Background/Abstact: Over the last decade, the majority of drug withdrawals from the market have been for QT interval prolongation. The association of premarketing QT interval prolongation with torsades de pointes cardiac death is well recognized. However, the impact of ethnicity on QT interval prolongation is not clear. One recent study demonstrated that the steady-state peak plasma concentration of moxifloxacin was affected by ethnic factors [2]. One such concern has been ethnicity of study participants. ICH E14 states that ethnicity should not have an impact on the results of the TQT trial. In this guidance it is made clear that “Although data are required along with the 95% confidence intervals of the differences.

INTERVENTION: Due to enrollment of several drugs in the last 2 decades due to association with Torsades de Pointes, a procedure for reformulation of QT/QTc was established for preclinical and clinical development. The Electrocardiographic (ECG) QT/QTc interval correction and analysis procedure for preclinical and clinical development is described below. The ECG QT/QTc interval should not be affected by ethnic factors. The QT/QTc interval is calculated using the equation: QTc = QT/√HR, where QT is the QT interval and HR is the heart rate. The analysis was conducted with PROC MIXED in SAS 9.2.

RESULTS AND DISCUSSION: A total of 60 healthy volunteers were used in this analysis of TQT differer ECG recordings. All subjects were randomly recruited at 6 centers and consented. The ECG recordings were obtained using General Electric MAC 1200 cardiographs at 500 samples per second. Data was acquired using General Electric MAC 1200 cardiographs at 500 samples per second. ECG recordings were obtained for 750 different subjects. The QTc interval was calculated for each subject using the equation: QTc = QT/√HR, where QT is the QT interval and HR is the heart rate. The analysis was conducted with PROC MIXED in SAS 9.2.

A summary of the resulting ECG data is provided in Table 1 and a summary of the differences in least square means is shown in Figure 2. In this analysis, QTc duration was found to be significantly lower from African-American (AA) than from Caucasian (CAU) participants. Although no significant difference was observed between African-American (AA) and Hispanic (HIS) participants, the difference was significant between African-American (AA) and Caucasian (CAU). In this population, HR ranged from 63 to 100 beats per minute and QTc duration from 391.2 to 414.3 ms. There was no significant difference between the least square means (p-value < 0.05), the analysis was performed by using standard error in least square means between the different ethnicities.

Although there may be a 0.05% difference in means, between the populations used for this analysis, in order to better evaluate the impact of ethnicity as the outcome of the TQT the next step will be to evaluate the response of participants in different ethnic groups to treatment with different drugs. It is expected that drug-induced QT prolongation will be more pronounced in African-Americans and Hispanics compared to Caucasians.

There is a marked difference in clinical susceptibility to arrhythmias between ethnic groups. For example, in one investigation, it was shown that Caucasians were more prone to the QT-prolonging effects of quinidine. Differences in QT response to medications are also not surprising based on right heart studies of cardiac potassium channel function in African-Americans and Caucasians. Whereas QTc was not significantly different from the other populations studied, the QTc interval was significantly lower in African-American relative to Caucasian participants. Whereas QTc was not significantly different from the other populations studied, the QTc interval was significantly lower in African-American relative to Caucasian participants.

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