

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:

The CSRS/FSA workshop: results from the CiPA Phase 1 ECG team

The CSRC/FDA Workshop held in Washington DC on April 6th 2016 (The Proarrhythmic Assessment of New Chemical Entities) focused on two key aspects of cardiac safety. In the first part, the discussion concentrated on the ongoing paradigm changes for early phase drug development (with emphasis on whether a positive control is needed) and on alternative methods to establish the study's sensitivity in lieu of a pharmacological positive control. In the second part of the workshop, there was an update on the work of the CiPA (the Comprehensive In Vitro Proarrhythmia Assay) Phase 1 ECG team followed by a discussion on short term and midterm implementation aspects.

It is well established that drug-induced QT interval prolongation is not always proarrhythmic when multiple ion channels are affected. An important part of CiPA is to determine if the drug's effect on humans is similar to that which would be expected based on the preclinical ion channel data. It is thus vital to establish reliable biomarkers (ECG-derived measurements) that would confirm (or not) what has been observed at the preclinical level and which would ideally link in with specific ion channel alterations.

To date, several ECG repolarization parameters that have shown an association with ion channel changes (drug-related or congenital) have been investigated. From a technical standpoint, these parameters could be divided into two categories:

parameters that depend on the identification (automated or otherwise) of specific ECG calipers (i.e. intervals and amplitudes such as the JT_p and TpTe intervals and the amplitude of the T-wave) and parameters derived using alternative approaches aimed at extracting other features of the repolarization pattern, primarily morphological but also including surrogates of intervals and amplitudes. Some examples of the second category are the parameters described by our group (AMPS) based on Gaussian Mesa function modeling [1], the index described by Xue and colleagues based on a morphology index [2], and the parameters based on the T-wave loop described by Couderc at the University of Rochester [3].

The CSRC/FDA workshop provided an ideal opportunity for a detailed review, but the highlight of the meeting was surely the presentations in which the FDA research fellows Dr. Johannesen and Dr. Vicente presented recently published data [4], [5]. According to their results, the (shortening of) the heart-rate corrected JT_p interval (J-to-T_{peak}) seems to be *the best of eight studied biomarkers for detecting late sodium current block in presence of QTc prolongation caused by hERG block*. By directly assessing the presence of a late sodium channel blockade, the JT_{pc} interval alone would thus appear to be the marker that determines which hERG-related QT-prolonging drugs are proarrhythmic (e.g. dofetilide, where the JT_{pc} is also increased) and which are not (e.g. ranolazine, where the JT_{pc} is shortened by the balanced effect of the blocked sodium current).

These are surely fascinating results from a remarkable study which however stirred a certain amount of skepticism from a few of the opinion

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leaders attending the workshop. This was due to clinical doubts (the JTp interval does not reflect a clear cut moment in the ECG cycle) and also the additional technical complexity in detecting more fiducial markers on the ECG. Indeed, the J point can be as problematic as the Toffset, but the T apex is also not as easy as it may appear, particularly with the flat T-waves that are frequently observed in drug studies.

The workshop adjourned with a consensus that further research on more compounds is still required and that we should continue to work cautiously—an approach that the CiPa Phase 1 ECG team can surely achieve.

AMPS Views on:

Beyond the QT interval; where are we?

By Fabio Badilini, PhD, FACC, AMPS llc.

We share an extract from the post hoc ECG analysis from a Single/Multiple Ascending Dose (SAD/MAD) study recently conducted using the full suite of AMPS tools, namely FatQT, Bravo, and CalECG (see previous issues of AMPS QT for further details, or visit www.amps-llc.com). Timing could not be better if we consider the ongoing discussion and debate regarding the search for new (better than the QT interval) ECG biomarkers that could lead to channel-specific information. Rather than using the term *biomarker*, which can be in some case misleading, the term *parameters* seems to be more adequate, as we are referring to measurements derived from the ECG signal, parameters that like the QT can be different time intervals (e.g. JTp or TpTe), but that can also be amplitudes or (for example) indexes of T-wave morphology.

The CiPA meeting just held in Washington DC (see the editorial), set quite loudly and clearly the tone of the discussion and highlighted the importance for further inspection of the parameters that so-far seem to be the best candidates, namely the heart-rate corrected JTp interval, whose reduction appears to be strictly related to a late-sodium current blocking (protective) effect, and the TpTe interval, which seems mainly linked to the arrhythmogenic hERG channel inhibition [4], [5].

