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Comments on ICH E14 draft guidance (June 10, 2004)

The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential For Non-Antiarrhythmic Drugs

General comments

Inclusion of Positive Control

We recognize that the inclusion of the positive control adds some risk to the subjects. This requires that the studies be conducted at sites where the safety can be closely monitored and quick action can be taken, in case of TdP or other related adverse events. In some situations, due to the type of subjects and/or disease conditions, it may not be feasible to include a positive control.

It is not clear from the guidance whether the positive control has to be significantly different from placebo at just one time point or for a pre-specified time-period, based on the pharmacokinetics and pharmacology of the positive control. It is also not clear how the study would be interpreted if the positive control was found to be significantly different from placebo, but did not have an effect close to the suggested 5 ms.

Thorough QT/QTc Study

If a detailed preclinical CV program and the clinical program indicate no QT/Qc issues, then a thorough QT/QTc study may not be needed for proper evaluation of the cardiovascular safety of the drug.

The timing of the 'thorough QT/QTc study' is stated as 'early in clinical development'. However in many situations, it may be most appropriate to defer the timing of such a study until formal dose ranging studies have been performed, and/or until the target C_{max} (and its intrinsic variability) in the target population is known. A wide flexibility in the timing of the thorough QT/QTc study is crucial.

Even though a negative thorough QT/QTc study is defined using the 'largest time-matched mean difference between the drug and placebo (baseline –corrected) for the QTc interval' (Lines 262-263), it is not clear that any study that is not negative is automatically positive. Can there be a situation where the study is inconclusive? The guidance document should be made consistent in the use of wording as “negative”, “positive”, “absence”, “substantial”, etc.

Requiring that the largest time-matched mean difference between the drug and placebo (baseline –corrected) QTc interval is around 5 ms or less with one-sided 95% confidence interval that excludes an effect > 8ms (lines 262-265), implies that the one-sided 95% confidence interval should exclude an effect of > 8ms for every time point of measurement. Although this may be scientifically the most correct approach, it leads to

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multiplicity issues and would inflate sample size to impractical levels. If ECG measurements are taken at 10 post dose time points, and 9 of the one-sided 95% confidence intervals exclude 8 ms while the 10th confidence interval has an upper limit of 9ms, do we conclude that the drug has an effect on QT/QTc prolongation? To minimize the multiplicity issues arising from having to establish non-inferiority at each time point, sponsors may choose to take measurements only at a minimum number of time points. With this requirement, a sponsor who chooses to measure ECG at several time points is penalized for being more thorough.

There is also an apparent discrepancy between the requirement of detecting a 5ms difference from placebo for the positive control and non-inferiority approach for the study drug. Shouldn't the comparison of study drug or positive control to placebo follow the same principle?

Although the spirit of the document is to provide guidelines for identifying decision points for the sponsor to consider in drafting a "thorough QT" protocol, in some instances more definitive direction is warranted.

Non-clinical Evaluation

One could argue for some standardization of criteria under which a thorough QT study is indicated for regions in which preclinical data do not exclude an effect of the drug on QT interval. Given that the goal of this ICH document is to introduce a degree of uniformity on the regulatory review process, current trends to simultaneous global drug development programs, and the need for sponsors and regulatory agencies to consider the complete body of available evidence when calibrating risk – benefit decisions, it might be timely to take this opportunity to suggest actual preclinical data configurations that would suggest a need for further clinical evaluation (e.g., positive HERG channel assay, etc.). There has been a very steady growth in the sophistication and quality of the in vitro and preclinical in vivo models for identifying cardiovascular risk prior to initiating any studies in man. We would like the guidance to reflect this with a statement allowing flexibility in the timing of the formal thorough Clinical cardiovascular study based on the integrated risk assessment from a detailed preclinical CV program.

Special considerations

Several of the recommendations in this guidance are ill-suited to oncology drug development (although some exceptions are mentioned in passing) specifically: (a) use of healthy subjects in tests of cytotoxic compounds; (b) the relatively high proportion of open label studies in oncology development programs; (c) the desire to explore multiples of the therapeutic dose for agents with narrow therapeutic indices

Similar comments apply when the drug at very high doses is not safe for administration to healthy subjects, since supra-therapeutic levels are targeted for the thorough QT/QTc study.

