Technical Feasibility and Special Considerations when using Göttingen Minipigs in Embryofoetal Development Studies

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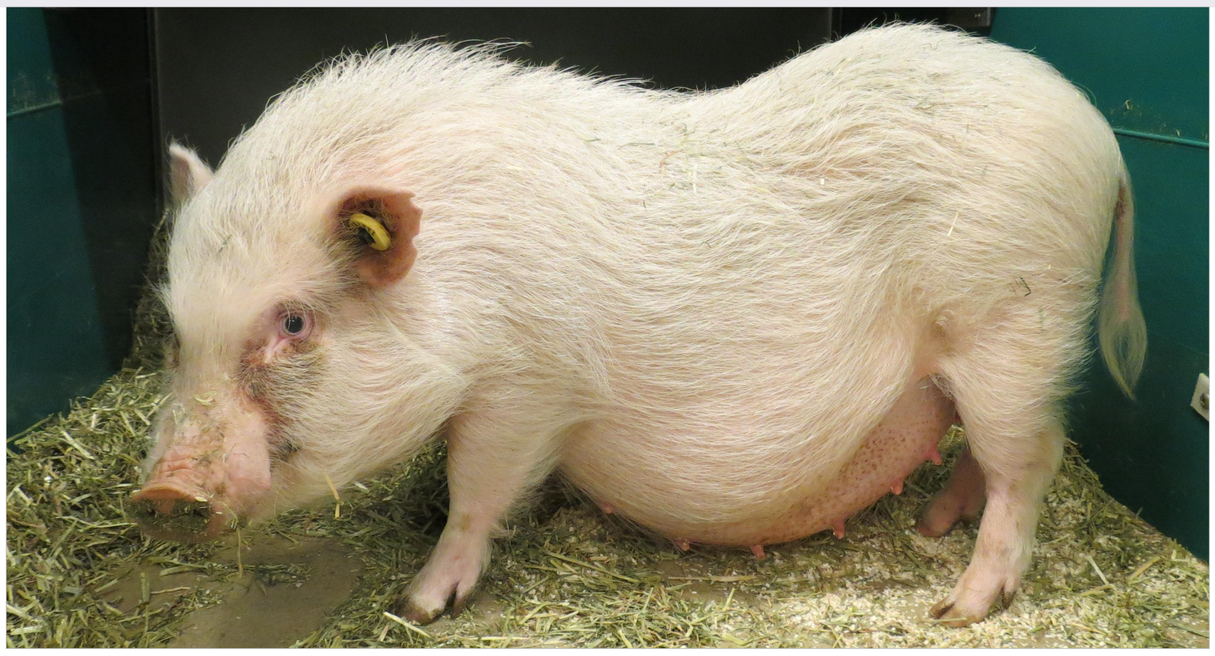


Choice of Species

For an embryo-foetal developmental study it may be necessary to use a species not routinely used if rabbits does not exhibit the desired pharmacodynamic response (S5 (R3)). The guideline also states that it can be a good idea to use the same specie as has already been used in the general toxicity studies. This will save animals for a DRF study as the information to start a repro study (dose levels and kinetics) will be available. If the specie selected is well-known and considered relevant for the compound, the guideline is open for selection of a non-rodent specie other than the rabbit.

Minipigs fulfill these criteria as they are often used in general tox studies and is well-known model relevant for many compounds and dose routes.

Advantages

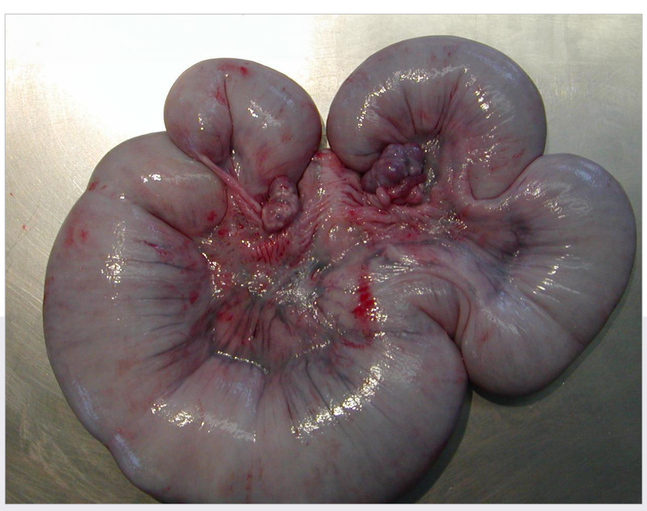
- Alternate non-rodent for general toxicity testing
- Short period of organogenesis (GD 11-35) = dosing is only needed for 25 days
- All dosing routes performed in standard toxicology studies available, including dermal, PO (gavage and capsules), IV, SC and IM
- Defined genetic background and specific-pathogen-free animals
- Sexual maturity by 4-6 months
- Larger litter size compared to NHP (5-6 piglets in average, up to 10)
- Suitable for serial semen sampling and mating studies
- Sufficient historical background data on reproductive endpoints
- The background incidence of malformations were less than 0.3% (external) and 0.6% (visceral).