The results we are about to disclose are from a compound which is still in the early development phase and which, at the highest dosage of the SAD part of the cited study, showed a significant (> 30 ms) QT prolongation effect. Channel-specific patch clamp analysis is not yet available, with the exception of the hERG channel, which, even at the highest dosage concentrations where the QT prolongation was observed, exhibited minimal-to-nil blocking effect (Cmax of the highest dose was a factor of three below hERG IC50).

The scope of this brief report is twofold: on one side it gives us the opportunity to describe the AMPS suite of tools used in the analysis, and on the other, despite the limitation of partial results, to demonstrate how the whole context of ECG parameters may be more complex than what current results seem to indicate.

The Study

Data here reported come from post-hoc analysis derived by a standard SAD/MAD study with primary objective to assess the safety and tolerability of single and repeated ascending doses of the compound as compared to placebo when administered to healthy male volunteers. The goal of the post-hoc optimization study was to focus on the ECG assessment on standard intervals (PR, QRS and QT) and to integrate the analysis with parameters describing the morphology of the repolarization pattern, and in particular the JTp and TpTe intervals, the amplitude of the T-wave (Tamp) and the symmetry of the T-wave.

The SAD part of the study was conducted according to a single-center, randomized, double-blinded, placebo-controlled, single-dose escalation, and alternate crossover design in two cohorts of healthy male volunteers where six single doses of the compound were assessed with an escalation scheme which ensured adequate control of the dosage increases. A total of 12 healthy male volunteers (aged 18 – 55 years) and divided into two cohorts (three dose levels each) were enrolled. Similarly, the MAD part of the study was conducted according to a single-center, randomized, double-blinded, placebo-controlled, multiple-dose escalation, parallel group design, where three dose levels of the compound

were administered. The results we report are extracted and limited to the SAD part.

ECG Parameters

The post hoc analysis focused on the following parameters:

Standard parameters (intervals)

- PR, QRS, QT intervals,
- QTcF interval, Fridericia's corrected QT.

Indirect parameters of morphology based on intervals and amplitudes (caliper dependent)

- JTp interval, i.e. the interval from the J point to the T-wave apex.
- TpTe interval, i.e. the interval from the T-wave apex to the end of the T-wave.
- T-wave amplitude, the amplitude in microvolt units of the T-wave.

Parameters of morphology (caliper independent)

- Ascending phase velocity, a parameter that correlates with the ascending speed of the T-wave.
- Descending phase velocity, a parameter that correlates with the descending speed of the T-wave.
- T-wave symmetry, and index of repolarization morphology based on the symmetry of the T-wave.

ECG Assessment

All ECGs ($n = 1104$) were processed and analysed with the AMPS highly automated approach which (briefly) consists of the following steps:

- Automated classification of all ECGs into two groups (high and middle-low quality) based on automated measurements of several quality metrics (noise content, presence of abnormal beats) by Fat-QT.
- Automated measurement of all ECGs using AMPS proprietary measurement algorithm (BRAVO). For

this study, all cardiac measurements (both interval and morphology parameters) were computed on the 12-lead vector magnitude (VM, e.g. the square root of the sum of squares at each digital sample) derived from the individual median beats.

- Expert cardiologist review of the ECGs from the middle-low quality group using CalECG. This task was performed using the Global Superimposed Median Beat display mode (see Figure 1), which allows the cardiologist to review the position of the automated calipers from the superimposition of the 12 individual median beats [6]. Of note, about 20% of the ECGs ($n=198$) were reviewed, and about 5% ($n=51$) had been overwritten (at least one caliper position modified) by the cardiologist. This review applied to standard intervals (PR, QRS, QT), amplitudes (T-wave), and interval-related parameters of morphology (JTp and TpTe).

