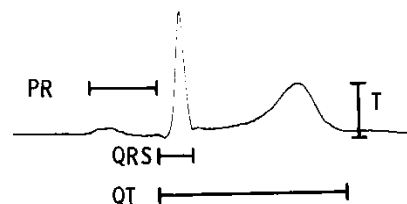


Thorough QT studies

Some people are born with prolonged QT interval, but others have prolonged QT interval thrust upon them – by medicines that affect cardiac repolarisation. QT prolongation predisposes to a disorganised heart rhythm called *torsade de pointes*, which can degenerate into ventricular fibrillation and death. In the last decade or so, several valuable drugs have been withdrawn from the market, or have had their use greatly restricted, because they can prolong QT interval and are associated with a risk of sudden death. Examples include prenylamine, terfenadine, astemizole, cisapride and sertindole.



Torsade de pointes – note QT prolongation



Regulatory authorities now expect to see a thorough QT study of a new medicine – a rigorous assessment of its potential to prolong QT interval – even if preclinical work shows no sign of

any problem. At HMR, we have successfully completed many definitive studies of the potential of new medicines to cause QT prolongation. We use industry-standard MAC5000 ECG machines to record high quality digital 12-lead ECGs, which can be coded and analysed ‘blind’ by the sponsor’s choice of specialist contractor, anywhere in the world. We capture the 24h ambulatory ECG (Holter) using the ELA SyneFlash system, which records continuous 12-lead ECG. SyneFlash allows continuous beat-to-beat automated measurement of QT interval and hourly estimation of mean QT, with immediate online analysis of relationships between QT and RR intervals. In our definitive QT studies, we use repeat-dose regimens to achieve steady state. Sometimes we include a CYP3A4 inhibitor, such as ketoconazole. We maximise safety by keeping the subjects resident in our wards: our 16-channel Spacelabs ECG telemetry system allows us to monitor them continuously throughout the research facility. We have done many QT studies of new and existing medicines.

Our track record shows that we can give sponsors the thorough QT study data that the regulators demand – safely, securely, and to strict timelines. To discuss your needs, contact:

Steve Warrington
Medical Director

swarrington@hmrlondon.com

020 8961 4130

Hammersmith Medicines Research
Cumberland Avenue
London NW10 7EW
England



References

1. The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. CPMP/986/96
2. Haverkamp W, Breithardt G, Camm AJ *et al*. The potential for QT prolongation and pro-arrhythmia by non-anti-arrhythmic drugs: clinical and regulatory implications. *Cardiovasc Res* 2000; 47: 219–233.
3. **Boyce M, Dunn K, Warrington S**. Hemodynamic and electrocardiographic effects of almotriptan in healthy volunteers. *J Cardiovasc Pharmacol* 2001; 37: 280–289.
4. Malik M, Hnatkova K, Ford J, *et al* . Near-thorough QT study as part of a first-in-man study. *J Clin Pharmacol* 2008; 48: 1146-1157.
5. **Boyce M**, Kerstens R, Beyens G, Vandeplassche L, Ausma J. Cardiovascular safety of prucalopride in healthy subjects: results from a randomized, double-blind, placebo-controlled, cross-over trial. 16th United Gastroenterology Week, 18-22 October 2008, Vienna. Poster PO892.
6. **Warrington SJ, Baisley KJ , Boyce MJ**. Pharmacokinetic and pharmacodynamic interaction between domperidone and ketoconazole in healthy men and women – a thorough QT study. (In preparation).
7. **Boyce MJ , Warrington SJ, Baisley KJ** . Pharmacokinetic and pharmacodynamic interaction between domperidone and erythromycin – a thorough QT study. (In preparation).