AMPS-QT

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AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

Editorial

As the most attentive observers knew already since the beginning the request by the FDA to submit, when available, continuous recordings to the warehouse in the context of T-QT studies, opened the door to a whole new world of possibilities, but also raised a whole new set of questions in the mind of the Core Labs and the Sponsors. Moving from a classic 10-seconds ECG to a continuous recording of even only 10 hours represent an increase of 2 orders of magnitude of data potentially available to be verified and analyzed. The step is huge, the existing tools used for 10 seconds ECGs not adapted, the guidelines about what to look for non-existent…. A pretty scary scenario for the less informed and quite a challenge even for the best experts. In this issue we gladly publish the contribution of Dr. Catherine Ortemann-Renon of Sanofi. Catherine Ortemann-Renon obtained her PharmD and PhD from Universite Claude Bernard in Lyon, France. She joined Sanofi 19 years ago and has been working in Clinical Pharmacology for 16 years. She was introduced to cardiac safety and ECG and Holter analysis in the early years of 2000 in particular with Alfuzosin (Uroxatral(r)) and has been passionate about the subject ever since. Initially based in France (Montpellier), she moved to the US (Pennsylvania) in 2004 from where she very attentively follows all the industry developments. We hope her contribution, followed by an AMPS assessment on the subject, will allow our readers finding themselves in a very thick fog to see a little bit more light on the subject.

A Noteworthy Contribution:

Continuous ECG data collection: a Pharma perspective.

Catherine Ortemann-Renon Pharm.D, Ph.D, Sanofi-Aventis SA, New Jersey, USA

There is a growing attention toward the usage of continuous ECG data collected from pharmaceutical clinical trials. On this very same bulletin, members from both regulatory bodies (1,2) and academic environment (3) already stressed out the importance of storing continuous ECG data. Initially, and so far, the focus has been primarily concentrated on having a mean to double check the portion of ECG data selected to extract timepoint references. However, the management and consequent storage of continuous ECG could also serve as a valuable platform to assess cardiac safety aspects beyond those ruled by ICH-E14 guidelines. Today, the ECG Warehouse has been extended to accept continuous data. As of today, several studies have already been submitted.

In our company, 12-lead 24-h continuous ECG data are routinely collected in Thorough QT and Multiple Ascending Dose studies, both during baseline and steady state conditions of the drug under investigation. In the present environment of "Fast to Proof of Concept", these data are collected in healthy subjects but sometimes also in patient populations.

My personal opinion is that we cannot collect 24h of ECG recording just for the sake of extracting 10-second ECG strips. From a Clinical Pharmacology perspective, a rhythm and conduction analysis of the

full 24-h makes sense, but we also need to keep in mind the way these data can be "statistically" analyzed in a clinical development framework. This means that we have to consider both the harmonization of the data analyzed by the core labs and the adaptation to the clinical development needs.

In our company we have tried to harmonize the data collected from Holter recordings. Unfortunately it showed to be a difficult and finally not desirable task coming from a single sponsor. Our Holter records are centrally read by different core labs whose cardiologists follow different training and guidelines dictated by the core lab they work for. Harmonization can't be a single sponsor or core lab task. Today in our company, while we do a rhythm and conduction analysis of the Holter collected, it is limited at some pre-specified events of concern like ventricular tachycardia.

That's the reason why initiatives of collaboration, like the one presented at the last annual CSRC meeting in February of this year, are welcome. We need a joined effort from core labs and sponsors alike to first get a better definition of "normal" events and the frequency of some events in the healthy subject population taking into account the inter- and intra-individual variability. Baseline recordings as well as placebo groups can help in this matter. As sponsor I would also appreciate the use of code lists that are less diagnostic or pathology oriented but that could help identify more potential drug related effects.

However there are limitations in the use of continuous ECG recordings. Holter is mainly performed in resting conditions to get high quality ECG data, avoid noise, and decrease the variability in the measured ECG parameters (allowing keeping the sample size of the clinical studies reasonable). There is also the potential need for longer periods of recording with non-invasive methods in the case of long half-life drugs for example.

Finally if regulators are expecting sponsors to submit the full length of recording to the upgraded ECG warehouse, the raw data will have to be entirely validated at the core lab level. This means that core labs have to be ready for the validation of beat annotations providing the exact location (position) of each cardiac beat together with the beat type (e.g., normal rather than ventricular) on the full 24h time interval or at least the time point windows of ECG data considered for extraction (e.g., a 15 minute segment around the nominal timepoint). This will dictate both the content/length of recording and when our company will be able to submit these data to regulators.

