
CHDR
Centre for Human Drug Research
High precision
QT analysis

High precision QT analysis

CHDR's Cardiology Services team provides tailor-made advice for the consistent, efficient, and comprehensive collection and interpretation of electrocardiography (ECG) data. Drawing on our many years of experience, we are able to evaluate QT/QTc interval prolongation by means of high precision QT analysis, in accordance with the ICH E14 clinical guideline[1] and Garnett et al.'s white paper on concentration-QTc modelling (2018, *J. Pharmacokinet Pharmacodyn*).[2]

Exposure-response characterisation is an integral component of studies performed at CHDR. By relating ECG measurements to drug concentrations, we can characterise the exposure-efficacy and exposure-safety relationship in all types of clinical trials.

[1]ema.europa.eu/en/ich-e14-clinical-evaluation-qtqtc-interval-prolongation-proarrhythmic-potential-non-antiarrhythmic
[2]www.ncbi.nlm.nih.gov/pubmed/29209907

QT prolongation

It is essential to investigate the effect of a compound on cardiac repolarisation during drug development, in accordance with the International Council for Harmonisation (ICH) E14 guideline. We perform continuous Holter ECG monitoring, which enables the measurement of RR and QT intervals from ECG strips. The QT interval is then ascertained using the Global Median Beat approach and manual adjudication, whereby automated measurements are reviewed and manually adjusted where necessary.

Data analysis

A concentration-QTc analysis is performed that incorporates the data from all dosing levels tested in the study, in accordance with Garnett et al.'s white paper on concentration-QTc modelling (2018, *J. Pharmacokinet Pharmacodyn*). The default dependent variable for the analysis is the change from baseline in the Fridericia-corrected QT interval (ΔQTcF). The statistiscal model is used to compute the placebo-corrected ΔQTcF (ΔΔQTcF) and 90% confidence interval of ΔΔQTcF at a range of concentrations, which can be compared with the 10 msec threshold. The results of this analysis can be submitted to regulatory bodies to obtain a thorough QT/QTc (TQT) study waiver.

Highlight

In a first-in-human study[1] we conducted to evaluate the safety and tolerability of a novel KCa2 channel blocker (AP30663), we performed a concentration-effect analysis, including a QT subinterval analysis using global median beat analysis, to investigate the effect of AP30663 on ventricular repolarization. We found a concentration-dependent increase in the QTcF interval, mediated through increases in both the J-point to T-peak interval, corrected for heart rate (Jp-Tpc) and T-peak-T-end (Tp-Tend) intervals, but not on the QRS duration (figure 1).

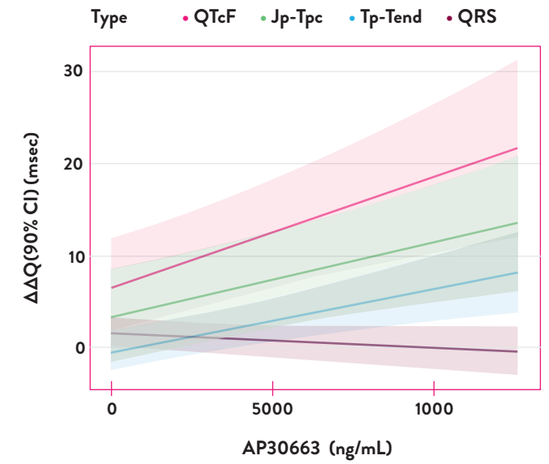

Figure 1: Concentration-effect analysis of KCa2 channel blocker AP30663 and QtcF and QT Fridericia's formula (QTcF) subintervals.

[1] https://ascpt.onlinelibrary.wiley.com/doi/full/10.1111/cts.12835

Figure 2: Workflow of our services.

High-quality deliverables

We offer a range of documentation to support your needs:

- Holter Analysis Plan
- Holter Analysis Report, including concentration-effect analysis
- Dataset used for the concentration-effect analysis
- Annotated FDA ECG warehouse compliant ECGs (XML format)
- Overview of the ECGs
- Tabulated ECG parameters

Additional documentation is possible to meet particular study requirements.

Structured and standardised services

We are committed to upholding high standards across all our services. We deliver well-structured, clean and consistent data to support the claims in your clinical study report, while adhering to competitive timelines. CHDR's own Standard Operation Procedures (SOPs) for the collection of Holter data lead throughout the execution of the study, unless otherwise agreed. A Holter specialist accredited by the Dutch training foundation for heart function analysts (*Stichting Beroepsopleiding Hartfunctielaboranten*, SBHFL), blinded to time of measurement, treatment and subject number, performs all measurements for a single study, to avoid inter-observer variability. We work in close collaboration with Intermark Technology B.V. (Someren, the Netherlands), our partner in the field of Holter analysis.

Why choose CHDR?

The Centre for Human Drug Research specialises in early-phase clinical drug research. CHDR's overall mission is to improve the drug development process by collecting as much information as possible regarding the candidate drug in the early phases of development. This information helps sponsors make informed decisions regarding the course of clinical development for their product.

Why choose CHDR?

Research at CHDR covers a wide range of fields, including the central nervous system (CNS) and pain, the cardiovascular system, haemostasis, immunology, and dermatology. In addition, CHDR is at the forefront in developing novel biomarkers and methods for measuring drug-related effects in all of these research areas.

Pharmacology matters

Whether studying a new cognitive-enhancing drug, a next-generation painkiller, or a new monoclonal antibody designed to treat rheumatoid arthritis, the goal is to determine how the compound's effects correlate with both the dose and blood concentration at any given moment. In addition, understanding which biological systems are activated is an essential first step towards quantifying this relationship. At CHDR, our focus on pharmacology is reflected clearly in what we call question-based drug development.

Question-based drug development

CHDR actively uses question-based drug development - or QBD - as a more rational approach to drug development compared to conventional approaches. QBD can be best described as a series of questions that are addressed throughout the process. These questions often seem simple enough, but failing to answer even one question - or even addressing the questions in the wrong order - can have dire consequences. Thus, using this approach can potentially save companies millions of dollars by helping predict a catastrophic issue early in the development process, before the more expensive latter stages (for example, large-scale clinical trials or the marketing phase).

From a general perspective, the most important questions are:

1. Does the biologically active compound and/or active metabolite(s) reach the intended site of action?
2. Does the compound cause its intended pharmacological and/or functional effect(s)?
3. Does the compound cause any unintended pharmacological and/or functional effect(s)?
4. Does the compound have a beneficial effect on the disease and/or clinical pathophysiology?
5. What is the compound's therapeutic window?
6. How does any variability with respect to the drug response in the target population affect the product's development?

Contact

To learn about CHDR's full range of services, contact us today.

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