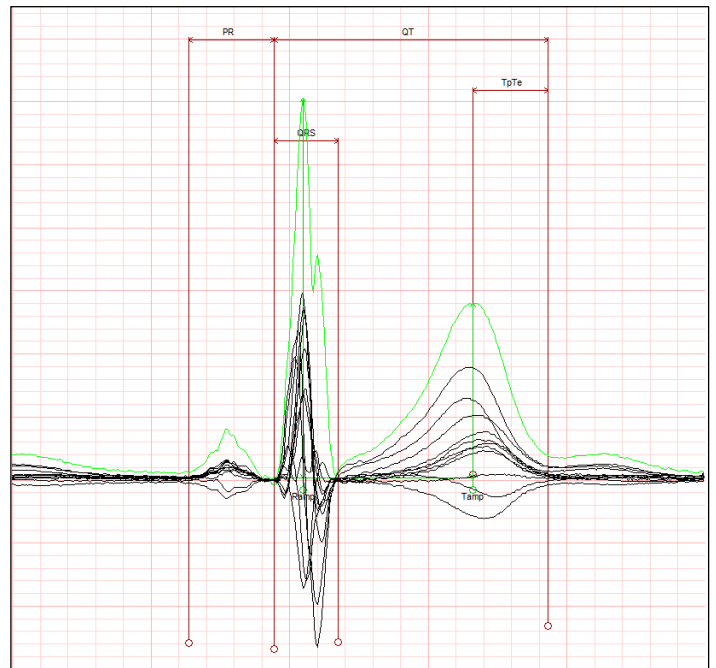


Figure 1

Interval-independent morphology analysis was computed using a proprietary fully automated (i.e. no review) approach based on Gaussian Mesa function modeling (GMF) of the repolarization waves [1]. Briefly, the ascending and descending phases of the VM T-wave are fitted by two independent half-Gaussian curves (see Figure 2). The standard deviations of these functions (σ_1 and σ_2) and indicators of the ascending/descending speed and their ratio σ_1/σ_2 is an indicator of the symmetry of the T-wave. A $\sigma_1/\sigma_2 = 1$ would indicate a perfectly

symmetric T-wave, $\sigma_1/\sigma_2 < 1$ a T-wave with a slower/longer descending phase, and $\sigma_1/\sigma_2 > 1$ a T-wave with a slower/longer ascending phase.

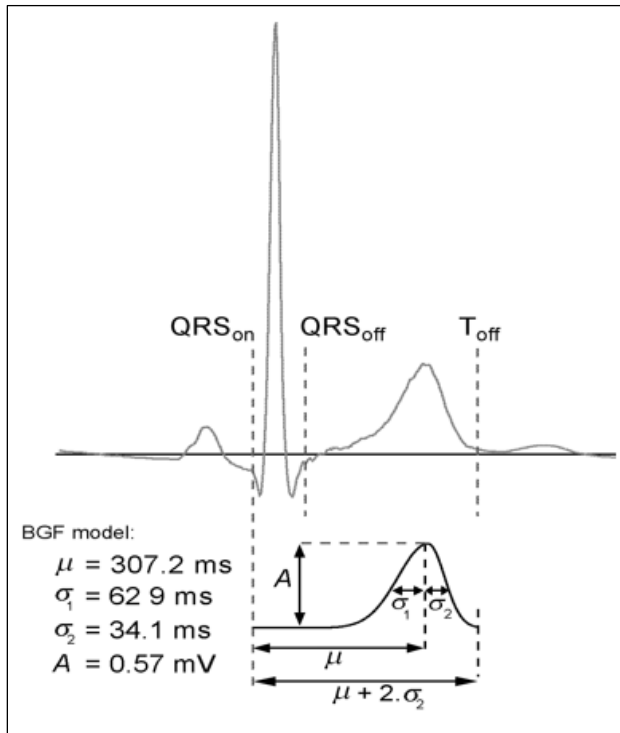


Figure 2

Results

The compound showed a sensitive effect (increase) on heart rate; at the highest dosage level (2000 mg), the increase reached a maximum of 10.3 bpm (median value), at 2h post-dose.

Figure 3 reports the QTcf central tendency results

(differences versus pre-dose at each hourly-based timepoint) of the SAD part of the study for the six dosing levels and for the placebo pooled data (black line). At the highest dose level (2000 mg), the prolongation effect is quite evident and it peaks already at the first timepoint (1h after dosing). The largest median baseline increase observed was 46.8ms (1 hours post-dose), whereas the largest individual change was 64.7ms (2h post-dose). Of note, among all the ECG from the overall study (including the MAD part), clinically significant changes were only observed in the peak concentration ECGs from 2 subjects of the 2000mg subgroup, and did not include the appearance of notched and/or bumps on any (all leads) of the T-waves.

When broken down into its sub-intervals, the components of the QT interval exhibit different patterns.

