EXECUTIVE SUMMARY

Assessment of ECGs during the development of oncology compounds is challenging. Toxicity of these compounds often precludes the inclusion of healthy volunteers while a higher variability of ECG parameters in oncology patients can be expected due to disease, co-medications, and co-morbidities. Recently, it was shown that the extraction of ECG data using the High Precision QT technique of iCardiac and Exposure Response analysis can result in a conclusive ECG assessment with a limited number of volunteers. Applying these techniques in a small-sized oncology study with dedicated PRA Health Sciences staff presents a unique opportunity for a conclusive and efficient cardiac safety assessment by ECG.
INTRODUCTION

ECG Evaluation in PRA Studies

PRA has performed many thorough QT (TQT) studies in our Clinical Pharmacology Units (CPUs) in the US and The Netherlands. Many of these studies have resulted from repeat business, demonstrating the satisfaction of our clients.

During the last 5 years, PRA has conducted 195 single- and/or multiple-ascending dose (SAD-MAD) studies. Since the results of the IQ-CSRC (Cardiac Safety Research Consortium) study were presented (Darpo, 2015), an extensive evaluation of drug-induced ECG effects is often included in these early clinical studies. The early studies involved an approach utilizing serial ECGs extracted from continuous recordings (Holter) with exposure response (ER) analyses that related any potential ECG effects to plasma concentrations of the drug. In collaboration with iCardiac, PRA used this new approach in several studies.

QT Analysis by iCardiac

iCardiac’s High Precision QT (HPQT) technique utilizes more data and a more consistent approach to QT interval measurements than conventional techniques and is today widely used in TQT studies. The technique results in a substantially better precision of the QT interval measurements and thereby improves the ability to exclude a small QT effect. With subsequent ER analysis, data from all subjects and time points are analyzed simultaneously (Figure 1), which is in contrast to the “by time-point” analysis that evaluates potential effects by individual time points. The combination of HPQT and ER analysis thereby provides a unique ability to exclude small QT effects in small-sized, standard clinical studies.
Figure 1: A negative QT assessment using ER analysis.

Figure 1 shows the placebo-corrected change from baseline (y-axis) vs. plasma concentrations of selisistat administered to healthy volunteers in a multiple-ascending-dose study. The solid black line with grey-shaded area is the ER, analysis-based, estimated QTc effect with 90% confidence interval (CI). As demonstrated, the 90% CI is below 10 ms throughout the observed range of plasma concentrations. The vertical, red bars show the observed delta data QTcF with 90% CI within each plasma concentration decile (plotted at the median concentration of each decile). The red bars demonstrate that the ER model captured the data well (Westerberg, 2015).

ECG ASSESSMENT FOR ONCOLOGY DRUGS

ECG assessment for non-oncology drugs is usually done in healthy volunteers. Effects on ECGs in healthy volunteers can be assumed to be predictive for patient populations, even though the absence of disease, co-morbidities, concomitant medication, adverse events, and electrolyte abnormalities reduces variability and confounding factors. Due to tolerability or genotoxicity concerns; however, new, development-stage agents in oncology are not necessarily appropriate to evaluate in healthy subjects. Moreover, since the clinical-dose level is often pushed to optimize efficacy, supratherapeutic doses are often too toxic and cannot be applied in healthy subjects.

Instead, QT assessment of oncology drugs is often performed in the setting of a Phase II/III study in a subset of patients across several sites. Based on the benefit-risk assessment in oncology, studies intended for conclusive assessment of the QT effect are typically powered to exclude a somewhat larger QT effect, that is 20 ms rather than the 10 ms threshold set for TQT studies in healthy volunteers (Rock 2009). Obviously,
the severity of the targeted oncological indication also impacts the level of QT assessment, ranging from a full TQT study in the adjuvant setting, to summarizing clinical ECGs in severe, life-threatening conditions with no available therapies (Strnadova, 2010). In general, a designated study for conclusive QT assessment will be required, supplemented with ECGs from late-stage clinical trials in the targeted indication.

For a study intended to include a QT assessment, factors that impact the variability of the QT interval measurement include the:

• Number of sites.
• Familiarity of the site in performing these types of studies.
• Inclusion of healthy subjects or patients with underlying cardiovascular diseases or other confounding factors, such as co-morbidities, concomitant medication, adverse events (nausea, vomiting), and electrolyte disturbances.
• Lack of placebo when evaluating an oncology agent in cancer patients. Based on ethical reasons, a placebo is often not deemed appropriate, which reduces the power to exclude a small QT effect; to some extent, this can be balanced with the use of a full-time, matched baseline day.

