



Bristol-Myers Squibb Company

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December 8, 2004

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

Re: Docket No. 2004D-0377; International Conference on Harmonization: Draft Guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs; Availability; 69 Federal Register 55163 (September 13, 2004)

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products, is pleased to have the opportunity to offer comments on the Draft ICH E14 Guidance *The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*. Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. For this reason, we are interested in commenting on the Draft Guidance. Our comments are set forth below.

Summary of BMS Comments on Proposal

We commend the ICH for drafting guidance to provide recommendations to sponsors concerning clinical studies to assess the potential of a new drug to cause cardiac arrhythmias, focusing on the assessment of changes in the QT/QTc interval on the electrocardiogram as a predictor of risk. We recognize the intent to encourage the assessment of drug effects on the QT/QTc interval as a standard part of drug development and to encourage early discussion of this assessment with the FDA. There are, however, aspects of the proposed guidance that require clarification or appear contrary to the ICH's stated objectives. These are cited below.

Line 137. "The recommendations contained in this document are generally applicable to new drugs having systemic bioavailability."

Recommendation: It would be helpful to have greater clarity on the drugs to which these recommendations are applicable. Should biologics or radiopharmaceuticals routinely have a 'thorough QT study' as proposed? Should oncology drugs and other drugs for life-threatening diseases be required to have similar studies?

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Lines 212-213. “If not precluded by considerations of safety or tolerability due to adverse effects, the drug should be tested at substantial multiples of the anticipated maximum therapeutic exposure.”

Recommendation: The exposure that meets the criteria of “substantial multiples” of the anticipated maximum therapeutic exposure should be more clearly defined for drugs which do not have safety or tolerability limitations.

Lines 251-254. “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. Absence of a positive control should be justified and alternative methods to establish assay sensitivity provided.”

Recommendation: For compounds that have to be studied in patients (e.g. oncology, neuroleptics), it may be preferable that the active control arm be optional. Perhaps the use of a comparator in the same class could be used as either a positive or negative control. Such an approach may be preferable to using moxifloxacin, for example. The text should allow for circumstances where there may not be an alternative method to establish assay sensitivity.

Lines 256-260. “However, drugs that prolong the mean QT/QTc interval by around 5 ms or less do not appear to cause TdP. On that basis, the positive control (whether pharmacological or non pharmacological) should be well-characterized and consistently produce an effect corresponding to the largest change in the QT/QTc interval that is currently viewed as clinically not important to detect (a mean change of around 5 ms or less)”

Recommendation: The proposed 5 ms mean change in the QT/QTc interval is an estimate of a low risk group based on limited data. The choice may be too conservative. Despite current methods, the measurement of QT interval can still be imprecise. The currently recommended threshold may result in an inappropriate risk classification for some drugs. Pending definitive data which would allow a more precise estimate of risk, consideration should be given for a more liberal threshold. One consideration would be to increase the proposed statistical boundary such that upper bound of the one-sided 95% confidence interval would exclude an effect of > 10 ms rather than > 8 ms.

Lines 262-266. “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. This upper bound was chosen to reflect the uncertainty related to the variability of repeated measurements. As with other data, the presence of outliers (see section 3.2.2) should also be explored.”

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Recommendation: We suggest rewriting and taking the following into consideration: "A negative thorough QT/QTc study is one in which the study drug is found to be non-inferior to placebo, given that the active control or alternative method used to assess study sensitivity has shown an effect consistent with previous clinical trials. Non-inferiority and thus no clinically relevant effect on QT/QTc prolongation can be concluded if all the upper limits of the one-sided 95% confidence intervals for the time-matched mean differences between study drug and placebo (baseline-subtracted) at every time point over the dosing interval when ECGs are recorded are less than 8 msec. Analyses at every nominal time post dose are to rule out potential effects on QT/QTc due to unknown pharmacokinetic or physiological factors. The testing procedure described above controls the overall type I error rate (chance of falsely concluding lack of QT/QTc prolongation) below 5%, but (with multiple ECG timepoints) may be extremely conservative and would adversely affect the power of the study. Therefore, careful consideration needs to be given to limiting the number of time-points that need to be tested. Also alternate and potentially more powerful procedures need to be investigated."

In selecting the upper bound of the one-sided 95% confidence interval, it is also important to consider its effect on sample size. In trials where a parallel design is necessary, adequate power to exclude the proposed treatment effect will require a large study which may not be feasible to conduct.

Lines 302-305. "One objective of this evaluation should be to fully characterize the dose-, concentration-, and time- relationships of the drug on the QT/QTc interval in the target patient population(s) at therapeutic and supratherapeutic serum concentrations. The latter can be achieved in two ways: through administration of high doses or use of metabolic inhibitors (if applicable)."

Recommendation: It would be useful for the document to provide some guidance on the expected supratherapeutic concentrations which should be tested in the target patient population if the 'thorough QT/QTc study' is positive.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA/ICH give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



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