Figure 4 shows the effect on the QRS interval which also exhibits a significant increase at the highest dosing level (largest median baseline increase observed 25.7ms (1 hours post-dose), whereas the largest individual change was 30.0ms (1h post-dose).

Figure 5 shows the effect on the JT_p interval (heart-rate corrected with the population-based formula recently proposes by Johannesen, based on a power-law model with an exponential index of 0.58 [7]) which shows a reduction effect (largest median baseline decrease observed 42.7ms at 2 hours post-dose).

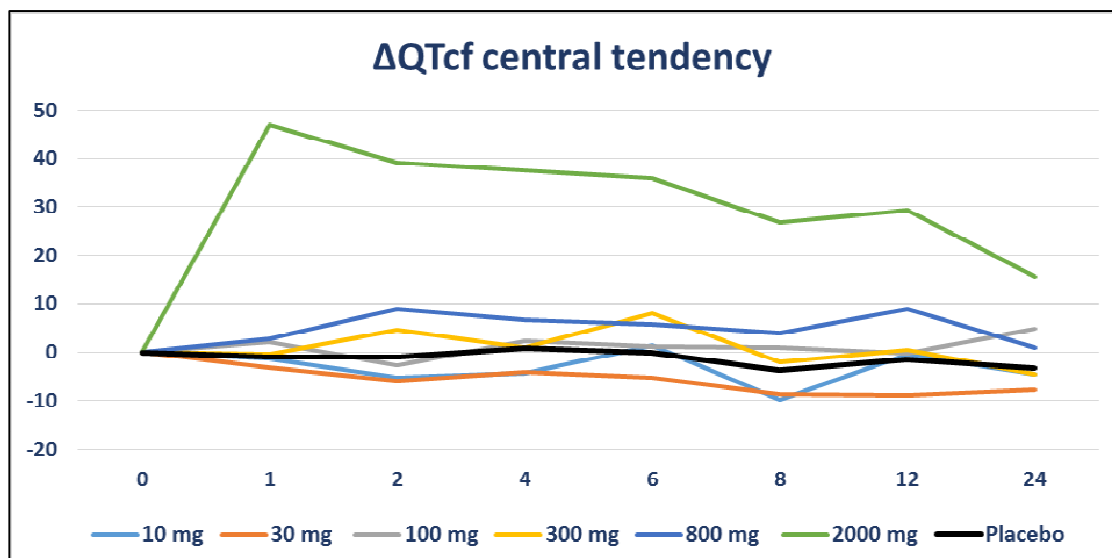


Figure 3

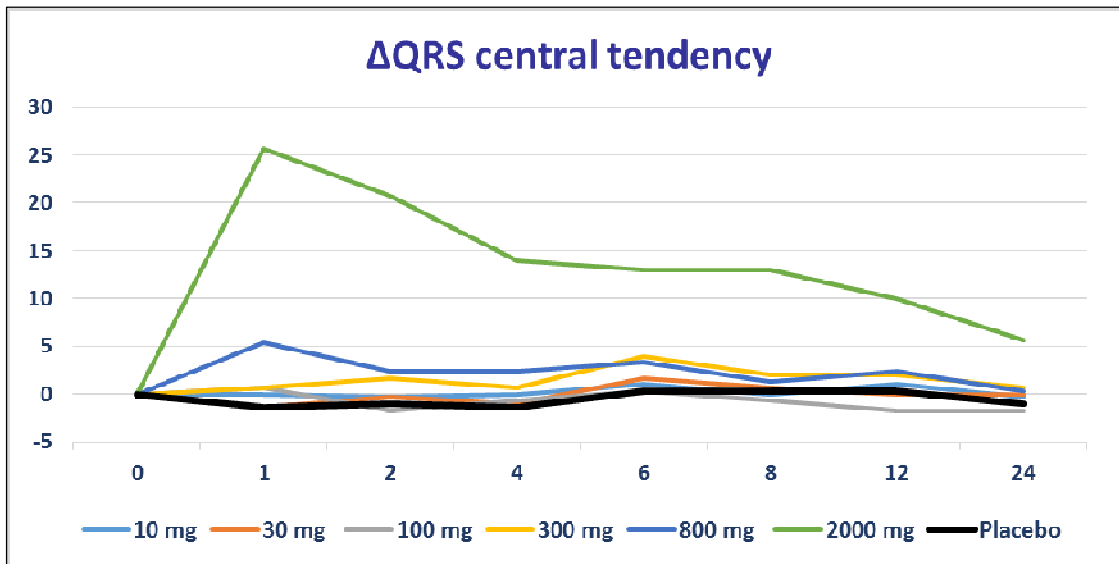


Figure 4

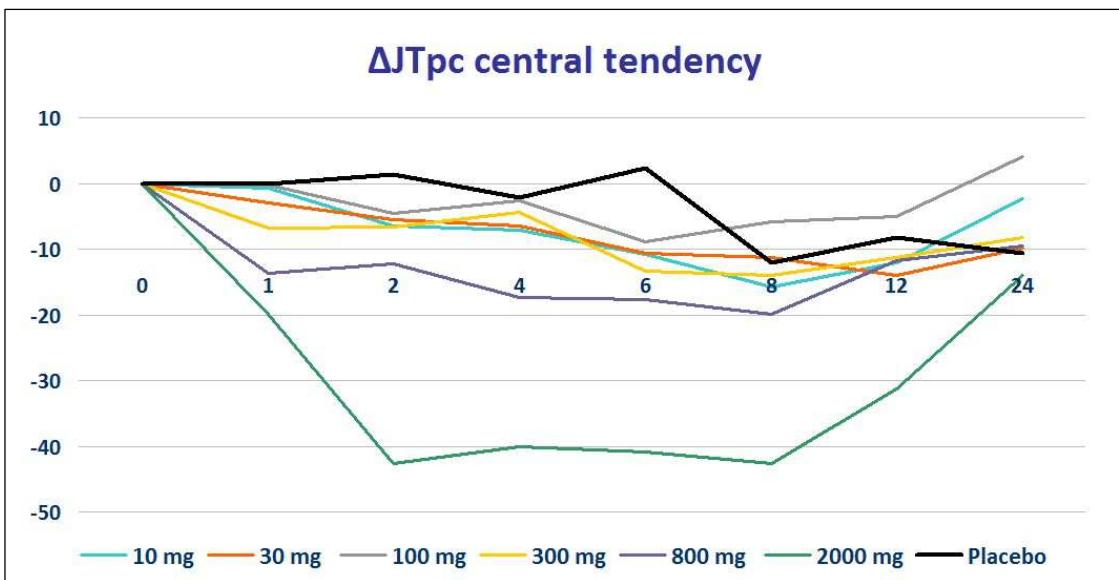


Figure 5

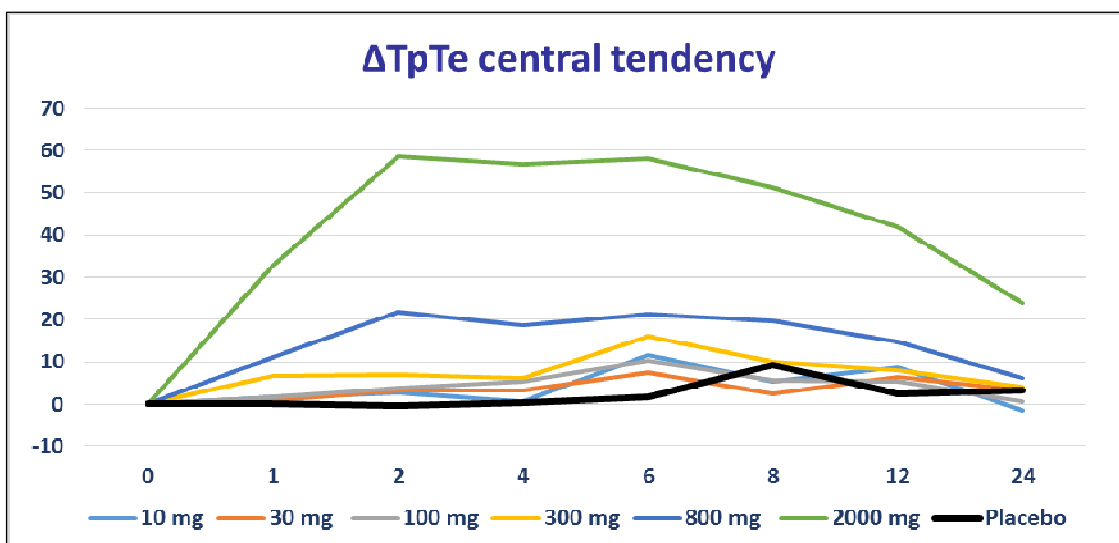


Figure 6

Finally, Figure 6 shows the effect on the TpTe interval. At the highest doses, 2000 mg, the largest median baseline increase observed was 58.7ms (2 hours post-dose), whereas the largest individual change was 76.0ms (2h post-dose).