ER analysis has been extensively used for the evaluation of QT effects and is routinely conducted as part of the FDA’s evaluation of TQT studies. In oncology, the role of ER is even more important, given the lack of formally powered studies and the more limited dose range (Figure 2).

Figure 2: The observed QT effect in one of the pivotal trials with vandetanib in 231 patients with medullary thyroid cancer (left panel) and the ER analysis of the same data (right panel; Caprelsa 2011).
The same analysis can be done in substantially fewer patients using the combination of HPQT and ER analysis. The example in Figure 3 from a study in cancer patients conducted at several sites demonstrates that a QT effect exceeding 10 ms could be excluded with only 19 patients.

![Figure 3: Exposure response analysis of data from a study with 19 oncology patients in whom serial ECGs and PK sampling were performed.](image)

In the study represented by Figure 3, one dose of the drug was administered and there was no placebo. The predicted QT effect (red solid line with 90% confidence interval as grey-shaded area) is clearly below 10 ms throughout the studied plasma concentration range.

**QUALITY ECG ASSESSMENT IN ONCOLOGY EARLY PHASE STUDIES**

The IQ-CSRC study demonstrated that by using high-quality ECG extraction and iCardiac’s HPQT methodology along with ER analysis, 9 healthy volunteers were sufficient to exclude a QT effect above 10 ms for a negative drug, while an effect above 10 ms was detected for several positive drugs (Darpo, 2015). Since mass-balance studies in oncology have a similar number of participants, these results open the opportunity for assessing QT effects in these studies.
The Opportunity

PRA’s and iCardiac’s new approach to combine mass balance studies with ER analyses has the potential to expedite early learning in clinical drug development as it provides cardiac safety information of the new agent at a very early stage.

PRA’s Patient Pharmacology Services group operates an 8-bed, Phase I, accredited unit at the Péterfy Sándor Hospital in Budapest, Hungary, which specializes in mass balance studies in oncology patients. The unit is fully equipped for early patient studies, while experienced nurses and physicians perform all study-related procedures, from drug storage to sample preparation and logistics. Also, this unit works closely with local oncologists and is located near the hospital’s oncology department and ICU.

Since 2010, PRA has been performing mass balance studies with 14C labelled oncology agents in cancer patients at this site, averaging 2-3 studies per year. Typically, these studies include 6 to 10 patients who remain in-house for 7 to 14 days under highly standardized conditions. They undergo blood, urine, and stool collection, and adhere to a controlled diet. A typical recruitment rate in these studies is 1 to 1.5 subjects per month.

The advantages of integrated ECG assessment in mass balance studies with oncology agents include:

- They are more cost-effective than conducting separate studies for mass balance and ECG evaluation
- Only one site is used with one type of equipment and operating protocol that follows standardized procedures
- The PRA staff is specifically trained on ECG assessment studies using ECGs extracted from Holters
- Our familiarity with studies in cancer patients in general (our staff helps and motivates patients to adhere to the restrictions needed for optimal ECG assessment)
- The implementation of real-time quality control of the continuous Holter recordings

This setting provides an environment with excellent conditions for the highly precise evaluation of ECG parameters, producing data that provide a conclusive assessment of a drug’s potential ECG effects. The lower variability of QT measurements with this approach, as compared with routine oncology ECG studies at several sites, means that a relevant QT effect (> 20 ms) can be excluded with as few as 8 evaluable patients, with a power of the study between 85% and 99%, assuming a small underlying effect and QT variability between 10 and 16 ms.
Dedicated Small QT Study

If a mass balance study is not planned, or has already been performed, another option is to design and execute a dedicated small QT study. A sample size for such a study would be 10 to 12 patients. Design considerations would be similar to a mass balance study. If possible, two dose levels should be studied, including a supratherapeutic dose, since this will result in a more adequate modelling. Both PRA and iCardiac specialize in drafting study designs and performing feasibility assessments.

Conclusions

Single-center oncology studies performed by dedicated PRA staff, combined with the High Precision QT approach of iCardiac, generates conclusive ECG data with a limited additional investment. Together, PRA and iCardiac offer unparalleled expertise and capabilities to integrate conclusive ECG assessments into small, routine oncology studies.

REFERENCES


CONTACT INFORMATION

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With 11,000+ employees covering 80+ countries, we bolster an impressive global presence with keen local insights. Our project teams harness their understanding of local regulations, standards of care, and cultural customs to effectively align our approaches with each study’s unique goals.

At PRA, we love what we do because we are making a difference in the lives of patients and their family members worldwide. Over the years, we have contributed to the development of numerous drugs now available to countless patients. From our scientific and medical experts to therapeutically aligned project managers and monitors, we provide the commitment and expertise needed for today’s complex studies.

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