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To the Division of Dockets Management:

Enclosed please find Novartis' comments to the **Draft Guidance on ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs** (Docket No. 2004D-0377).

Please contact me with any questions.

Sincerely,

Martin P Bedigian, M.D.  
Global Head, Cardiovascular Assessment Group

2004D-0377

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Step 1 Draft 2 (July 17, 2003) Draft 3 (November 12, 2003), Draft 4 (June 10, 2004)

**THE CLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION AND  
PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS**

**PRELIMINARY CONCEPT PAPER**

*For Discussion Purposes Only*

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78 **THE CLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION AND**  
79 **PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS**  
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81 **1.0 INTRODUCTION**

82  
83 **1.1 Background**  
84

85 An undesirable feature of some non-antiarrhythmic drugs is their ability to delay cardiac  
86 repolarization, an effect that can be measured as prolongation of the QT interval on the surface  
87 electrocardiogram (ECG). The QT interval represents the duration of ventricular depolarization  
88 and subsequent repolarization, beginning at the initiation of the QRS complex and ending where  
89 the T wave returns to isoelectric baseline. A delay in cardiac repolarization creates an  
90 electrophysiological environment that favors the development of cardiac arrhythmias, most clearly  
91 torsade de pointes, but possibly other ventricular arrhythmias as well. Torsade de pointes (TdP) is  
92 a polymorphic ventricular tachyarrhythmia that appears on the ECG as continuous twisting of the  
93 vector of the QRS complex around the isoelectric baseline. A feature of TdP is pronounced  
94 prolongation of the QT interval in the supraventricular beat preceding the arrhythmia. TdP can  
95 degenerate into ventricular fibrillation, leading to sudden death.  
96

97 While the degree of QT prolongation is recognized as an imperfect biomarker for proarrhythmic  
98 risk, there is a qualitative relationship between QT prolongation and the risk of TdP, especially for  
99 drugs that cause substantial prolongation of the QT/QTc interval.

100  
101 Because of its inverse relationship to heart rate, the QT interval is routinely transformed  
102 (normalized) by means of various formulae into a heart rate independent “corrected” value known  
103 as the QTc interval. The QTc interval is intended to represent the QT interval at a standardized  
104 heart rate of 60 bpm. For drugs that prolong the QT/QTc interval, the mean degree of  
105 prolongation has been roughly correlated with the observed risk of clinical proarrhythmic events.  
106 It is not clear, however, whether arrhythmia development is more closely related to an increase in  
107 the absolute QT interval or an increase in the relative (“corrected”) QT interval (QTc). Most  
108 drugs that have caused TdP clearly increase both the absolute QT and the QTc (hereafter called  
109 QT/QTc). The combination of QT/QTc interval prolongation and documented cases of TdP (fatal  
110 and non-fatal) associated with the use of a drug has resulted in regulatory actions, including  
111 withdrawal from the market, relegation to second-line status or denial of marketing authorization.  
112 Because prolongation of the QT/QTc interval is the ECG finding associated with the increased  
113 susceptibility to these arrhythmias, an adequate pre-marketing investigation of the safety of a new  
114 pharmaceutical agent should include rigorous characterization of its effects on the QT/QTc  
115 interval. The relevant non-clinical and clinical data will be used to make an integrated assessment  
116 of proarrhythmic risk for novel drug therapies.  
117

118 **1.2 Objectives**

119

120 This document provides recommendations to sponsors concerning the design, conduct, analysis,  
121 and interpretation of clinical studies to assess the potential of a drug to delay cardiac  
122 repolarization. This assessment should include testing the effects of new agents on the QT/QTc  
123 interval as well as the collection of cardiovascular adverse events. The investigational approach  
124 ~~used for a particular drug should be individualized, taking into consideration a drug's nonclinical~~  
125 ~~profile including its pharmacology and toxicology, clinical characteristics such as~~  
126 ~~pharmacokinetics, metabolism, pharmacodynamics and safety profile and its intended dosage and~~  
127 ~~indication, depending on the pharmacodynamic, pharmacokinetic, and safety characteristics of the~~  
128 ~~product, as well as on its proposed clinical use.~~

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130 The assessment of the effects of drugs on cardiac repolarization is the subject of active  
131 investigation. When additional data (non-clinical and clinical) are accumulated in the future, this  
132 document may be reevaluated and revised.