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Specific comments

Lines 111-113: “Most drugs that have caused TdP clearly increase both the absolute QT and the QTc (hereafter called QT/QTc).” Does this statement imply that drugs that increase QTc, but actually decrease QT are not problematic? In many cases, we see that due to an effect on heart rate, the QTc increases even though the QT decreases.

Lines 119-120: The document states that relevant clinical and non-clinical data will be used to make an integrated assessment of proarrhythmic risk. However, the document contains no reference to any nonclinical safety guidance to help elucidate what would constitute relevant non-clinical data.

Line 127: cardiovascular AEs – The AE classifications are to follow MedRA classifications.

Lines 137-138: “... new drugs having systemic bioavailability” should be clarified further, in particular whether this refers to any parent compound and/or metabolite detectable in the systemic circulation. We suggest the wording be changed to “...*potentially clinically relevant systemic bioavailability of parent drug and or metabolite...*”

Lines 142: The phrase “... significantly higher Cmax or AUC values” should be clarified, in particular whether this relates to a statistically significant higher Cmax or AUC (if so, at what level of significance) or a clinically significant higher Cmax or AUC. If clinical significance is of interest here, the guidance should clearly define what is considered as clinical significance. The guidance might also be applicable if there is a clinically significant increase in the rate-of-rise of plasma concentrations. We suggest the wording be adapted accordingly.

Lines 170-171: The meaning of the phrase “non-clinical data of concern” should be clarified and be made more specific (See comment to Lines 119-120).

Lines 170-175: The meaning of the word “positive” should be clarified and be made more specific. The meaning of “positive” should be aligned with the meaning of “negative”, and it should be clarified whether a ‘non-negative’ study automatically is classified as a “positive” or whether the outcome might instead be “inconclusive”.

Line 171: If the thorough QT/QTc study were negative, are regular ECGs (e.g. non-digital, no central lab, etc.) at screening and termination sufficient for future studies? This should be clearly stated by adding a sentence as follows: “If the thorough QT/QTc study is negative, no additional evaluation will be required other than what is current practice.”

Line 183-184: Does ‘until the effects of drugs on the QT/QTc interval have been characterized’ relate to conclusions from a thorough QT/QTc study or can a conclusion

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be based on cumulative evidence from Phase 1 studies done prior to the thorough QT/QTc study?

Lines 186-187: The phrase “marked baseline prolongation” is not specific enough. Also, the same limit may not apply to both genders. We suggest re-wording as, “A QT/QTc interval at baseline repeatedly exceeding the upper limit of normal (e.g. QTc > 450 ms in males or >470 ms in females)”. Also, please specify the correction method since the same limits may not apply to all correction methods.

Lines 186-187: Please clarify the discrepancy between the definitions of “marked QT/QTc prolongation” in lines 186-187 (>450 ms) with the definition in line 305 (>500 ms).

Lines 186-187: If subjects with ‘marked baseline prolongation’ are excluded from a study and yet, an expanded ECG safety evaluation is to be carried out in such a study, there is a tendency of observing increased values relative to the baseline, just due to regression towards the mean (see Lines 457-459). Hence, care should be taken to interpret and utilize such data, especially in parallel group design studies. A crossover design should be the recommended design for thorough QT/QTc study.

Lines 196-197: We recommend this statement be deleted. It is usually left to the investigator’s discretion to determine the scope of work-up.

Lines 206: This section does not address dose-effect relationships (except for a brief mention on line 209), even though it is included in the title to the section. Additionally, Section 3 on the analysis of ECG data does not include any discussion of dose-effect or PK/PD relationships.

Lines 208-214: The document suggests for a thorough QT/QTc study “... exploration of concentrations that are higher than those achieved following the anticipated therapeutic doses” and “... the drug should be tested at substantial multiples of the anticipated maximum therapeutic exposure”. How much higher should the concentrations go (2-fold, 4-fold, x-fold of maximum therapeutic exposure)? Please specify what “substantial multiples” mean. We suggest replacing the wording “substantial multiples” with “levels that are substantially higher”, and define what is meant by substantially higher.

Line 239-240: “...drugs with short half lives and no metabolite...”. This phrase could be misinterpreted in its current form. A more appropriate way for this statement would be “For drugs with short half-lives and/or without active metabolites....”

