AMPS-QT

The AMPS Quarterly - Issue n.10 - 2Q2011 Editors: Fabio Badilini PhD, FACC and Martino Vaglio MS

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

Some of our readers probably remember that we announced in the 4th issue of AMPS-QT (4Q2009), over a year ago, that Dr Fabio Badilini was collaborating with a panel of experts, including FDA officials, writing a white paper about methods to asses QT/QTc interval in the presence of drug-induced heart rate changes. The panel, coordinated by the Cardiovascular Safety Research Consortium (CSRC), progressed through the task with much debate, as could be expected given the relevance of the topic, but at a steady pace, and eventually came to agreement on a version to be submitted to the CRSC members for comments. Dr. Badilini reports on this 10th AMPS-QT issue about the status of this much awaited white paper, following the first public debate. As usual: enjoy!

AMPS Views on:

CSRC White Paper on Methods to assess QT/QTc interval in the presence of drug-induced heart rate changes: work in progress and new ideas.

By Fabio Badilini, AMPS llc.

On June 17th 2011 the CSRC held a public webinar to collect comments and reviews from members of the organization on the white paper that will address methods to assess QT/QTc interval in the presence of drug-induced heart rate changes. This was a very important milestone for the roadmap of the manuscript, as it was the occasion for all CSRC members to raise all sort of concerns and consequently to affect significantly the publishing process.

The general response and overall outcome of the webinar was excellent, with attendees expressing highly positive comments and appreciation. The manuscript will now undergo a final review process within the working group and should then finally be submitted for publication.

We are proud to be part of this remarkable initiative which we strongly believe will clarify many confusing aspects and a few misconceptions about the methods described. As a member of the writing group, and specifically for the section on the Holter bin approach, I think that the main goal of the initiative, which was to trigger a constructive debate that would lead ultimately to better science has been already and completely achieved.

While not endorsing any particular approach, the white paper represents a unique opportunity to understand the subtle and somewhat confusing aspects of each method and finally describes in details the differences on how each methods handles the effects of significant heart rate changes in the assessment of a potential QT interval prolongation.

Even before its publication, the discussion and the brainstorming generated by this initiative has already generated a series of new ideas for the immediate future. As far as Holter-bin is concerned, together with other members of the writing group, we thought about a way to modify the method to overcome one of the issues when dealing with ICH-E14 guidance, and specifically the intrinsic limitation of the approach to provide a time-based assessment of the QT effect during the drug administration period (and the assessment of maximum effect).

We have already presented the first and original AMPS Holter-bin approach in previous issues of AMPS-QT, and specifically in the issue n.4 (4Q2009), where Dr. Fabrice Extramiana nicely described the relevant facets of the method and in particular the differences between rate related binning, intended as the process to pool and signal average cardiac beats characterized by the same preceding hysteresis corrected heart rate, and time related binning, where the cardiac beats are averaged according to their time of occurrence.

In the modified version of the method, rate and time related ECG signal averaging are implemented simultaneously to obtain an ICH-compliant implementation. This implementation preserves the possibility to avoid the application of a QT-correction model. Briefly, the rate related Holter-bin is applied only on the baseline recording, and for a period of time matched with that following the drug administration (typically during 10-12 hours starting at dosing time). This analysis determines the drug-free QT/RR reference for the spectrum of RR intervals covered by the baseline recording. On the drug-day, a time related binning is applied instead, (or alternatively a standard 10-second ECG is extracted) at a predetermined time-resolution. The on-drug QT interval is then compared with that from baseline, considering the bin with a matched RR interval, and a single-delta QT at the same heart-rate is computed. The same process is repeated on the placebo day (at the on-drug time-matched time point) and a double-delta is finally derived. In conclusion, while providing a mean to generate time-trends, this "modified" Holter-bin approach preserves the intrinsic advantage of the method to provide a comparison at identical heart rate, as there is no need to correct the on-drug and the time-matched placebo QT intervals.

Preliminary results obtained on retrospective data both on compounds that affect and do not affect heart rate, indicate that this modified Holter-bin approach is capable of detecting the same magnitude of QT effect detected with traditional methods, while preserving the advantage of avoiding the need of modelling the QT/RR relationship and the need of generating a corrected QT interval. A new version of WinAtrec (the AMPS Holter-bin software tool) that will also include the implementation of the modified Holter-bin is expected to be released in 2012.

Products News

Looking forward

In Q3/Q4 AMPS is planning to release:

- an updated version of CalECG v.3 with enhancements to the automatic algorithm.
- FDAEcg Suite v.2: enhanced graphical interface, with advanced scoring display, new scoring metrics and optimized ECG management.
- an update version of FAT-QT with new scoring metrics, synchronized with FDAEcg Suite v.2.
- a new version of TrialPerfect, with enhanced graphical interface and optimized ECG workflow.

AMPS Notebook

Fabio Badilini has been co-chairman of the 36th **ISCE conference** that was held in San Jose, CA from April 13 to April 17 where he also chaired the Pre-conference Tutorial focused on Heart Rate Variability.
He has been appointed chairman for next year 37th **ISCE conference** that will be held in Birmingham, AL from April 20 to April 24, 2012.

AMPS People

We continue our round of staff introductions with Tiziana Cella who has recently joined AMPS in 2010.
She studied Psychology at the University of Milan where she graduated in 2004. She then continued her studies in "Communication Science" obtaining her Master degree in 2007 with a thesis on User Centered Design. She specialized in User Interface Design, Interaction Design, Usability and Accessibility of web sites.
Tiziana's expertise at AMPS is in both User Interface design and application testing.
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