REPRODUCTIVE TOXICOLOGY

A Dose Range-Finding Study in Pregnant Rats

Dose range finding studies in pregnant rats are most often used to select appropriate dose levels for embryo-fetal developmental (EFD) toxicity studies in accordance to the *International Committee for Harmonization* (ICH) S5 (R3) guideline on reproductive toxicology. Mated females are exposed to the test substance from gestational day (GD) 6 to 17 and parameters such as maternal toxicity, potential outcomes on embryo-fetal survival, intrauterine growth and external fetal morphology are investigated[1].

Test System: *Rattus norvegicus* (Sprague-Dawley).

Number of pregnant rats/group: 6 animals.

Number of dose groups: 4 (including 1 control).

Route of administration: upon request, according to ICH S5 (R3) guideline.

Main read-outs: Mortality, viability, general and detailed clinical signs, body weight, food consumption, gross necropsy, pregnancy status, gravid uterine weights, examination of placentas, evaluation for number of corpora lutea, implantation sites, live/dead fetuses, early/late resorptions, fetal weight, sex and examination for external fetal morphology.

Validation Data

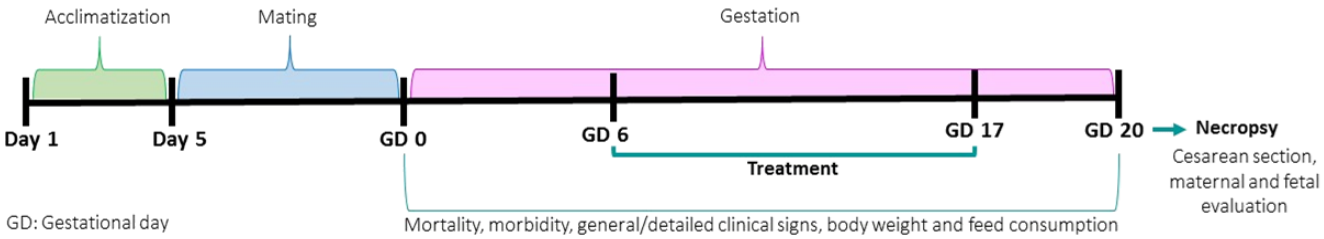

Table 1. Fetal and uterine parameters evaluated in the dose range-finding assay in pregnant rats treated orally with the Vehicle or the Test Item (500 mg/kg) from gestational day (GD) 6 to 17.

Parameters	Experimental Groups	
	Vehicle (1 mL/Kg, p.o.)	Test Substance (500 mg/Kg, p.o.)
Number of corpora lutea	14.50 ± 0.86	15.75 ± 4.32
Number of implantation sites	13.38 ± 2.45	12.50 ± 3.42
Pregnancy success (%)	93.55 ± 5.49	87.62 ± 10.28
Post-implantation losses (%)	6.51 ± 2.10	3.34 ± 1.94
Number of early resorptions	0.88 ± 0.83	0.25 ± 0.50
Number of late resorptions	0.00 ± 0.00	0.00 ± 0.00
Number of dead fetuses	0.87 ± 0.29	0.50 ± 0.28
Number of live fetuses (both sexes)	13.38 ± 0.86	12.25 ± 1.54
Number of live fetuses (males)	7.37 ± 0.59	6.75 ± 1.79
Number of live fetuses (females)	6.00 ± 0.56	5.50 ± 0.28
Sex ratio (males)	55%	55%
Fetal body weight (g)	3.38 ± 0.11	3.16 ± 0.12

Values are expressed as mean ± SEM of 4-8 animals per group. Data were submitted to the Student t-test. P values of less than 0.05 were considered statistically significant. Pregnancy success: (number of implantation sites/number of corpora lutea) x 100; Number of dead fetuses: (number of dead fetuses + number of early resorptions + number of late resorptions); Post-implantation losses: (number of dead fetuses/total number of fetuses) x 100; Sex ratio: (number of male fetuses/number of live fetuses) x 100

To avoid bias and to allow reproducibility all *in vivo* experiments follow the ICH S5 (R3)[1]. Rat colony from Charles River Laboratories are breed and maintained in SPF conditions. The project includes study plan and final report. Raw data are inspected by quality assurance unity. The experimental procedures was previously approved by the CIEnP Committee on the Ethical Use of Animals.

References:

[1]ICH S5 (R3) guideline on reproductive toxicology: Detection of Toxicity to Reproduction for Human Pharmaceuticals. Committee for Medicinal Products for Human Use. EMA/CHMP/ICH/544278/1998. 17 February 2020.

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