133

134 **1.3 Scope**

135

136 The recommendations contained in this document are generally applicable to new drugs having  
137 systemic bioavailability. The focus is on agents being developed for uses other than the control of  
138 arrhythmias, as antiarrhythmic drugs can prolong the QT/QTc interval as a part of their  
139 mechanism of clinical efficacy. While this document is concerned primarily with the development  
140 of novel agents, the recommendations might also be applicable to approved drugs when a new  
141 dose or route of administration is being developed that results in significantly higher C<sub>max</sub> or AUC  
142 values. Additional ECG data might also be considered appropriate if a new indication or patient  
143 population were being pursued. The evaluation of the effect of a drug on the QT interval would  
144 also be considered important if the drug or members of its chemical or pharmacological class have  
145 been associated with QT/QTc interval prolongation, TdP, or sudden cardiac death during post-  
146 marketing surveillance.

147

148 **2.0 CLINICAL TRIALS**

149

150 **2.1 Design Considerations**

151

152 In general, drugs should receive an electrocardiographic evaluation, ~~beginning early in clinical~~  
153 ~~development, typically including a single trial dedicated with its primary objective of to evaluating~~  
154 ~~their a drug's effect effects on cardiac repolarization ('thorough QT/QTc study'). The ability of a~~  
155 ~~drug to prolong the QT/QTc interval is linked to pharmacologic effects that can be investigated in~~  
156 ~~non-clinical models as well as clinically. At present, whether non-clinical testing can exclude a~~  
157 ~~clinical risk for QT/QTc prolongation is controversial. Therefore, Conduct conduct of the~~  
158 ~~'thorough QT/QTc study', as described in section 2.1.2, would be needed in almost all cases for~~  
159 ~~regions where non-clinical data are not considered able to preclude risk of QT/QTc prolongation.~~  
160 For regions where non-clinical data are considered informative enough about the risk of QT/QTc  
161 prolongation in humans, the recommendations in this guidance for the clinical evaluation of  
162 QT/QTc could be modified. Additional factors that could influence the need for such a study  
163 include duration of treatment, metabolic profile, pharmacodynamic duration of action, and  
164 previous experience with other members of the same chemical or pharmacological class.

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166 As discussed below, the results of the 'thorough QT/QTc study' will influence the amount of  
167 information collected in later stages of development:

- 169 • A negative 'thorough QT/QTc study', even in the presence of non-clinical data of  
170 concern, will almost always allow the collection of ~~on-therapy~~ ECGs in later stage  
171 development in accordance with ~~the current practices~~ practice in the respective ~~each~~  
172 ~~therapeutic area~~ and with consideration of the need to monitor other cardiovascular  
173 safety parameters ~~to constitute sufficient evaluation during subsequent stages of drug~~  
174 ~~development~~ (see section 2.1.3);
- 175 • A positive 'thorough QT/QTc study' will almost always call for an expanded ECG  
176 ~~safety evaluation during later stages of drug development~~ (see section 2.1.3).

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#### 2.1.1 Subject Enrollment, Safety Monitoring, and Discontinuation Criteria

180 Subject enrollment, discontinuation criteria and safety monitoring for a given trial would be  
181 influenced by the clinical and non-clinical information available on the effects of the drug on  
182 cardiac repolarization.

