

## **PHARMACOKINETIC AND TOLERABILITY STUDY OF JNP0201, A NOVEL 17 $\beta$ -ESTRADIOL AND PROGESTERONE INTRAVAGINAL RING, IN SHEEP**

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**Objective:** To evaluate the pharmacokinetics and local tolerability of JNP0201, a novel intravaginal ring delivering 17 $\beta$ -estradiol and progesterone, in drug-naïve ovariectomized female Dorset crossbred sheep.

**Methods:** Animals were randomized to treatment groups one or two (comparator ring, with 50 or 100  $\mu$ g/day 17 $\beta$ -estradiol, respectively, N=5), groups three or four (JNP0201, 160  $\mu$ g/day 17 $\beta$ -estradiol with five and 10 mg/day progesterone, respectively, N=5), or group five (160  $\mu$ g 17 $\beta$ -estradiol and 10 mg progesterone intravenously, N=3). Intravaginal rings were placed on day one and remained in place through day 29. Animals underwent daily examinations to confirm ring placement, and external vaginal irritation was scored from 0 (none) to four (severe). Blood samples were taken at scheduled times for pharmacokinetic analysis. Postmortem examinations performed on groups 1-4 included internal vaginal irritation, macroscopic and microscopic evaluations, including irritation scoring and histopathology.

**Results:** Intravaginal rings were retained over 28 days in all but one animal (group four). Clinical observations showed no significant abnormal findings. Pharmacokinetic analysis in JNP0201 animals showed sustained release of 17 $\beta$ -estradiol and progesterone (respective area under the curve 0-672 hours: group 3: 17,400 pg\*hr/mL and 240,000 pg\*hr/mL; group 4: 21,000 pg\*hr/mL and 485,000 pg\*hr/mL). For both external and internal vaginal irritation, mean scores were typically 0-1 and did not exceed two for any group. Irritation scores and microscopic assessments were consistent with foreign object placement; microscopic tests showed minimal to mild leukocytic infiltration and ulceration.

**Conclusions:** JNP0201 intravaginal rings were well tolerated. Pharmacokinetic results will be used to guide future human clinical studies.