

Comments on
ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and
Proarrhythmic Potential for Non-Antiarrhythmic Drugs
(CHMP/ICH/2/04, ICH Step 2, 10 June 2004)

German Region of the International Biometric Society

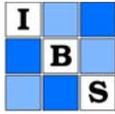
General comments

1. Determination of the QT/QTc interval

The guideline gives only little information about the determination of the QT/QTc interval. Are the intra-patient measurements stable or do they depend, apart from the heart rate, on different parameters, as e.g. the selected lead for measurement, the position of the patient, the circadian rhythm, etc? If these parameters had an influence, a standardized method should be recommended. Is there enough knowledge about the distribution of the QT/QTc interval dependent on several parameters to give specific recommendations in the guideline? If not, a large study without any medication would be required in healthy volunteers beforehand.

2. Risk of QT/QTc interval prolongation

There seems to be not much knowledge about the effect of QT/QTc interval prolongation on proarrhythmic risk. This is reflected in the recommendation to perform multiple analyses using different endpoint definitions for QT/QTc interval prolongation: maximum time-matched difference in absolute measurement, 3 different cutpoints for categorical analyses of absolute QTc interval prolongation, 2 different cutpoints for categorical analyses of relative QTc interval prolongation. Does the guideline require the statistical exclusion of a difference between verum and placebo with respect to each of these endpoints (i.e. multiple non-



inferiority tests)? The rationale for such a strong requirement is not clear. The power calculations would be extremely difficult, e.g. assumptions about the multivariate distribution of repeated QTc measurements over time would be necessary. In any case, the number of patients required would be very large.

Better quantitative knowledge about the influence of the length of the QTc interval on the proarrhythmic risk is required. If this does not exist, a large epidemiological study would be required investigating this thoroughly. Based on the results, the requirements in the guideline have to be stated more precisely, limiting the number of endpoints.

Specific comments

1. p.6: 2.1, Design considerations, first sentence

Is a thorough QT/QTc study necessary dedicated solely to this aim, or is it possible to do the thorough QT/QTc evaluation within another study in the development process?

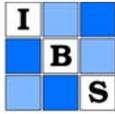
2. p.8: 2.1.2, 5th paragraph, 3rd sentence

“The confidence in the ability of the study to detect QT/QTc prolongation can be greatly enhanced by the use of a concurrent positive control group to establish assay sensitivity.”

It is unclear what this means. Potential interpretations are that it would be necessary to include a control group of patients with known QT/QTc prolongation; or that it is necessary to include a group of patients treated with a drug known to affect QT/QTc prolongation. Please clarify.

3. p.8: 2.1.2, 6th paragraph

First sentence “Based on similar considerations, a negative ‘thorough QT/QTc study’ is one where the largest time-matched mean difference between the drug and placebo (baseline-



subtracted) for the QTc interval is around 5 ms or less, with a one-sided 95% confidence interval that excludes an effect >8.0 ms.”

It should be clarified whether it is sufficient to show that the prolongation is less than 8 ms (e.g. a one-sided 95% confidence interval that excludes an effect >8.0 ms), or whether it is additionally necessary that the observed difference is less than 5.0 ms. Knowledge on which interpretation actually holds true is essential for study planning. In both cases, power calculations are rather difficult, since this requirement has to be fulfilled for every measurement point. Hence, assumptions about the multivariate distribution of repeated QTc measurements over time are necessary.

Second sentence “This upper bound was chosen to reflect uncertainty related to the variability of repeated measurements.” A more detailed explanation of this consideration should be given.

4. p.13: 3.2.2, 1st paragraph, last sentence

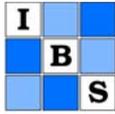
“As with all QT/QTc interval analyses, categorical analyses are most informative when it is possible to compare the rate of supra-threshold readings in the treatment and control groups.”

It is not clear what is meant by this sentence.

5. p.13: 3.2.3, QT/QTc interval dispersion

The chapter on QT/QTc interval dispersion is not quite clear. The 1st sentence “QT/QTc interval dispersion, defined as the difference between the shortest and the longest QT/QTc interval measured on the 12-lead ECG, has been thought to reflect the regional heterogeneity of cardiac repolarization.” indicates that the dispersion within one single ECG is meant.

It is unclear what the 3rd sentence “Absolute values of ≥ 100 ms and changes from baseline of $>100\%$ have been suggested as clinically noteworthy signals for categorical analyses.” means in this context. This should be clarified.



6. p.14: 4.1, 2nd paragraph, 4th sentence

The incidence of multiple types of adverse events shall be compared between verum and placebo. Additionally, sub-group analyses in terms of age, gender, pre-existing cardiac disease, electrolyte disturbances, and concomitant medications shall be conducted.

Is it meant that, additional to the thorough QT/QTc interval evaluation, it should be shown statistically that there is no difference between verum and placebo with respect to the incidence of the different adverse events in the mentioned sub-groups? This would seem to be a rather unrealistic requirement as the required sample size would be huge.