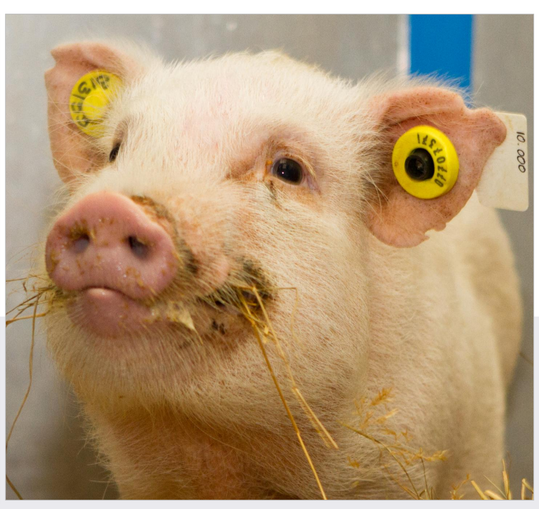
Disadvantages

- Limited number of experienced laboratories
- Long gestation (114 days = 3 months, 3 weeks and 3 days)
- Uses a large amount of test material (~18 kg animal)
- Minimal to no prenatal transfer of antibodies

Study design

The full regulatory study in minipigs follow the setup for rabbits and rats as stated in the guideline, normally including 4 groups, 1 control and 3 dosed. The guideline asks for 16 litters per group and therefore 18 dams per group are included to be sure to obtain that. This means a total of 72 females in a study. Minipigs can be acquired time-mated from the supplier or mating can be performed inhouse.





Practical Aspect when Mating

- 25 naïve males for 72 females are included of similar size as the females
- Estrus synchronization with staggered start for logistical purposes.
- Keep track of brother/sister relationships - mating sister and brother is no-go
- As far as possible avoid sisters in same group
- As far as possible the females in a group should be mated with different boars
- Staggered dosing to allow 6-8 dames going into heat every day
- Dames mated on a specific day needs to be divided into different groups
- Heat synchronization: Altrenogest (a synthetic progestagen) in diet for 18 days
- Staggered dosing with progestagen allow 6-8 dams going into heat every day
- First successful mating is GD0
- Each dam is mated twice daily over a period of 1-3 days (or until the dam is not interested). However, maximum of 3 successful matings.
- Boar visits dam, not the other way around

Timelines

- Arrival: estrus synchronization (if not time mated by supplier)
- 4-5 days after estrus synchronization: heat and mating.
- GD0: first successful mating
- GD11-36: dosing period. TK sampling on GD11 and GD36.
- GD20-: Observation for signs of oestrus
- GD25: screening for pregnancy by ultrasound.
- GD110: C-section, 3-4 days prior to natural birth

Examinations

- Examination of placenta, uterus and ovaries.
- External examination of fetuses including nose to rump length and jaw length as measures of growth
- Fresh visceral examination of fetuses.
- Skeletons are stained and 50% of heads are fixed for Wilson sectioning.

Conclusion

The minipig is a suitable species for embryofetal developmental studies as it fulfil the criteria of the S5(R3) guideline and is a well-known model relevant for many compounds and dose routes. The minipig has a suitable litter size and sufficient background data on fetal evaluation, with a low incidence of spontaneous malformations.

References:

(1) The Minipig in Toxicology, Ove Svendsen, 1998.
ICH guideline S5(R3) ; Chapter 19 The Minipig in Regulatory Guidelines for DART and Juvenile Toxicity Studies from The Minipig in Biomedical Research, 2nd edition, CRC press, 2026