Lines 248: The phrase “*where possible*” should be added to ‘appropriate blinding’. There are situations where blinding is not possible (e.g. easily detectable pharmacological effect), and where placebo might not be ethically acceptable (e.g. proven efficacious drug for serious/lethal disease that can only be investigated in the target patient population).

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Lines 248: If blinding has to be properly carried out, the ECG and PK sample collection times should be based on ADME profiles of both the study drug and the positive control. This may increase the number of measurements when the T_{max} and the time of maximum effect differ substantially between the study drug and positive control. In a crossover design, this may lead to impractical numbers of ECGs and blood samples. A digital Holter ECG with continuous recording will be a better option in this situation.

Lines 251-254: It would help to add recommendations for agent/dose for positive control (e.g. moxifloxacin 400 mg).

Line 255: The phrase ‘mean QT/QTc’ is used here and in several places. It is not clear how this would be derived. Does this refer to mean QT/QTc at each time point or is it ‘time-averaged’ mean QT/QTc? Instead of using the phrase ‘mean QT/QTc’ universally throughout the documents, a change in terminology is needed to make the distinction of which mean is being referenced.

Lines 256: The “prolongation around 5ms or less” remains unclear. Based on the literature for amoxafloxin, we recommend that this be a mean placebo-corrected change from baseline.

Lines 256-260: This is a tall order. What if, for example, the control results in 8 ms in a particular trial? Does that mean that assay sensitivity at the level of the highest change that is not clinically important has not been demonstrated? Does this mean that the trial failed and the results from the trial are invalid, even if the study drug is found to be similar to placebo? Please clarify.

Line 260: The phrase ‘mean change in QT/QTc’ is used throughout the document. It is unclear how this would be calculated, especially in the thorough QT/QTc study. Does the term ‘change’ relate to change from baseline or from placebo (placebo-corrected change), or the difference between drug and placebo in the change from baseline? Is the mean to be calculated (i) over all time points of measurement for each subject, (ii) over all subjects at each time point or (iii) over all time points for each subject and then over all subjects? The guidance should clearly state how to calculate the various endpoints (or derived variables) mentioned in the guidance.

Lines 262-265: The 5ms for the mean and 8 ms for the one-sided 95% confidence intervals criteria stated may not be appropriate for all QTc correction methods for QTc. Is it enough if the 8ms criterion holds just for the primary correction method chosen?

Lines 262-265: The 5ms for the mean and 8 ms for the one-sided 95% confidence intervals criteria stated may not hold for all time points of measurements, even for a “safe” drug. In addition, applying the criterion to each time point leads to multiplicity issues. Even if the true effect is ≤ 5 ms, when ECG measurements are taken at several time points, the probability that the upper limit of the one-sided 95% confidence intervals will fall above 8 ms for at least one time point, can be high. See next comment on sample size.

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Lines 262-265: The condition that the one-sided 95% confidence interval for the placebo-subtracted difference exclude an effect of 8 ms translates statistically into a hypothesis testing for non-inferiority of the drug to placebo with a non-inferiority criterion of 8 ms. The phrase ‘largest’ implies that the one-sided 95% CI should exclude 8 ms for every time point. Implicitly this means that the thorough QT/QTc study has to be adequately powered for non-inferiority testing at every time point. Even with a crossover design, the sample size needed to properly power the study may not be practical. The following table gives the sample size needed for crossover (2-way) and parallel group (2-arm) studies for concluding non-inferiority of study drug to placebo at a single time point, using the 8 ms criterion for the change from baseline in QTc (Δ QTC) when the true difference between study drug and placebo = 0, 3 or 5 ms (the inter-subject and intra-subject SD for Δ QTC were assumed to be 14 ms and 10 ms respectively for this calculation, which is a reasonable assumption. The scenario does not take into account the additional subjects that may be needed for including the positive control into the study.) Thus, when the true difference equals a 3 ms, which is considered ‘safe’ according to the guidance, the sample size needed for concluding non-inferiority with 80% power, at a single time point, will be 56 and 196 subjects respectively for crossover and parallel group designs. When the number of time points increase, the sample size will increase considerably from the numbers given in this table.