184 For drugs which have preclinical data indicating a possible proarrhythmic potential ~~Regarding~~  
185 ~~subject enrollment, until the effects of the drug on the QT/QTc interval have been characterized,~~  
186 the following exclusion criteria are suggested until the effects of the drug on the QT/QTc interval  
187 have been characterized:

- 189 • A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc  
190 interval >450);
- 191 • ~~A history of additional risk~~ Risk factors for TdP (e.g., heart failure, hypokalemia, history  
192 of or family history of Long QT Syndrome);
- 193 • The use of concomitant medications that prolong the QT/QTc interval;

195 ~~If supported by the QT/QTc interval safety data from the early studies, later clinical trials could~~  
196 ~~expand the eligibility criteria to include a broader spectrum of patients who are likely to receive~~  
197 ~~the drug once approved.~~ [Comment: a positive QT study does not necessarily preclude expanded

198 phase III patient population criteria, particularly for life threatening indications such as cancer,  
199 transplantation, sepsis and shock.]

200

201 Regarding safety monitoring, the procedures to follow if a patient experiences an adverse event  
202 suggestive of TdP should be specified in the clinical trial protocol.

203

204 Discontinuation of a subject from a clinical trial should be considered if there is a marked  
205 prolongation of the QT/QTc interval during treatment with the study drug, especially if the  
206 measurement is obtained from more than one ECG. While increases in QT/QTc to >500 ms or of  
207 >60 ms over baseline are commonly used as thresholds for potential discontinuation, the exact  
208 criteria chosen for a given trial will depend on the risk-tolerance level considered appropriate for  
209 the indication and patient group in question.

210

#### 211 *2.1.2 The 'Thorough QT/QTc Study': Dose-Effect and Time Course Relationships*

212

213 An adequate drug development programme should ensure that the dose-response and generally the  
214 concentration-response relationship for QT/QTc prolongation have been characterized, including  
215 exploration of concentrations that are higher than those achieved following the anticipated  
216 therapeutic doses. Data on the drug concentrations around the time of ECG assessment would aid  
217 this assessment. If not precluded by considerations of safety or tolerability due to adverse effects,  
218 the drug should be tested at substantial multiples of the anticipated maximum therapeutic  
219 exposure. Alternatively, if the concentrations of a drug can be increased by drug-drug or drug-  
220 food interactions involving metabolizing enzymes (e.g., CYP3A4, CYP2D6) or transporters (e.g.,  
221 P-glycoprotein), these studies can be performed under conditions of maximum inhibition or with  
222 drug doses having similar exposure as with maximum inhibition. This approach calls for a  
223 detailed understanding of the absorption, distribution, metabolism and excretion of the drug. In  
224 general, the duration of dosing or dosing regimen should be sufficient to characterize the effects of  
225 the drug and its active metabolites at relevant concentrations.

226

227 The 'thorough QT/QTc study' is intended to determine whether the drug has a threshold  
228 pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation. The study is  
229 typically carried out in young healthy volunteers (up to 45 years of age to exclude subjects with  
230 occult conditions which could increase their risk of having a drug induced arrhythmia during the  
231 trial) ~~(as opposed to individuals at increased risk of arrhythmias)~~ and is used to determine whether  
232 or not the effect of a drug on the QT/QTc interval in target patient populations need to be studied  
233 intensively during later stages of drug development. Although data are limited, it is expected that  
234 the results of the 'thorough QT/QTc study' would not be affected by ethnic factors.

235

236 The 'thorough QT/QTc study' would typically be conducted early in clinical development to  
237 provide ~~maximum~~ guidance for later trials, although the precise timing will depend on the  
238 specifics of the drug under development. It would usually not be the first study, as it is important  
239 to have basic clinical data for its design and conduct, including tolerability and pharmacokinetics.  
240 It would most often be conducted in healthy volunteers. Some drugs might not be suitable for  
241 study in healthy volunteers because of issues related to tolerability or toxicity (e.g., neuroleptic  
242 agents, chemotherapeutics).

