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IN THIS ISSUE:

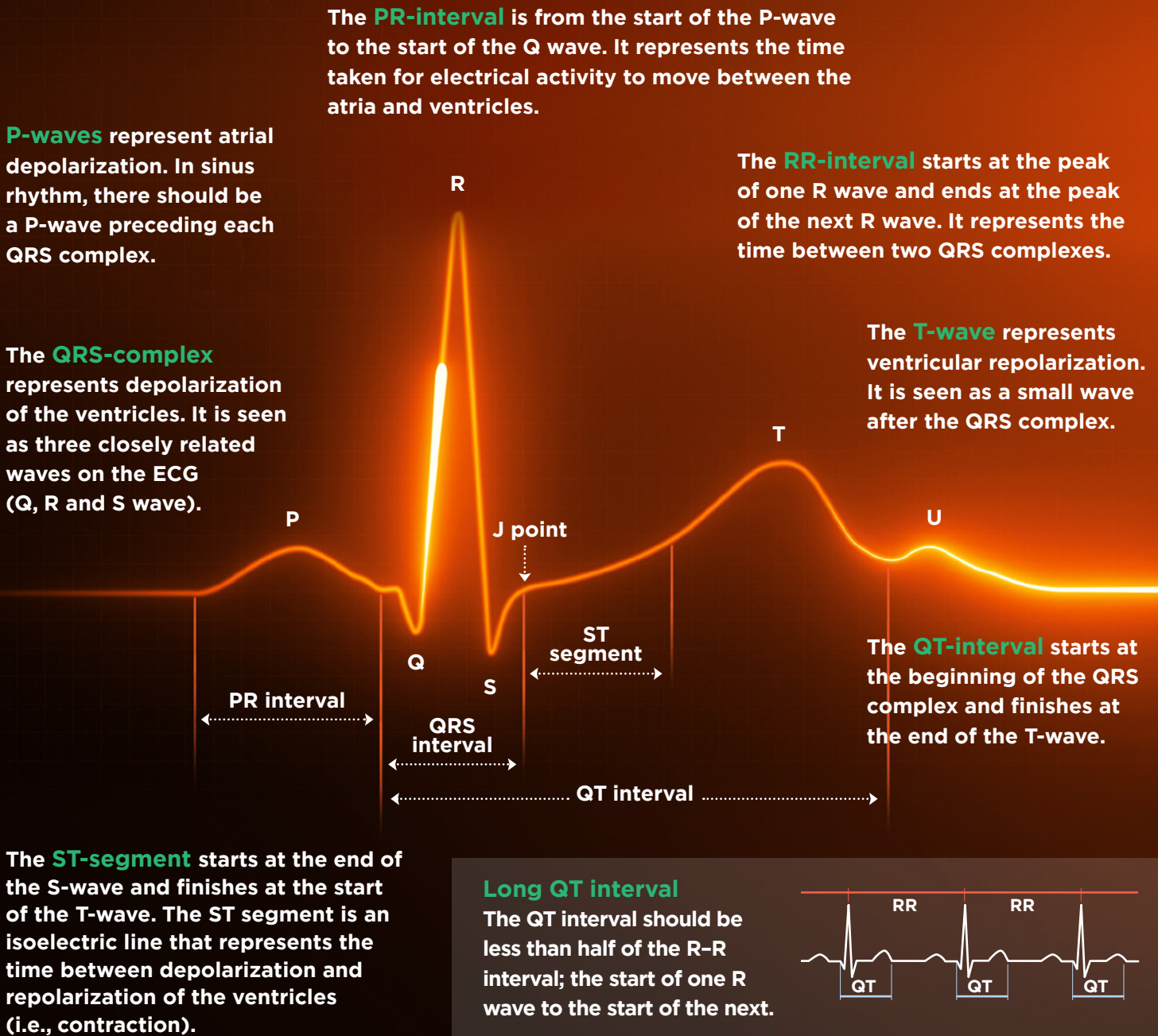
- Electrocardiography primer
- Global regulations, design, and timing of QT assessment
- Case Study — QT assessment in a novel cannabis trial involving 80 subjects

CARDIAC ASSESSMENT in Clinical Trials

Electrocardiography (ECG) is an integral part of the new drug regulatory environment. Mandated by regulatory bodies the world over, the thorough and precise evaluation of a new drug's cardiac effects is a critical element of new chemical entity (NCE) development. Sponsors must submit all NCEs with systemic exposure to a dedicated thorough QT (TQT) study to understand the drug's impact on ECG parameters and determine whether the compound prolongs the QTc interval. A positive finding of QT prolongation usually has a significant negative impact on a drug's development pathway, necessitating extensive additional ECG assessments, and potentially resulting in approval delays or even discontinuation of the program.

