

DETAILED COMMENTS, ANNOTATED TO EACH SECTION OF THE DRAFT GUIDANCE

1. INTRODUCTION

1.1 Background

Line 110: We note that the statement “it is not clear...whether arrhythmia development is more closely related to an increase in the absolute QT interval or an increase in the relative (“corrected”) QT interval (QTc)” is inconsistent with the examination of changes described in section 3.2.2, which should be based on both QT and QTc. The statement in line 110 should be amended or section 3.2.2 updated to include assessment of the change in uncorrected QT and RR.

2.0 CLINICAL TRIALS

2.1 Design Considerations

Line 157: The following wording causes us significant concern: “At present, whether non-clinical testing can exclude a clinical risk for QT/QTc prolongation is controversial. Conduct of the ‘thorough QT/QTc study’, as described in section 2.1.2, would be needed in almost all cases **for regions where non-clinical data are not considered** able to preclude risk of QT/QTc prolongation. For **regions where non-clinical data are** considered informative enough about the risk of QT/QTc prolongation in humans, the recommendations in this guidance for the clinical evaluation of QT/QTc could be modified.” (emphasis added). It seems contrary to ICH principles to generate a harmonized document that allows for regional differences in data requirements. Clarification is needed about what nonclinical data could preclude the need for a thorough clinical QTc study, and in what regions of the world. It seems that E14 requires definitive proof that a compound will not produce QTc prolongation in humans. This is not required of any other nonclinical test. If the E14 document continues to state that the definitive QT study in humans will occur with all compounds and be the criteria for defining the risk of QT prolongation and Torsades, then we question the role and utility of the studies described in S7B. If the intent of S7B is to define the predictive value and/or appropriate timing of nonclinical studies relative to clinical development it still has value as a harmonized regulatory guidance.

Lines 170, 262 and 324: The guidance needs to clarify what ‘negative’ and ‘positive’ relate to. A negative study would be one in which there was no evidence of prolongation - which of course would be a successful outcome for a QT/QTc study. We recommend clarification or modification of the terms ‘negative’ and ‘positive’.

2.1.2 The ‘Thorough QT/QTc Study’: Dose Effect and Time Course Relationships

Line 253: The active control is included in the thorough QTc study for assay sensitivity. The guidance should confirm that this would not be a comparative treatment group, and that each test treatment would still be compared against placebo. We request addition of statements 1) to confirm the expected magnitude of the active control e.g., a mean ≥ 5 ms, or a lower 95% CI of 5ms or more and 2) to confirm that the positive control is not used for formal statistical comparisons, and to state the required magnitude of the positive control.

Line 260 and 642: 5 msec is well within the potential for detection due to random variability in such small, well-controlled, thorough studies. Regulators should consider increasing this magnitude to 7-8 msec (with corresponding upper confidence bound of 10 msec) to avoid regular, false detection of effect.

Line 263: Reference to “placebo subtracted” would be more appropriately referred to as “baseline adjusted” as essentially this means fitting baseline as a covariate in the analysis. We suggest that this terminology be used throughout the document.

Line 273: Where crossover/parallel group is mentioned it would be worth also mentioning that balanced incomplete block designs (a combination of these approaches) may also be a useful design option.

Line 289: The exact intent of the last paragraph of this section is ambiguous; it could be interpreted to mean eliminate variability to maximize sensitivity of the study, or alternatively that it is evaluating how QT/QTc is affected by intrinsic variability. The wording should be revised to remove this ambiguity.

2.1.3 Clinical Trial Evaluation After the ‘Thorough QT/QTc Study’

Line 297: For evaluation of ECG within the clinical program is it expected that a PK assessment would be made at the same time as the ECG assessments?

Line 314: It may be unlikely that patient subgroups can be thoroughly investigated through a single clinical study. We suggest adding a statement that highlights the value of conducting subgroup analyses on appropriately integrated data from similar studies.

Line 324: If there is any guidance on a suitable minimum number of subjects that would be required to establish a lack of effect for QTc in a clinical program, or examples from recent programs, this information should be provided.

2.2 Collection, Assessment and Submission of Electrocardiographic Data

Line 330: Consideration should be given to providing guidance on avoiding collection of critical ECG measurements shortly after meals or during sleep where QT prolongation will naturally occur.

3. ANALYSIS OF ECG DATA FROM CLINICAL TRIALS

3.1 QT Interval Correction Formulae

Line 429: The guidance should be clear that QTcF should be used for primary inference with other data (QTcB, QT, RR, etc) being supporting. This is becoming common practice.

3.2.2 Categorical Analyses

Line 480: Multiple ECG assessments are collected at each timepoint within studies. In the analysis of central tendency (section 3.2.1), it is common practice for the average across these multiple assessments to be taken, and for this average value to be used in subsequent statistical assessment of central tendency. For the categorical analysis (section 3.2.2), the guidance should address whether the change from baseline QTc values are based on the maximum amongst the multiple QTc values at each timepoint and at baseline, or whether the average across the multiple assessments should be used in keeping with the analysis of central tendency.

3.2.3 QT/QTc Interval Dispersion

Line 508: The dispersion will depend on the number of assessments taken at a timepoint (and also the number of timepoints). A study could minimize dispersion by using 2 recordings at a single timepoint, at the expense of overall variability. The guidance could state a preferred number of recordings at each timepoint. The dispersion parameter should be calculated for each single timepoint (rather than over all post-baseline timepoints).

4. ADVERSE EVENTS

Line 537: It may be unlikely that patient subgroups can be thoroughly investigated through a single clinical study. We suggest adding a statement that highlights the value of conducting subgroup analyses on appropriately integrated data from similar studies.