TOXICOLOGY SERVICES
- General toxicology:
  - Rodents
  - Non-rodents: dogs, NHPs and minipigs
- Inhalation
- Dermal
- Ocular
- Immunotoxicology
- Reproductive toxicology including minipigs and NHPs
- Carcinogenicity studies also in rasH2 and p53+/- mice
- Genetic toxicology: ICH compliant package
- In vivo toxicology: BCOOP, MUSST, OPRA, Photo 3T3, Episom™
- Agrochemical / Chemical / REACH
- Qsar
- Physical chemistry
- Ecotoxicology: wide range of test species

SAFETY PHARMACOLOGY
- Integrated Safety Pharmacology in Toxicology Studies
  - CV (JET), RP
  - Respiratory (JET), plethysmography
  - CNS (FOB) and JET-EEG
- Safety pharmacology core battery
- Early safety pharmacology screening
- Rodent and non-rodent LVP telemetry
- Anaesthetized models: ECG, ABP, LVP and QA

DMPK AND BIOMARKERS
- Radiolabeled DMPK in all species
- Bioanalysis LC-MS/MS, GC-MS/MS, LC-ICP/MS, ELISA, RIA
- Toxigenomics, miRNA: Affymetrix™ Accredited service provider, Next Generation Sequencing (Illumina™)
- Immunology: 10-color flow cytometer, LumineX, Mesoscale

SPECIALIZED EXPERTISE
- Juvenile studies including minipigs
- Fertility studies in rodents and NHPs
- Radiation safety and efficacy studies
- Tissue Cross Reactivity: human and animal tissue banks
- Gene therapy vector biodistribution via qPCR
- ES cell testing: devTOX™ and cardioTOX™ (with Stemina)
- Lead optimization and predictive toxicology services: Leadscreen™

GLP CERTIFIED

www.citoxlab.com
QT interval correction for drug-induced changes in body temperature in dogs
Abdel-Ilah El Amrani, Francine El Amrani-Callens, Stéphane Loriot, Pramila Singh and Roy Forster
CiToxLAB, Eurex, France

INTRODUCTION
QT interval prolongation is used as a marker of pro-arrhythmic activity in safety pharmacology studies, and as QT interval is dependent on the duration of the cardiac cycle, accurate assessment of an effect on repolarisation requires QT interval correction for changes in heart rate (QTcV); the van de Water formula (Van de Water et al., 1989) is routinely used in dogs for this purpose. Changes in core body temperature (BT) may also influence QT interval duration, and a correction formula to compensate for changes in BT (QTcVcT) was proposed by van der Linde et al. in 2008.

Continuous simultaneous monitoring of QT interval and BT is usually performed in animals implanted with telemetry devices during GLP-compliant stand-alone safety pharmacology studies. When cardiovascular assessment is integrated into regulatory toxicology studies, jacketed external telemetry (JET) is considered to be the most appropriate approach, as it is non-invasive and allows continuous measurement of ECG parameters in non-restrained animals. It does not, however, allow accurate assessment of core body temperature as JET uses skin temperature measurement.

METHODS
Animals
3 males and 3 females Ti - 30
3 males and 3 females Ti - 20
3 males and 3 females Ti - 10
3 males and 3 females Vehicle control - 0

Treatment
Single administration on Day 1 followed by a 4-week observation period
Dosage volume
0.5 ml/kg

RESULTS
On Day 1, dose-dependent increases in QT (Figure 1) and QT interval corrected for heart rate (QTcV) (Figure 2) were observed, along with transient increases in heart rate and dose-dependent decreases in BT (Figure 3). At 2 hours after administration, QTcV values were 227±9; 265±28 (p<0.05); 285±22 (p<0.001) and 284±12 (p<0.001) ms, and BT values were 38.4 ± 0.2 °C; 37.0 ± 1.0 °C (p<0.01); 35.1 ± 0.4 °C (p<0.001) and 34.1 ± 0.6 °C (p<0.001), respectively.

The effect on QT interval was no longer observed after further correction of QTcV for changes in BT according to the van der Linde formula (Figure 4). The Ti had no effect on PQ interval or QRS complex duration. The Day 1 ECG results in the figures are those quantified at the BT-measurement time-points.

DISCUSSION AND CONCLUSION
The present study demonstrates that core body temperature can easily be monitored using a conventional rectal thermometer at appropriate time-points (according to the toxicokinetic profile of the test item) or its pharmacological activity, but has given permission for use of the data presented here. The Ti does not inhibit HERG (data on file).

REFERENCES