ELECTROCARDIOGRAPHY

Figure 1. The basic pattern of electrical activity across the heart.



The QT interval represents the time taken for the ventricles to depolarize and then repolarize. A long QT interval indicates delayed repolarization of the heart, and can result in loss of consciousness and sudden death. Since the discovery some decades ago that even non-cardiac drugs can affect the heart rhythm, analysis of the QT interval has become a requirement for new drug approval. During drug development, both robust preclinical and clinical assays, along with concentration QT modeling, are used as methods to analyze whether delayed ventricular repolarization is present.

Global Regulations

In 1999, British regulators drafted a paper entitled “Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products”. This document, which is no longer available online, was the first step towards regulatory agencies worldwide focusing their attention on the arrhythmic potential of drugs that had been deemed to be safe.

In 2000, the European Society of Cardiology published a paper entitled “**The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications**”. In 2001, Canada developed a similar document, also no longer available online, entitled “Assessment of the QT Prolongation Potential of Non Antiarrhythmic Drugs”. Still, no formal testing protocol was enumerated.

In 2003 (updated in 2005), the International Conference on Harmonization published the **ICH S7B** guidance, outlining the strategy for nonclinical assessment of QT prolongation of non-cardiovascular drugs.

Also in 2005, regulators from the U.S.A., Europe, and Japan drafted the seminal clinical guidance document **ICHE14**, which provides recommendations to assess the QT prolongation and arrhythmic risk of investigational human non-cardiac pharmaceuticals. Both the FDA and the EMA published the ICH E14 under their own auspices.

ICH E14 has not yet been fully revised in its entirety, but it has been updated with **Q&A responses** on multiple occasions in 2008, 2012, 2014, and 2015.



QT/QTc STUDY DESIGN

A thorough QT/QTc study is usually conducted at the end of Phase II or in parallel with Phase III studies. It would generally include 40 to 60 healthy subjects as a crossover design, or up to 240 in a parallel design format. The trial design typically involves healthy male and female subjects, in a double-blind (except for the use of a positive control), randomized, single-site, crossover study.

Depending on the pharmacokinetics of the study drug, parallel designs for TQT investigations may also be used. For crossover studies, subjects are randomized to each of the following treatment groups, with appropriate washout periods as required according to the drug's pharmacokinetic profile.

- GROUP 1:** Placebo
- GROUP 2:** Positive control
(e.g., moxifloxacin 400 mg IV)
- GROUP 3:** Therapeutic dose of study drug
- GROUP 4:** Supratherapeutic dose of study drug

Sponsors may also choose to assess QT/QTc prolongation concurrently with other early phase studies, as early as Phase I/first-in-human (FIH) healthy participant studies and/or late phase clinical trials. Earlier evaluation involves intensive ECG sampling combined with paired pharmacokinetic sampling (high precision exposure-response analysis) or of sparse sampling of blood concentrations in a population PK approach.¹

The Consortium for Innovation and Quality in Pharmaceutical Development (IQ) and the Cardiac Safety Research Consortium (CSRC) collaborated to design a clinical study in healthy subjects demonstrating that the desired objectives of a successful TQT study can be achieved through robust ECG monitoring and exposure-response analysis of data generated from SAD or MAD studies.²

The results of this study resulted in clarifications to the ICH E14 guidance as summarized in **ICH E14 guidance Q&A (R3)**³, finalized in June 2017. This document outlines important considerations for sponsors planning to use the exposure-response (concentration-response) modeling approach.

In summary, in lieu of conducting a separate dedicated cardiac safety study, this methodology allows definitive testing to be embedded into an existing Phase I study. The methodology incorporates both concentration-effect modelling, as well as high precision analysis of 10 times more data than conventional measurement methods. This provides an alternative path to cardiac safety testing by leveraging large amounts of precisely analyzed ECG data from a standard Phase I study.

If investigational compounds cannot be administered to healthy participants, other approaches may be used to investigate the potential for pharmacological QT/QTc interval prolongation.

TIMING OF QT ASSESSMENT

The timing of a TQT study is impacted by a number of factors, such as:

- The results of relevant nonclinical investigations like hERG assays
- Therapeutic class considerations related to arrhythmia induction potential
- Sponsor-related variables such as budget considerations and risk tolerance

For example, TQT clinical studies can be conducted in Phase I of a development program to de-risk further development of a compound, or a TQT study can be conducted later, at the end of Phase II or beyond if prior proof-of-concept efficacy data is needed to justify the expense of conducting a TQT study.