More than the other intervals, TpTe also showed a sensitive pattern at the next high dose level (800 mg), where the largest median baseline increase observed was 21.7ms (2 hours post-dose) and the largest individual change was 36.7ms (2h post-dose).

In summary, the effect of the compound at the highest SAD dosage is sensitive prolongation of the QT interval which however is characterized by multiple effects: the QRS and TpTe intervals are both prolonged, whereas the (heart-rate corrected) JTp interval is reduced.

Figure 7 is a representative example from one of the subjects in the highest dose group (2000mg) of the SAD part of the study (for simplicity the example shown is taken from lead II). The black-colored curve is from a pre-dose ECG, whereas the red-colored curve is from the ECG taken at peak concentration.

The two curves had been overlapped after being synchronized with respect to the QRS onset point. In the peak concentration ECG, the heart rate has increased by 14 bpm (as clearly visible from the two strips at the bottom), and the changes on repolarization described in the previous graphs are nicely confirmed.

Both the QRS and TpTe intervals are clearly prolonged (respectively by 20 and 48 msec), whereas the JTp interval has strongly decreased (JTpc reduction: 50msec), resulting in an overall QTc prolongation of 26msec.

The T-wave shape has completely changed with a decrease in the T-wave amplitude of almost 1mV (939 μ V) and a shift of the symmetry index of about 56% (of note, $\sigma_1/\sigma_2=1.79$ before drug, and 0.79 at peak concentration).

Are T-wave morphology changes a consequence of the shortening/prolongation effect of the JTpc/TpTe intervals or is it rather the contrary?

The results recently published by Vicente and colleagues seems to favor the first scenario [5], although it is fair to state that in their work T-wave morphology was assessed with a different set of parameters. In Figure 8, the central tendencies for the σ_1/σ_2 symmetry ratio are shown. The pattern of the example in Figure 7 are clearly confirmed, with a striking similarity to those seen with the TpTe ration (Figure 6). Regardless of which effect is causing the other, from a pure technical point of view, a significant advantage of interval-independent morphology indexes (either AMPS, but also other recently described [2], [3]) is that they *truly* go beyond the notorious limitations of the QT interval, i.e. the need to detect problematic ECG markers such as the end of the T-wave (or even worse, in the case of the JTp interval, the end of the QRS complex).