Sample Size for concluding non-inferiority <i>at one time point</i>				
Non-inferiority criterion = 8 ms				
Assumption: SD(Δ QTC) = 14 ms; Intra-subject correlation = 0.5; Intra-subject SD(Δ QTC) = 10 ms				
True Difference in mean (Δ QTC) between study drug and placebo	Crossover Design (2-way) <i>Total N</i> (Intra-sub) SD = 10 ms		Parallel Group (2-arm) <i>Total N</i> SD = 14 ms	
	80% Power	90% Power	80% Power	90% Power
0 ms	22	30	78	108
3 ms	52	70	196	270
5 ms	140	192	540	748

Lines 262-265: To minimize the multiplicity issues arising from having to establish non-inferiority at each time point, sponsors may choose to take measurements only at a minimum number of time points. With this requirement, a sponsor who chooses to measure ECG at several time points is penalized for being more thorough.

Line 265, Footnote #2 in the bottom of page 7: The 5 ms, 8 ms criteria presumably are from five "thorough QT/QTc studies", but the references are not readily available. It would be important to provide detailed data for these studies, so that their validity can be evaluated.

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Lines 269-271: We suggest that this recommendation be removed from the guidance because to include an equipotent therapeutic dose for the positive control may lead to unacceptable safety risks if the new investigational drug has a much wider separation between efficacy and safety/tolerability than the reference positive control.

Lines 291-293: "essential to address intrinsic variability..." can be accomplished several ways including collection of multiple ECGs at baseline and during the study. We suggest including in the guidance for the sponsor some of the other ("several ways") means of addressing intrinsic variability.

Line 297: Please clarify whether "absence of QT/QTc interval prolongation" is identical to the definition of "negative" in lines 262-265.

Line 304: If it is decided that there any guidance on what is acceptable further clarification on what qualifies 'supra-therapeutic serum concentrations' will need to be provided in the guidance. Please specify what supra-therapeutic means (2-fold, 4-fold, x-fold higher). Also see comment for lines 208-214.

Line 309: Please clarify the discrepancy between the definitions of "marked QT/QTc prolongation" in line 305 (>500 ms) and lines 182-183 (>450 ms).

Lines 314 - 322: "If the "thorough QT/QTc" is positive, analyses of ECG and adverse event data from certain sub-groups are of particular interest. These lines are confusing regarding what the sponsor has to do. Does this mean that, if the sponsor has any of these types of patients enrolled in other protocols receiving the same experimental drug being evaluated in the QT study, the ECGs of these types of patients from other studies should be specifically analyzed? Or does it mean that these subgroup analyses should be done for the thorough QT/QTc study? If the latter is the case, other than female patients, the other patient types would have been excluded from the QT study (patients with hypokalemia, CHF, renal or hepatic failure and patients <16 and > 65 years of age) and it would not be possible to carry out these subgroup analyses. These lines need some clarification.

Line 315: An additional subgroup of interest for clinical and post marketing studies would be individuals who have been exposed to drugs that are known to prolong QT concomitantly with the experimental drug.

Line 321: We are not sure there are sufficient data to warrant a mandatory subgroup analysis for female patients and not male patients. It may be more appropriate to say that subgroup analysis should be conducted using age, gender, etc. as classification variables. The way it is worded now, it implies that female patients would have more QT prolongation problems and would be of more interest than the males.

Line 326: The guidance should include some specifics on what additional investigations are being proposed.

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Lines 348-350: While it is appropriate for one blinded reader to read all ECG recordings from a given subject, it may not be sufficient for a parallel group design. For a parallel group design, care should be taken to make sure a blinded reader reads not only all ECGs from a subject, but also the same percentage of subjects from each treatment group.

Lines 350-352: Should a subset of ECG have to be reread for every study? Or just for the thorough QT/QTc study? Or, is it just once to qualify the reader and central lab?

Lines 406 - 409: "it is important to apply the most accurate correction available" Does this make it mandatory or optional for the sponsor to use methods using individually derived RR and QT relationships?

Line 407: Requiring that the studies be designed to detect a 5 ms difference contradicts the requirement of 95% confidence interval to exclude 8 ms (Line 258-261).

Line 413: The optimal correction approach is not the subject of controversy: methods using individual subject's relationships between RR and QT intervals are clearly most accurate, as specified in lines 408-409. The guidance document should be consistent in this matter, and clarify that controversy only exists in cases where methods using individually derived relationships between RR and QT intervals are not feasible due to the absence of sufficient off-treatment data for individual subjects.

Lines 416-419: "individual patient correction" should not be considered a novel correction approach. These methods are well established as indicated in lines 408-409. See also comment on line 413.

