

Study Background

- Dapagliflozin is a first-in-class SGLT2 inhibitor currently in phase 3 clinical trials for the treatment of type 2 diabetes.
- As part of the clinical development program, to rule out effects on cardiac repolarization, which favor the development of cardiac arrhythmias, a thorough QT_c study needs to be conducted. ICH E14 calls for the thorough QT study to characterize the dose-response, including exploration of concentrations that are higher than those achieved at a therapeutic dose.
- In early phase 1 trials of dapagliflozin, at doses much higher than the therapeutic dose, the QT_c interval was not observed to be prolonged.

Study Results and Implications

- This study confirmed that dapagliflozin has no effect on the QT interval at doses up to 15 times the maximal dose under investigation in clinical trials.
- Although a presumed therapeutic dose of dapagliflozin was included in this study, a thorough QT study may consider omitting the therapeutic dose when early phase 1 data at supratherapeutic doses do not support an effect on the QT_c interval. A concentration-response model can then be fitted to the supratherapeutic dose, eliminating the need for therapeutic dose.