



DEC 21 2004

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2004D-0377
Response to FDA Call for Comments
International Conference on Harmonisation; Draft Guidance on E14 Clinical
Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-
Antiarrhythmic Drugs

Dear Sir or Madam:

Reference is made to the September 13, 2004 Federal Register announcing the request for comments on International Conference on Harmonisation; Draft Guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

AstraZeneca has reviewed this guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Steven Miller, Vice-President, Regulatory Affairs at 302-885-1816.

Sincerely,

Peter M. DiBattiste, MD
Executive Director, Clinical Research

for

Philip Sager, Sr. Director
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PS/LAW

Enclosure

2004D - 0377

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| Location in document (line number or Section) using the Step 2 E14 document published at http://www.fda.gov/cder/guidance/6378dft.pdf | / Reference/ Rationale | Suggestion/Proposed replacement text |
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| Line 91-93 | <p>“The QT interval represents the duration of ventricular depolarization and subsequent repolarization, beginning at the initiation of the QRS complex and ending where the T wave returns to isoelectric baseline”</p> <p><u>Comment</u> Should be changed to permit common methodologies of measuring the QT interval, such as the tangent method, to be utilized.</p> | <p>Proposed change: “the duration of ventricular depolarization and subsequent repolarization”, Change to: “The QT interval represents the duration of ventricular depolarization and subsequent repolarization, beginning at the time from the initiation of the QRS complex to the end of the T wave.”</p> |
| Line 229 | <p>“The ‘thorough QT/QTc study’ would typically be conducted early in clinical development to provide maximum guidance for later trials”</p> | <p>Proposed change “The ‘thorough QT/QTc study’ would <i>often</i> be conducted <i>relatively</i> early in clinical development to provide maximum guidance for later trials.”</p> |

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| <p>Line 262-265</p> | <p>“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”</p> <p><u>Comment</u> Given the variability of placebo measurements of QT/QTc, the upper bound of the confidence interval should be extended to 10ms and the interval should be described as a two-sided 90% confidence interval.</p> | <p>Proposed Change</p> <ol style="list-style-type: none"> 1. 8 ms to 10 ms 2. one-sided 95% to two-sided 90% <p>“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 two-sided 90% confidence interval that excludes an effect ≥ 10.0 ms .”</p> |
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| <p>Line 274</p> | <p>Crossover or parallel group study designs can be suitable for trials assessing the potential of a drug to cause QT/QTc interval prolongation. Crossover studies at least have two potential advantages:</p> <p style="padding-left: 40px;">They usually call for smaller numbers of subjects than parallel group studies, as the subjects serve as their own controls and hence reduce variability of differences related to diurnal variations and inter-subject variability;</p> <p><u>Comment</u> Cross-over studies do not reduce between subject variability, but they do minimize the contribution of this factor. Thus suggest wording be changed to "...cross-over studies minimize the contributions of between subject variability."</p> | <p><i>Suggested wording:</i></p> <p>"They usually call for smaller numbers of subjects than parallel group studies, as the subjects serve as their own controls, cross-over studies minimize the contributions of between subject variability."</p> |
| <p>Line 288</p> | <p><u>Comment</u> While women have a higher incidence of drug-associated torsade de pointes, there is not data suggesting a gender-based difference in drug-induced QT prolongation</p> | <p>Suggest adding the following sentence after the section ending: "If multiple doses or treatment groups are to be compared" the following sentence</p> <p>"Given the lack of data that men and women have different changes in QT/QTc when exposed to a test drug, it is adequate for a definitive QT study to be performed solely in males."</p> |

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| 292-293 | <p>"This can be accomplished in several ways, including the collection of multiple ECGs at baseline and during the study."</p> <p>Comment Baseline should be defined as "prior to initiation of the test substance."</p> | <p>Proposed Change "This can be accomplished in several ways, including the collection of multiple ECGs at baseline, prior to initiation of the test substance, and during the study."</p> |
| Lines 297-298 | <p>"In the absence of QT/QTc interval prolongation in the 'thorough QT/QTc study' (see section 2.1.2), the collection of baseline and periodic on-therapy ECGs in accordance with the current investigational practices in each therapeutic field is, in general, considered appropriate"</p> <p>Comment The thorough QT study is the definitive controlled scientific investigation of QT changes and is specifically designed and powered to find very small QT prolonging effects, if they exist, Thus a negative thorough QT study obviates the need to report QT and other ECG intervals on subsequent EKGs collected for diagnostic safety purposes. These latter ECG's are collected in a far less controlled manner than those in the thorough QT study,</p> | <p>Suggest replace : " In the absence of QT/QTc interval prolongation in the 'thorough QT/QTc study' (see section 2.1.2), the collection of baseline and periodic on-therapy ECGs in accordance with the current investigational practices in each therapeutic field is, in general, considered appropriate"</p> <p>With: "Beyond a clearly negative Thorough QT study (see section 2.1.2), there is no formal need to continue reporting QT or other ECG measurements and ECGs may be confined to diagnostic purposes according to standard procedures for safety."</p> |
| Line 305 | <p>"...through administration of high doses or use of metabolic inhibitors (if applicable). "</p> <p>Comment Inhibition of transporters can also result in increases in Cmax</p> | <p>Change to: "...through administration of high doses or use of inhibitors of metabolism or transporters (if applicable) "</p> |

