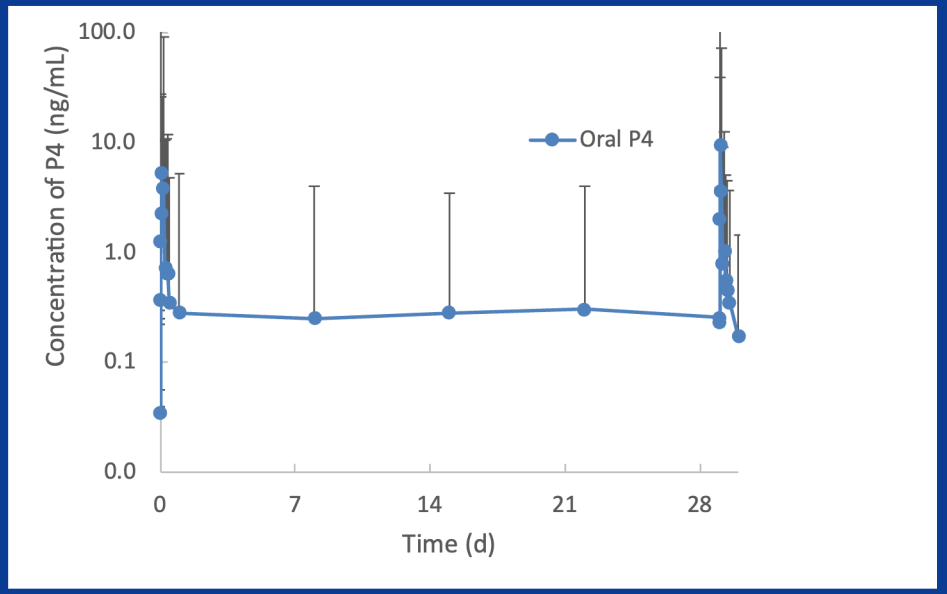


Plasma Concentrations of P4 from 80/4 and 160/8 IVRs and Oral Prometrium (100 mg P4)

80/4 and 160/8 IVRs



Oral Prometrium (100 mg)



DARE-HRT1-001 PK Parameters (E2 and E1)

Treatment	T_{max} (h)	C_{max} (pg/mL)	$AUC_{D1-D30/24\,h}$ (h*pg/mL)[b]	C_{ss} (pg/mL)
	E2			
80/4 IVR	76.4 (201)[a]	144 (73.9)	20,806 (10,618)	20.6 (16.8)
160/8 IVR	11.0 (8.15)	279 (97.8)	34,925 (9,663)	32.5 (9.33)
Oral Comparator	5.32 (3.73)	47.8 (14.5)	849 (217)	35.4 (11.2)
	E1			
80/4 IVR	113 (193)	57.2 (28.0)	16,956 (10,073)	22.1 (16.6)
160/8 IVR	35.3 (16.6)	82.7 (31.7)	21,003 (9508)	26.3 (11.4)
Oral Comparator	4.73 (2.72)	296 (98.3)	5,012 (1,621)	208 (67.6)

[a]Means (SD); all values are baseline-adjusted
[b]AUC_{D1-D30} for IVRs; AUC_{24h} for oral E2 at Day 29

DARE-HRT1-001 PK Parameters (P4)

Treatment	T_{max} (h)	C_{max} (ng/mL)	$AUC_{D1-D30/24\,h}$ (h*ng/mL)[b]	C_{ss} (ng/mL)
	P4			
80/4 IVR	20.5 (16.7)[a]	4.53 (2.56)	1,143 (254)	1.32 (0.195)
160/8 IVR	13.6 (14.0)	8.64 (3.33)	1,797 (555)	2.23 (0.614)
Oral Comparator	2.50 (2.29)	13.2 (17.9)	19.0 (17.2)	0.792 (0.719)

[a]Means (SD)
[b]AUC_{D1-D30} for IVRs; AUC_{24h} for oral P4 at Day 29

DARE-HRT1-001 Tolerability/Acceptability

- There were no serious adverse events reported during the study
- Overall, the IVRs were well tolerated with a high level of acceptability
- > 80% of subjects reported the IVRs as comfortable or very comfortable

Conclusions

- DARE-HRT1 IVRs (both 80/4 and the 160/8) produced similar E2 C_{ss} concentrations as approved hormone therapy drug products for the treatment of VMS and other vaginal conditions associated with menopause
  - The C_{ss} values of E2 were 20.6 pg/mL (80/4 IVR) and 32.5 pg/mL (160/8 IVR)
- P4 C_{ss} from the 80/4 and 160/8 IVRs should be sufficient to suppress estrogen-induced endometrial hyperplasia

Conclusions

- **Thank you – any questions?**