A NOVEL APPROACH TO COST EFFECTIVE THOROUGH QT STUDIES UTILIZING A HIGHLY AUTOMATED HYBRID PHASE I/ECG CORE LABORATORY

Bill Wheeler, MD, FACC and Joy Olbertz, PharmD, PhD
Celerion

UNMET NEEDS:

ICH E4 mandates a dedicated study for essentially all small molecules to assess the risk of QT prolongation on the ECG that can lead to potentially lethal cardiac arrhythmias, Torsade de Pointes. The high cost associated with Traditional QT/G10 (TQT) study is expensive and a challenge for sponsors to perform. Traditional ECG core labs have realized the implementation of cost-effective approaches for ECG processing in TQT studies. We present a comprehensive plan to simplify planning, bidding, contracting, and executing of TQT studies while markedly decreasing overhead and ECG processing costs by about 50%. By using optimal automation of ECG processing over the system and presented that data to the FDA.

PROPOSED SOLUTION:

Based upon experience working with all the major ECG core labs in 36 TQT studies and over 140 Phase I studies with intensive ECG monitoring, Celerion has identified three areas where costs efficiencies could be realized while maintaining or increasing data quality. These areas are hybrid Phase III ECG core lab formation, equipment selection and ECG processing.

Traditional ECG core labs were designed to service large, global late stage trials that require much greater resources than do TQT studies. One traditional ECG core lab recently revealed that 93% of their costs for an ECG were not related to ECG processing, but to support of that overhead. By combining the functionality of both the Phase I unit and the ECG core lab into a single Hybrid Phase III ECG core lab serving only Celerion Phase I units we are able to eliminate most of the overhead of traditional ECG core labs and duplication of service already operating in Celerion clinics. Combining the two functions also allows us to focus on cost savings.

Another opportunity for cost savings was identified in equipment selection. Celerion selected the Global Instrumentation M12R Holter monitor for our 12-lead ECG data collection device. The M12R has been tailored specifically for Phase I use.

Finally, implementation of optimal automation in the processing of ECGs was another opportunity for significant cost savings. Celerion helped develop and implement a suite of software with AMPS, LLC a world leader in ECG processing.

SUMMARY:

Celerion has developed a Hybrid Phase I/ECG core lab that minimizes overhead and utilizes Bluetooth Holter monitors that eleminate the need for stand alone ECG machines and decreases data entry errors. The highly automated ANAMPS Antares software is used to automatically extracts optimal 10 second ECG recordings from the Holter recording based upon beats to beat heart rate variability and artifact level. The closer to the zero line the better the correlation. The M12R Holter monitor stores data on an SD card, which has a lower failure rate than Compact Flash cards used in many Holter monitors.

Potential Commercial Market:

- All nonclinical, small molecule compounds in development targeting FDA approval.
- 50 Phase I centers for software property of AMPS, LLC and Global Instrumentation

Potential Collaborators:

AMPS, LLC and Global Instrumentation

REFERENCES:

1. Mozgunov, J. Kubo Algorithm vs Manual Measurement of ECGs. presentation given at DIA Cardiovascular Safety in Drug Development; Antwerp, Belgium, 18-20 April 2018

Figure 1: Antares® Optimal ECG Extraction. The time window selected around nominal time point is at the top. On the right side the preceding HR and artifact level are acceptable. On the right side at the nominal time extraction there is significant preceding HR instability and artifact. Decreasing HR instability and artifact decreases variability.

Figure 2: This graph shows the correlation of automated ECG measurements with manually adjudicated measurements. The closer to the zero line the better the correlation. Although statistically the correlation is good, there are outliers that increase variability. FATQ's ability to identify outliers based upon specific criteria in the recording and assign the same criteria to a cardiologist is performed. The regression curve with standard error or other characteristics that prevent accurate automated measurements are routed to a cardiologist for review while the automated measurements are recorded directly into the database (Fig. 3).

Figure 3: Change in baseline adjusted, placebo extracted (so-called double delta) moxifloxacin effect on QTPF interval in Celerion trial. Note typical magnitude and time course of the effect. For a TQT study to be judged adequate by the FDA, the moxifloxacin effect must have a lower 95% confidence intervals (CI) greater than 5 ms (red dashed line) around maximal effect. At 24 hours moxifloxacin effect has decreased to 5 ms. At the 5 ms effect level this study would be able to exclude a upper 95% CI of 10 ms (green dashed line), the criteria for a positive study.

Figure 4: The sample size for a TQT study is related to the square of the variability (σ²). Typically a within subject variability of approximately 10 ms is used for sample size calculations. With an assumed 3 ms drug effect that variability results in Sample size of 45. Using the variability obtained in our trial, average of 6.5 ms, that sample size would be about 20.