When routine cardiac assessment first became standard, stand-alone thorough QT (TQT) assessment studies were being conducted for almost all new drugs in development which exhibited systemic exposure. At a cost of approximately \$2 to 4 million USD per study, TQT represents a significant investment and development risk for sponsors, as a positive finding can result in late-stage or post-approval commitments for safety monitoring. It can also completely end the development of a novel compound.

As referenced in the previous section, the QT assessment can now be conducted as early as during the first-in-human dosing study. This cost-effective approach allows pharmaceutical companies to evaluate and de-risk potential therapies earlier in development, potentially receiving a waiver for a TQT study later in development. It provides more product valuation for companies looking for further

investment or partnering and, most importantly, creates an early translation of preclinical cardiac safety studies into viable human data and a safety platform for further clinical trials.

In 2015, Altasciences' Kansas City facility became the first clinical research unit to be a Certified Site by iCardiac (now ERT), with joint studies initiating in 2015. This certification process by one of the co-author companies of the CSRC-FDA paper has incorporated documented on-site training in the cardiac monitoring activities of physicians, research nurses, and paramedics at Altasciences. Today, all of Altasciences' clinical units are ERT-certified, and we conduct stand-alone TQT trials, as well as incorporate QT assessment in FIH trials.



CASE STUDY — FIH Clinical Trial Involving QT Assessment

Altasciences recently conducted a FIH clinical trial involving QT assessment on a novel cannabis formulation, the results of which are presented below:

A Double-Blind Phase I Study to Assess Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of Single and Multiple Daily Ascending Doses of Cannabis (Delta-9-tetrahydrocannabinol/Cannabidiol) by Smoking/Inhalation in Healthy Male and Female Volunteers/Fasting State

This was a single center, double-blind, placebo-controlled, randomized-within-dose, single-and multiple-dose escalating study. The study included 80 subjects evaluated in 2 parts — Part A (single-ascending dose) and Part B (multiple dose) in healthy volunteers.

A cardiodynamic ECG assessment was conducted in Part B of the study to evaluate the effects of a novel cannabis formulation on the corrected QT interval (QTc) using Fridericia's formula (QTcF). Because the QT interval is directly dependent on the heart rate in an obvious way, (i.e., a faster heart rate produces a shorter R-R and QT interval), the collected data is adjusted accordingly for accuracy and to improve arrhythmia detection.

QTc evaluation was conducted following cannabis administration over 1 and 7 consecutive days by smoking/inhalation using a titanium pipe in an escalation fashion to healthy male and female subjects.

Three different multiple-dose groups (1x, 2x, and 3x daily dosing) were evaluated. Altasciences worked with ERT as our central ECG laboratory to help extract and analyze the ECGs.

Ten 14-second digital, 12-lead ECG tracings were extracted from a Holter monitor, using the 'TQT Plus method', at protocol-specified timepoints. This method enabled extraction of ECGs through continuous cardiodynamic recordings while minimizing HR variability and noise. High-precision QT analysis was subsequently performed on all analyzable beats in the 10 ECG replicates.

In all dose groups evaluated for this cannabis formulation, it was determined that the change from baseline QTcF was small and that although a shortening of the PR interval was observed, there was no clinically meaningful effect on the QRS interval.



Cardiac Assessment Specialization

In order to accommodate the specialized needs of cardiac assessments, important considerations include:

- Ensuring fully-trained and expertly qualified staff, working with the latest monitoring equipment
- Limiting blood draws or other procedures that affect heart rate in close proximity to the time of an ECG
- Ensuring sufficient space around the bed for staff to perform multiple operations with ease

At Altasciences, our collaborative relationships with core ECG labs complement our clinical expertise. We have preferred relationships with two eminent providers in the field, ERT in North America and Banook in the EU. These labs provide the necessary niche expertise in assisting with the design, and performing the analysis of the cardiac monitoring elements of our trials, and we have the fully-trained staff, state-of-the-art equipment, modern facilities, and clinical capabilities. Ensuring accurate, reliable data that protects patient safety is of the utmost importance to all.

REFERENCES

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ABOUT ALTASCIENCES

Altasciences is a forward-thinking, mid-size contract research organization offering pharmaceutical and biotechnology companies of all sizes a proven, flexible approach to preclinical and early phase clinical studies, from lead candidate selection to proof of concept. For over 25 years, Altasciences has been integrating into clients' projects to help support educated, faster, and more complete early drug development decisions. Altasciences' full-service solutions include preclinical safety testing, clinical pharmacology, bioanalysis, program management, medical writing, biostatistics, data management and more, all of which can be tailored to specific sponsor requirements.

Altasciences... helping sponsors get better drugs to the people who need them, faster.