Support: Pharmacokinetics and Safety in a Sheep Model

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ABSTRACT

Intravaginal rings capable of releasing progesterone (P) at three different rates (4, 8, or 12 mg/d) were evaluated in a sheep model to assess P pharmacokinetics (PK) and tolerability over two 14-day test periods. The control groups received Crinone® 8% gel or Prometrium® 200 mg capsules once-daily. PK results showed sustained release of P over the two-week dosing period. Irritation and microscopic assessments were consistent with the rings being well tolerated. The results suggest that these rings (DARE-FRT1) may be suitable for luteal support in IVF.[1]

OBJECTIVES

The objectives of this work were to evaluate the in vitro release and in vivo pharmacokinetics and local tolerability of DARE-FRT1, a novel, segmented ethylene-vinylacetate (EVA) intravaginal ring (IVR) delivering P in drug-naïve Dorset crossbred sheep. These rings are being developed to provide luteal phase support and supplementation during ART cycles and early pregnancy.

METHODS

IVRs were prepared by hot-melt extrusion to create segments of varying length and drug content. The appropriate segments were heat-welded to created segmented IVRs (5 mm x 55 mm) capable of releasing P at rates of about 4, 8, or 12 mg/d over 14 days. Release rates of P were measured in vitro using 200 mL 0.5% sodium dodecyl sulfate as a release medium, in shakers at 37°C.

Ovariectomized female Dorset crossbred sheep were randomized into one of six treatment groups: group 1) Crinone 8% gel (90 mg), group 2) Prometrium 200 mg capsules, group 3) placebo IVRs, group 4) P IVR 4 mg/day, group 5) P IVR 8 mg/d, or group 6) P IVR 12 mg/d. All IVRs were inserted Day 1 and remained in place through Day 14; the rings were removed and a new IVR inserted on Day 15. The second ring remained in place through Day 29 when it was removed. Blood samples were taken at scheduled times for PK analysis. Concentrations of P in plasma were measured using a validated LC/MS-MS method. Postmortem examinations included vaginal irritation, macroscopic and microscopic evaluations, including irritation scoring, and histopathology.

RESULTS

Following a relatively large amount of released P on Day 1, in vitro release rates confirmed P was released at approximately 4, 8, or 12 mg/d over Days 2 – 14. IVRs were retained over 28 days in all animals with two exceptions. In-life observations showed no significant abnormal findings. Plasma concentrations over Day 14 (Crinone and Prometrium) or Days 1 to 14 (IVRs) are shown in Figure 1.

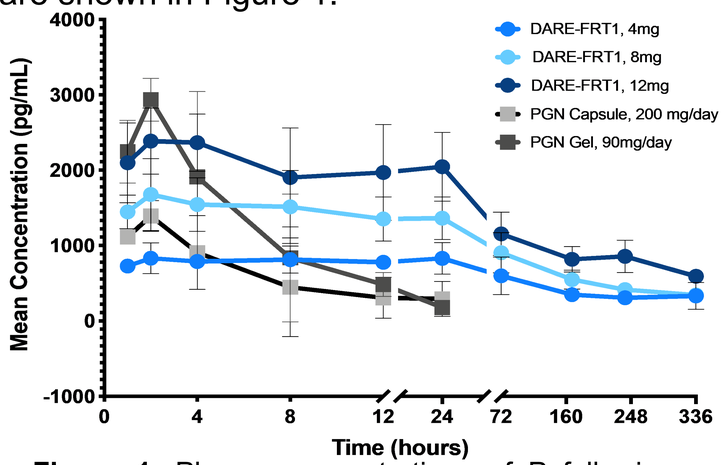

Figure 1. Plasma concentrations of P following vaginal administration of DARE-FRT1 (4 mg/d, 8 mg/d, and 12 mg/d), Crinone 8% gel, and Prometrium capsules.

PK parameters from the three IVRs and the two reference products are summarized in Table 1. PK parameters from the three different IVRs were consistent with the in vitro release rates. C_{AVG} increased in a dose-related manner, with mean values of 455, 682, and 1,040 pg/mL for the 4, 8, and 12 mg/day IVR groups, respectively.

Table 1. PK Parameters

Treatment	C_{max} (pg/mL)	AUC (h*pg/mL)	C_{AVG} (pg/mL)
Crinone[a]	3,020 ± 140	20,700 ± 1,640[c]	863 ± 68.5[d]
Prometrium[b]	1,390 ± 206	12,000 ± 4,090[c]	501 ± 170[d]
FRT1 4 mg/d	969 ± 145	153,000 ± 38,900[e]	455 ± 116[f]
FRT1 8 mg/d	1,820 ± 469	229,000 ± 40,700[e]	682 ± 121[f]
FRT1 12 mg/d	2,520 ± 432	350,000 ± 73,900[e]	1,040 ± 220[f]

[a]90 mg dose is ~ 1.5 mg/kg based on 60 kg sheep
[b]200 mg dose is ~3.3 mg/kg based on 60 kg sheep
[c]$AUC_{0\text{-}24\ h}$
[d]$C_{AVG} = AUC_{0\text{-}24\ h}/24$ h
[e]$AUC_{0\text{-}336\ h}$
[f]$C_{AVG} = AUC_{0\text{-}336\ h}/336$ h

The lower dose Crinone gel (90 mg) showed substantially greater relative bioavailability compared with the higher dose Prometrium capsules (200 mg). Irritation scores and microscopic assessments were consistent with the IVRs being well-tolerated following 28 days of exposure.

CONCLUSIONS

The data obtained from this study demonstrate that the DARE-FRT1 EVA-based IVRs are capable of sustained release of P at different rates over a 14-d period. The rings were well-tolerated with minimal to mild irritation. These results suggest the rings are suitable for evaluation in a Phase 1 clinical study in women for safety and PK. It is expected that these rings will perform in a manner demonstrated in other studies using P-releasing IVRs for luteal phase support in IVF.[2-4]

REFERENCES

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