Line 416: If the best correction approach is a subject of controversy, pre-specifying a "primary correction method" does not seem warranted.

Lines 424-439: All correction formulae should include the units for QT, RR and QTc.

Lines 430-432: Bazett's formula is known to over correct/under correct for heart rates that are either considerably different from 60 bpm (already included in lines 430-432) or when there is a considerable increase or decrease in heart rate (not yet included in lines 430-432). The wording should be changed to reflect both situations.

Lines 434-439: This section needs re-wording to give the formula for QTc explicitly. The equation $QT = a + b RR$ represent the regression model that will be fitted to the baseline and placebo ECG data. The formula for correction will be $QTc = QT + \hat{b} (1 - RR)$, where \hat{b} is the estimated slope from the regression line. This needs to be explained clearly. Currently, only an example (Framingham's correction) is given and not the general formula. Also include the units for QTc, QT and RR.

Lines 434-441: Linear regression technique has been suggested for study-specific correction while linear or nonlinear regression is suggested for large pooled database. It is

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not clear why nonlinear regression can be used for large database only and not for study-specific correction.

Lines 434-439: It is very important that the “no-treatment group” from which the population-derived correction formula is derived, is representative for the “on-treatment group”. This is not mentioned. This also applies to the “positive control group”. Several aspects are important: (1) the population of subjects is a big issue for the placebo-group in a parallel design, or the placebo-treatment in a crossover. For the “thorough QT/QTc study” the control group should always be part of the trial, preferably one of the arms/treatments; and (2) the total number of ECGs/subject, the timing throughout the day, and the conditions of measurement (fasting etc.).

Line 446: It is unclear how to make sure that pre-therapy QT/QTc interval data is measured over a range of heart rates. Bias might be introduced if the pre-therapy conditions do not match the on-therapy conditions. It is preferable to match the ECG measurement conditions for pre-therapy, concurrent placebo and study drug. This can be done more effectively using digital Holter ECG than by 12-lead ECG, which is the recommended approach in this guidance.

Lines 447 - 448: "These approaches are considered most suitable for the ‘thorough QT/QTc’ study..." Does "most suitable" mean they are optional or mandatory? Please clarify.

Lines 455-457: The guidance document should mention another major source of apparent changes not related to drug therapy, namely circadian rhythms in RR, QT and QTc. This is the basis of the (correct) recommendation to compare time-matched on-treatment values with multiple baseline values (lines 263 and 473). The study design of the thorough QT/QTc study should address this source of variation.

Line 469: Although comparison of multiple baseline values with multiple, time-matched on-treatment values is generally appropriate, it does not solve the issue of regression to the mean nor does take full advantage of all information embedded in the data. At least as a supplementary analysis, the development of an integrated mixed-effect population PK/PD model should be encouraged. Such modeling approaches can include fundamental basic biological characteristics of the phenomenon such as circadian rhythms, independent and interdependent drug effects on QT and RR, (patho) physiological covariates, etc. We recommend you include a new paragraph to encourage sponsors, at least as supplementary analysis, to develop integrated mixed-effect population PK/PD models to describe the dose-concentration-effect relationship (if any). The following wording is suggested: *“Sponsors are encouraged to develop and report integrated mixed-effect population PK/PD models to describe the dose-concentration-effect relationship for drug effects on the QT/QTc interval, if any. For several trial design and outcome scenarios, and if appropriately justified, such modeling approach could be considered the primary analysis to show the absence or presence of a clinically relevant drug effect on QT/QTc at clinically relevant dose and exposure levels.”*

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Lines 472-476: Seems to imply time matched differences should be primary, while time-averaged can only be done "additionally". In some circumstances, time-averaged QT/QTc as a primary endpoint may be more appropriate. Looking at each time point leads to a multiplicity issue (see comments for Lines 262-265).

Line 472-474: What does "analyzed using the largest time-matched mean difference" actually mean? Do we first do descriptive stats per time point, then pick out the time point with the largest effect, and do inference (95 % CI and p-value) for this time point only? Is this really appropriate? We let also chance decide what time point we take. For example, what if, by chance, the largest effect occurs at a physiologically unlikely time point, for example 48h after the last dose?