Unfortunately, looking back at Dr. N. Stockbridge announcements of FDA's interest in receiving continuous ECG data as well as the Holter workshop organized by AMPS and Mortara in December 2013, I realize that the pace has been slow and that the joined effort of all is required to get this really started and moving. I am looking forward to future collaboration to get this done.

References:

1.C. Garnett (AMPS-QT Q1-2012 issue),
2. N. Stockbridge (AMPS-QT Q1-2013 issue)
3. P. Maison-Blanche (AMPS-QT Q4-2013 issue)

The following are additional comments by Fabio Badilini on the Submission of 24h data to the FDA Warehouse.

At the moment, regulators are particularly interested receive the full acquired record (e.g., the Holter raw data), together with information on which timepoint windows of ECG data have been considered for extraction (e.g., a 15 minute segment around the nominal timepoint) and, ultimately, which analysis windows (the actual ECG extraction) have been processed. Annotations (e.g., PR/QRS/QT intervals) are only required within the analysis windows.

To this end, all core labs have been rapidly adapting their internal procedures (mostly using the software technology provided by AMPS LLC) and are now capable of submitting continuous data to the FDA ECG Warehouse. From the sponsors' perspective, there is a justified concern on how the core lab generated data for the FDA Warehouse could be validated as adequate monitoring tools are still not available.

But the new paradigm also raises a number of additional points of reflection. First of all it would seem reasonable, while submitting the continuous data, also to document (i.e. attach) the information about all beat annotations, i.e. to provide the exact location (position) of each cardiac beat, together with the beat type (e.g. "normal" rather than "ventricular"). This type of information (typically referred to as beat annotation), is the cornerstone of each cardiac safety / cardiac arrhythmia report, which is normally performed whenever continuous ECG data is used in whichever variant of clinical trials. As of today, regulators are not used to handle this type of information and, partly for this reason, do not consider it a priority.

However, this could change soon for a number of reasons. First of all regulators may soon wonder, maybe not for TQT Study paradigm, how precisely the cardiac safety profile had been validated and thus may need to review all the abnormal (but also the normal) activity from a rhythm point of view (more or less the way an Holter record is reviewed in the clinical environment). But more importantly, we may have the opportunity to standardize the documentation of arrhythmias. Imposed standardizations are sometime ugly processes that slow down innovation, but the lack of an accepted way to report cardiac arrhythmia is well known, as is the need of methods that can reliably track occurrences of false positives and false negatives arrhythmic episodes. Maybe this is not an immediate goal, but once again with the help and the power of data collected in the FDA Warehouse and probably with the support of other organizations (such as CDISC and/or CSRC) this achievement could be soon a reality.

Products News

Looking forward
In Q2 of 2015 AMPS is planning to release:

- The first version of ABILE algorithm for beat detection and arrhythmia assessment for Continuous ECG Recordings.
- A new version of CER-S, using the new ABILE algorithm, including the following platforms:
  - Continuous ECG beat detection and classification
  - ECG beat editor
  - Arrhythmia detection and Arrhythmia editor
- A new version of our 12-leads measuring algorithm, BRAVO, taking advantage of the benchmark study we have performed in the last several months
- A new version of CalECG, Fat-QT and TrialPerfect with the latest version of BRAVO algorithm.

AMPS Recommends

In this is issue of AMPS-QT we highlight the paper "T-wave morphology analysis of competitive athletes" [1] recently published in the Journal of Electrocardiology from the group of the University of Copenhagen, that talks about T-wave morphology in an athlete population.
The paper reports how T-wave morphology differs between the athletes and non-athletes population, with interesting effects by the sport practiced (soccer vs. cycling).
The analysis of T-wave morphology, which is also a target of interest of AMPS (AMPS-QT Q1-2009, [2]), has been receiving growing attention particularly in the Pharmaceutical assessment of Cardiac safety.

Reference

[1] Hong L, Andersen LJ, Graff C, Vedel-Larsen E, Wang F, Struijk JJ, Sogaard P, Hansen PR, Yang YZ, Christiansen M, Toft E, Kanters JK. T-wave morphology analysis of competitive athletes. J Electrocardiology 2015; 48: 35-42.

[2] Dubois R, Extramiana F, Denjoy I, Maison-Blanche P, Vaglio M, Roussel P, Babilini F, Leenhardt A. A Machine Learning Approach for LQT1 vs. LQT2 Discrimination. Computing in Cardiology 2012; 39: 437-440.

AMPS Notebook

Fabio Badilini attended the **CSRC Annual Meeting,** held in Washington DC on February 19, 2015.

Fabio will soon be attending the 40th **ISCE Conference** that will be held in San Jose, CA from April 15th to 19th, 2015.