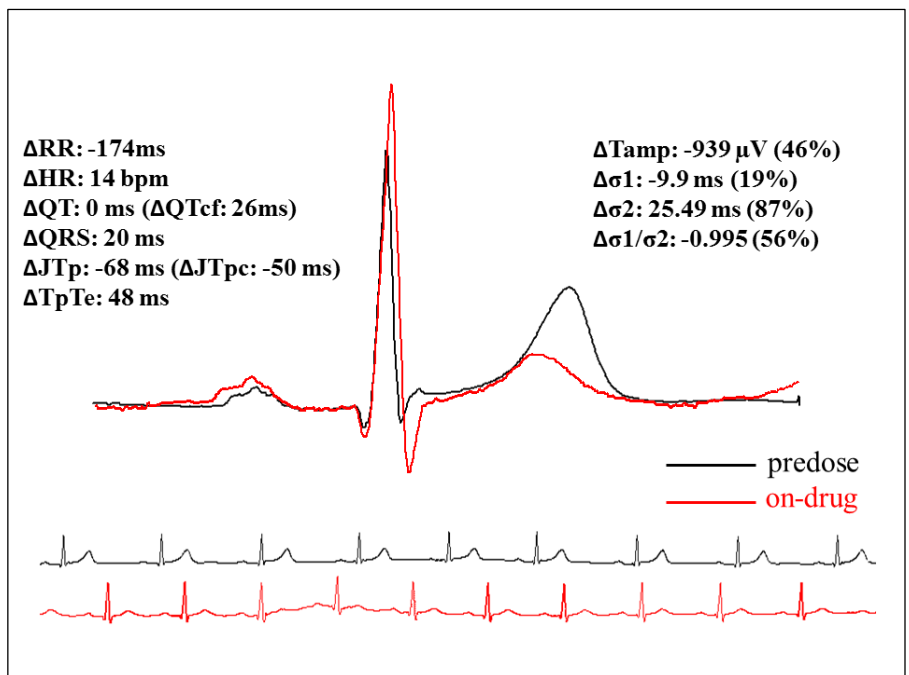


Figure 7

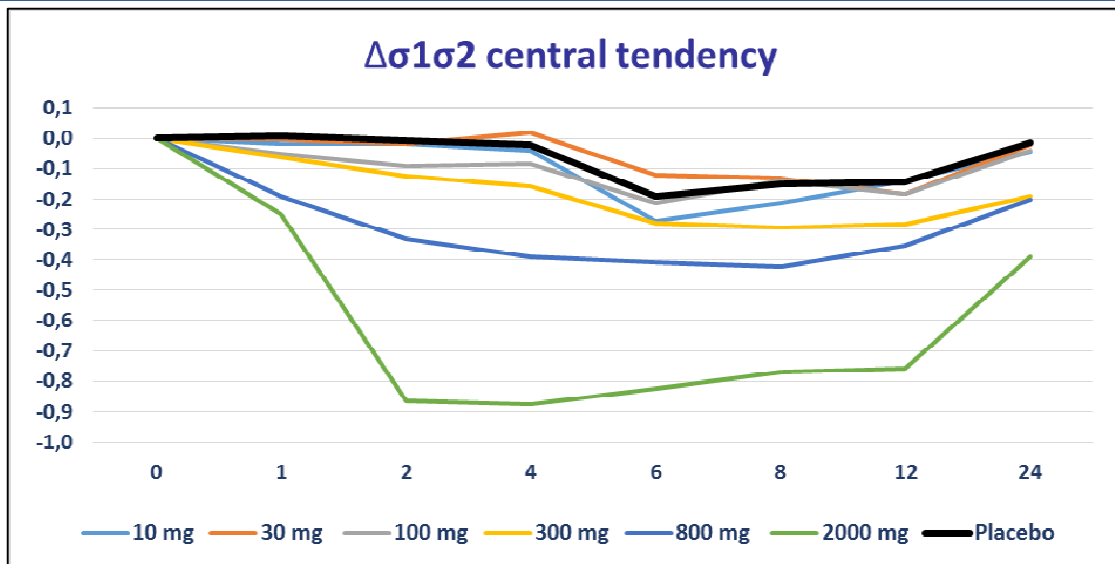


Figure 8

Conclusion

Any further conclusion is premature and requires the multi-channel patch clamp results to be released, particularly with respect to a potential late-sodium channel blockade, which would justify the observed shortening effect on the JTpc interval. But the (already known) lack of an hERG blockade of the compound and the associated strong increase observed in the TpTe interval already provide sufficient evidence that things are perhaps more complex than what they have been thought to be. It is the author's strong opinion that further analysis is still required before a conclusive association between one or more ECG parameters (biomarkers....) and channel-specific blockade can be drawn.

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Products News

Latest Releases

In Q1 2016 we have released a new version of CSPER (Command line Suite for Processing ECG Recordings) for customizable PDF ECG report and ECG image generation.

Looking forward

In Q2 2016 AMPS is planning to release:

- A new version of our 12-leads measuring algorithm, BRAVO, taking advantage of the benchmark study we have performed between Q4 2014 and Q2 2015.
- A new version of CalECG, Fat-QT and TrialPerfect with the latest version of BRAVO algorithm.
- A new version of CER-S, including the following revised platforms:
 - Continuous ECG beat detection and classification
 - ECG beat editor
 - Arrhythmia detection and Arrhythmia editor
 - aECG Generator

AMPS Notebook

We announce the release of the PMB-AMPS Holter database a joint project with Dr. Pierre Maison-Blanche with the aim of launching an annotated Holter recording database, refer to the “News” section on our website www.amps-llc.com for more details.

Fabio Badilini attended the “2nd Annual Think Tank: **Prevention of Sudden Cardiac Death in the Young**” organized by CSRC, held in Miami, FL in February.

Fabio will be attending the **41st ISCE Annual Conference** that will be held in the next few days in Tucson, AZ.

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