Lines 495-499: The guidance document should recognize the gender difference in absolute QT/QTc values, and recommend (or at least allow) the a priori definition of different threshold values for males and females. Some explanation needs to be given on why the 470 ms limit for females specified in CPMP guidelines has been replaced by 480 ms for both genders. Whether the same limits apply to both QT and all QTC correction methods is also doubtful. This point should be clearly addressed. Also, please add units to the numbers.

Lines 508-516: If QT/QTc dispersion is not of much value as a measure of proarrhythmic risk, then this section can be deleted. The weight of efforts for getting this parameter estimated versus its usefulness may not be balanced.

Lines 518-524: Does this imply that the central reader always has to compare ECGs with the baseline ECG to evaluate changes? This would contradict lines 348-350 which requires the readers to be blinded. In order to keep the reader blinded and still assess the changes, a strict coding of morphologies would be needed. The guidance document should include specifically a definition of a minimum set of morphology elements that should be evaluated and reported. The accumulating standardized data possibly allows a future assessment on the predictive value of such morphology elements. We suggest the following descriptors for morphology:

1. For T-wave morphology: "normal" and abnormal ("flat", "negative", or "biphasic")
2. For U-wave morphology: "not present" or "present".

We suggest the following analysis for analysis of morphology:

1. T-wave: Frequency analysis for study drug, placebo, and active comparator. Display frequency of events with a change from a "normal" T-wave to "abnormal".
2. U-wave: Frequency analysis for study drug, placebo, and active comparator. Display frequency of events with a change from a "not present" U-wave to "present".

Line 545: "Dizziness" is listed as an adverse event potentially indicating a proarrhythmic effect. In clinical trials this is a very common event, also seen on placebo, and may

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indicate a direct effect on the central nervous system rather than indicating a proarrhythmic effect. Dizziness should be taken off this list.

Line 546: The inclusion of seizure as a possible sentinel event appears somewhat tenuous.

Lines 564-566: In analogue to this statement, because of the considerable fluctuation of QT/QTc in time, one can argue that non-normal on-therapy ECG measurements performed prior to or near the time of the adverse event cannot be regarded as proof of a possible role for QT/QTc interval prolongation.

Lines 598-599: Since the genotype-to-phenotype relationships have not been extensively characterized for the genes encoding cardiac ion channels, replace, "*are known to be linked*" with "*have been associated with*" to avoid implying a predictive value to these genes. Genotyping for these genes currently is very useful in generating hypothesis (upon observation of prolonged QT), but should not yet be viewed as predictive.

Line 601: Since rare polymorphisms have also been associated with prolonged QT, the word "*common*" is unnecessary and is best deleted. In some cases it may be deemed useful to examine the full panel of polymorphisms in these genes using high throughput methods or gene sequencing.

Lines 602-603: Since pharmacogenomic studies generally require a point of comparison (i.e. affected vs. non-affected), the sentence: "*When possible, and following informed consent, patients who experience marked prolongation of the QT/QTc or TdP while on drug therapy should be genotyped*" may be misleading by suggesting that only affected individuals be genotyped. Suggest replacing with, "*Where possible, DNA samples should be routinely collected in QT/QTc trials (from subjects consenting to genetic testing) to allow for the genotyping of candidate genes in the event of presentation of prolonged QT.*"

Lines 625-627: If a definitive clinical QT/QTc study is performed and is negative, that should be sufficient to support a marketing authorization, even in the absence of a full non-clinical program.

Lines 640-648: The thresholds (<5ms, >5 and < 20ms, and >20ms) presented in this paragraph need to be clarified: Are these placebo-corrected changes from baseline?

Lines 644 and 648: the proposed wording does not cover a change of 20 ms. It is suggested to change line 652 into: "...*interval by 20 ms or more have a...*"

Lines 644-648: If between 5 ms and 20 ms leads to inconclusive results, the 5 ms / 8 ms criterion appears to be too restrictive.

Lines 673-674: The description of the design and results of the trials investigating the effect on QT/QTc interval should include the data from both placebo and positive control

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in addition to the study drug, in order to evaluate the results properly. Describing that there was an 8 ms increase in QT/QTc for the study drug compared to placebo cannot be interpreted properly unless we know the corresponding increase for the positive control compared to placebo. The interpretation would be entirely different if the positive control had an increase of 4 ms or 12 ms.. This is especially crucial when the positive control is from the same pharmacological class.