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| <p>Section 2.1</p> | <p>2.1 Design Considerations <i>2.1.1 Subject Enrollment, Safety Monitoring, and Discontinuation Criteria.....</i> <i>2.1.2 'Thorough QT/QTc Study': Dose-Effect and Time Course Relationships</i></p> <p><u>Comment</u> The titles in this section are unclear. It is difficult to understand if the text is referring to a 'thorough QT/QTc study' or if it is referring to clinical trials in general. It is suggested that the section should be restructured</p> | <p>It is suggested that the section should be restructured e.g.</p> <p>2.1.1 Clinical trials excluding 'The thorough QT/QTc Study' 2.1.2 'The thorough QT/QTc study'</p> |
| <p>Line 350-352</p> | <p>"The degree of inter- and intra-reader variability should be established by having the assessors reread a subset of the data (both normal and abnormal) under blinded conditions.</p> <p><u>Comment</u> Since this sentence is for sponsors to know the laboratory characteristics, it should be deleted- having assessors reread ECGs in a blinded fashion adds complexity to the study. How will these estimates of variability be used in the analysis of the results? It is the sponsor's responsibility to make sure that the core laboratory has high quality and a low variability and this will be evident from the confidence intervals of the data.</p> | <p>Delete entire sentence, text will then read.</p> <p>"Readers of ECGs should be blinded to time, treatment and subject identifier, and one reader should read all the ECG recordings from a given subject. Criteria for ECG diagnoses and for identification of adverse events should be pre-defined by the sponsor."</p> |

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| Line 364-365 | <p>"While the most appropriate lead(s) and methodology to measure the QT interval have not been established, lead II is often used."</p> <p>Comment Leads V2 and V5 should be added to "While the most appropriate lead(s) and methodology to measure the QT interval have not been established, lead II is often used" as these leads are also commonly used, or remove the comment referring to lead II.</p> | <p>Proposed change "While the most appropriate lead(s) and methodology to measure the QT interval have not been established, leads V2, V5, and II are often used."</p> <p>Or "While the most appropriate lead(s) and methodology to measure the QT interval have not been established, a consistent approach should be used for a given trial"</p> |
| Line 406-409 | <p>"In early trials evaluating the effects of a new drug on the QT/QTc interval in healthy volunteers, designed to detect relatively small effects (e.g., 5 ms), it is important to apply the most accurate correction available (e.g., methods using individually-derived relationships between RR and QT intervals)."</p> <p>Comment Add extra text to end of sentence <i>"though no correction methodology is perfect and isolated changes in heart rate can effect the QTc determination"</i></p> | <p>Proposed change "In early trials evaluating the effects of a new drug on the QT/QTc interval in healthy volunteers, designed to detect relatively small effects (e.g., 5 ms), it is important to apply the most accurate correction available (e.g., methods using individually-derived relationships between RR and QT intervals), though no correction methodology is perfect and isolated changes in heart rate can effect the QTc determination."</p> |
| Line 501-504 | <p>Categorical changes - the categorical changes should be time matched placebo subtracted, to account for diurnal and other physiologic alterations, consistent with the central tendency analysis.</p> | <p><i>Add after Line 504:</i> "The categorical changes should be time matched placebo subtracted, to account for diurnal and other physiologic alterations, using the same methodology as employed for the central tendency analysis"</p> |

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| Line 512- 516 | <i>Section 3.2.3 QT/QTc Interval Dispersion</i> <u>Comment</u> Since QT dispersion has not been shown to be predictive of TdP, removing these lines should be considered. | Proposed change Consider removing lines 512-516 pertaining to QT dispersion |
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