243

244 The timing of the collection of ECGs and the study design (e.g., single or multiple dose, duration)  
245 of the 'thorough QT/QTc study' should be guided by the available information about the  
246 pharmacokinetic profile of the drug. For example, for ~~For~~ drugs with short half-lives and no  
247 metabolites, a single dose study might be sufficient. Studies should characterize the effect of a  
248 drug on the QT/QTc throughout the dosing interval. While the peak serum concentration does not  
249 always correspond to the peak effect on QT/QTc interval, care should be taken to perform ECG  
250 recordings at time points around the C<sub>max</sub>. Later timepoints in the dosing interval should also be  
251 well characterized as effects of metabolites or at maximum tissue concentration may occur beyond  
252 T<sub>max</sub>. As one intent of a positive control is to establish assay sensitivity, in multiple dose studies  
253 of new drugs, a positive control only needs to be used long enough to have its expected effect.  
254

255 The 'thorough QT/QTc study' should be adequate and well-controlled, with mechanisms to deal  
256 with potential bias, including use of randomization, appropriate blinding, and concurrent placebo  
257 control group. As this study has a critical role in determining the intensity of data collection  
258 during later stages of drug development, it is important to have a high degree of confidence in the  
259 ability of the study to detect differences of clinical significance. The confidence in the ability of  
260 the study to detect QT/QTc prolongation can be greatly enhanced by the use of a concurrent  
261 positive control group to establish assay sensitivity. Absence of a positive control should be  
262 justified and alternative methods to establish assay sensitivity provided. It is difficult to determine  
263 whether there is an effect on the mean QT/QTc interval that is so small as to be of no  
264 consequence. However, drugs that prolong the mean QT/QTc interval by around 5 ms or less do  
265 not appear to cause TdP. On that basis, the positive control (whether pharmacological or non-  
266 pharmacological) should be well-characterized and consistently produce an effect corresponding  
267 to the largest change in the QT/QTc interval that is currently viewed as clinically not important to  
268 detect (a mean change of around 5 ms or less)<sup>1</sup>. Positive controls with effects of approximately 5-  
269 10 ms should be used to minimize risks. If blinding of the positive control agent is difficult (eg,  
270 due to the lack of a matching placebo), a single blind approach is acceptable so long as the ECG  
271 analysis and interpretation are conducted in a blinded fashion.  
272

273 Based on similar considerations, a negative 'thorough QT/QTc study' is one where the largest  
274 ~~time-matched~~ [Comment: time matched is one method of calculation. The intent is to reduce the  
275 effects of diurnal variability. However, diurnal variability is of low frequency and of lesser  
276 magnitude than that due to heart rate and random variation. Other methods of calculation such as  
277 baseline averaged may be appropriate depending on the circumstances and may be the best point  
278 estimate of a subjects baseline. It is sufficient to state the values expected of the mean difference  
279 without requiring time matched as the only analysis of interest. Moreover, it is generally accepted  
280 that QT measurement is not stationary therefore it follows that QT measurements will not  
281 necessarily be of the same magnitude or variability at the same hour of the day between days]  
282 mean difference between the drug and placebo (baseline-subtracted) for the QTc interval is around  
283 5 ms or less, with a one-sided 95% confidence interval that excludes an effect >8.0 ms<sup>2</sup>. This  
284 upper bound was chosen to reflect the uncertainty related to the variability of repeated  
285 measurements. As with other data, the presence of outliers (see section 3.2.2) should also be  
286 explored.

<sup>1</sup> Comment is requested on the choice of the 5 ms as a threshold for clinical and regulatory concern.

<sup>2</sup> Comment is requested on the statistics here, including the 8 ms upper bound of the confidence interval. This interval is derived from an analysis of the variability observed for placebo data from five 'thorough QT/QTc studies'.

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If an investigational drug belongs to a chemical or pharmacological class that has been associated with QT/QTc prolongation, a positive control selected from other members of the same class is recommended to permit a comparison of effect sizes, preferably at equipotent therapeutic doses.

Crossover or parallel group study designs can be suitable for trials assessing the potential of a drug to cause QT/QTc interval prolongation especially for single dose trials using drugs with no likelihood of carryover effects. Crossover studies ~~at least~~ have ~~two~~ the potential ~~advantages~~ advantage of smaller sample size.

