A thorough QT study was performed on a new MRI contrast agent. The study was planned as a randomized and double-blind 5-period Williams-cross-over study with adequate wash-out phases. As negative control, a placebo group was used, as positive control a group with Moxifloxacin treatment. Three doses of the MRI contrast agent were applied, a low dose, the therapeutic dose and a supratherapeutic dose.

The analysis of the primary objective on the average QT, corrected by Fredericia (QTcF), showed no relevant prolongation for all three doses according to the current criteria of the ICH guideline. However, a slight increase in QTcF higher doses was seen but also the heart rate was increased after applying the higher doses, possibly induced by the increased volume of the treatment. Therefore it was suggested, that the slight QTcF prolongation was an artificial effect due to the hysteresis effect. Hysteresis is the time lag of QT (about 2 minutes in humans) to adopt to a changed heart rate. The correction of the QT by the heart rate from the same timepoint may lead to artificial QT prolongations. Therefore, for treatments, which cause rapid changes in heart rate, the QT correction for heart rate should take into account the hysteresis effect.