CV Safety Pharmacology Assessment in Anaesthetised Minipigs

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A webinar presentation for the Safety Pharmacology Society
Agenda

1. Model value in Cardiovascular Safety Pharmacology
2. General Aspects and Study Design of the Nycomed Model
3. Results of Validation Studies
4. Conclusions
Model Value in Cardiovascular Safety Pharmacology.
• Simultaneous assessment of multiple safety parameters
• Direct (invasive) measurement of parameters
• Elimination of environmental disturbances (e.g. noise, movement artefacts)
• Reduced heart rate variability
• Optimised ECG-Signal
• Good systemic exposure by intravenous infusion
• Administration of high doses
• Possible increase of safety margins
General Aspects and Study Design of the Nycomed Model.
CV Safety Pharmacology Assessment in Anaesthetised Minipigs

- Highly standardised test system
- GLP compliant
- Routinely used in candidate phase before FIM
- Specific scientific questions for LOP, pre-candidate or candidate decision
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• **Animals**
  - Female Göttingen Minipigs
  - Weight: 9 – 12 kg
  - n = 6

• **Anaesthesia and analgesia**
  - Induction by face mask (isoflurane)
  - Propofol infusion i.v. (20-40 mg/kg/h)
  - Buprenorphine i.v. (0.01 mg/kg)

• **Respiration**
  - Spontaneous
  - Artificial ventilation

• **Data acquisition**
  - Continuously
  - Computerised system
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• **Compound administration**
  - Right femoral vein
  - Intravenous infusion followed by a washout period
  - Vehicle control, 4 – 6 doses
  - Cumulative administration

• **Blood samples**
  - Left femoral artery
  - Pharmacokinetic evaluation

• **Blood pressure**
  - Abdominal aorta (via right femoral artery)
  - DAP, SAP, HR

• **Heart: left ventricular pressure + contractility**
  - Left ventricle (via left carotid artery)
  - LVP, dp/dtmax
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- **Pulmonary arterial pressure**
  - Pulmonary artery
    (via right external jugular vein and right heart)
  - PAP

- **ECG**
  - 6 leads (Nehb-Spörri and modified Goldberger)
  - RR, PQ, QRS, QT, QTc, arrhythmias
Validation: Results of Reference Compounds.
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Isoproterenol ($\beta$-adrenoceptor agonist)

Tachycardia

Mean ± SEM, pre-dose mean as bar, n= 4, paired t-Test (two-sided), *, **, *** : p<=0.05, 0.01, 0.001 (changes to pre-dose values)
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Sotalol (β-adrenoceptor antagonist / class III antiarrhythmic agent)

Mean ± SEM, pre-dose mean as bar, n= 5, paired t-Test (two-sided), *, **, *** : p<=0.05, 0.01, 0.001 (changes to pre-dose values)
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Kinetic evaluation: mean plasma concentration

[Graph showing mean plasma concentration over time for different doses, with error bars and legend for Vehicle control and doses 1 to 5.]
Conclusions.
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- Standardised study design
- Reliable and reproducible results
- Relevant species
- Guideline compliant

Excellent Animal Model for Cardiovascular Safety Pharmacology
Thank you.

Send your questions through “Q&A”

If you would like to speak click the hand icon below the participants list.

We will call on one person at a time.
Thank you for attending.

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