- ~~• 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;~~
- ~~• They might facilitate heart rate correction approaches based on individual subject data. [Comment: this is not necessarily true. The collection of triplicate baseline ECGs in a parallel study can provide sufficient data for individual correction factors.]~~

Parallel group studies might be preferred under certain circumstances:

- For drugs with long elimination half-lives for which lengthy time intervals would be required to achieve steady-state or complete washout;
- If carryover effects are prominent for other reasons, such as irreversible receptor binding or long-lived active metabolites;
- If multiple doses or treatment groups are to be compared.

A critical problem in the measurement of the QT/QTc interval is its intrinsic variability. This variability results from many factors, including activity level, postural changes, circadian patterns, and food ingestion. It is considered essential to address intrinsic variability in the conduct of the 'thorough QT/QTc study'. This can be accomplished in several ways, including the collection of multiple ECGs at baseline and during the study.

### 2.1.3 Clinical Trial Evaluation After the 'Thorough QT/QTc Study'

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.

If the 'thorough QT/QTc study' is positive, additional evaluation in subsequent clinical studies should be performed. 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).

Another objective of this evaluation should be to collect information on the adverse events that occur in the trials following the positive 'thorough QT/QTc study'. This would include patients who develop marked QT/QTc prolongation (e.g., >500 ms) or experience a serious ~~cardiovascular~~

333 adverse event that suggests an arrhythmia (e.g., TdP). Such patients should be evaluated closely  
334 for risk factors that might have contributed to this event (e.g., genotyping for Long QT  
335 Syndromes, see section 4.3).

336  
337 If the 'thorough QT/QTc study' is positive, analyses of the ECG and adverse event data from  
338 certain patient sub-groups are of particular interest, such as:

- 339
- 340 • Patients with electrolyte abnormalities (e.g., hypokalemia);
  - 341 • Patients with congestive heart failure;
  - 342 • Patients with impaired drug metabolizing capacity or clearance (e.g., renal or hepatic  
343 impairment, drug interactions);
  - 344 • ~~Female patients~~; [Comment: Most thorough QT studies include women. While females  
345 are at higher risk for TdP, there is no data to suggest that they are at higher risk for QT  
346 prolongation. Data thus far from thorough QT studies shows that female QT data does  
347 not differ significantly from male data.
  - 348 • Patients aged <16 and over 65 years.
- 349

350 Even if the 'thorough QT/QTc study' is negative, if other evidence of an effect in a patient  
351 population from subsequent studies (e.g., marked QT/QTc interval prolongation, TdP) were to  
352 emerge, then additional investigation would be needed.

353  
354 **2.2 Collection, Assessment and Submission of Electrocardiographic Data**  
355

356 The recommendations below are most relevant to the 'thorough QT/QTc study' and to any studies  
357 investigating a drug with a known effect on cardiac repolarization.

358  
359 *2.2.1 Collection of Standard 12-Lead Electrocardiograms (ECGs)*  
360

361 Until better ways are established to assess proarrhythmic risk during drug development, the  
362 measurement of the QT/QTc interval on the surface ECG is central to the detection of that risk.  
363 The clinical ECG database is typically derived from the collection of 12-lead surface ECGs,  
364 ~~although ambulatory ECG techniques show promise (see section 2.2.3).~~ [Comment: Continuous  
365 12 lead ambulatory ECG is now readily available with specifications identical to that of standard  
366 12 lead ECGs and has been utilized successfully in thorough QT trials.]

367  
368 *2.2.2 Assessment of Standard 12-Lead ECGs*  
369

370 Several methods for measuring ECG intervals have been used in clinical trials, and for a given  
371 trial, the sponsor should describe the accuracy and precision of QT/QTc interval measurements  
372 using the selected system. The method chosen will depend on the level of precision needed for a  
373 given trial. For example, the 'thorough QT/QTc study' would warrant particularly careful  
374 attention to interval measurement. At present, this would usually involve the measurement by  
375 trained analysts or a few skilled readers operating from a centralized ECG laboratory, although  
376 other methods (e.g., semi-automated ECG reading) can be acceptable when appropriately  
377 supported. Readers of ECGs should be blinded to time, treatment and subject identifier, and ~~one~~  
378 few readers should be employed to interpret ~~read all~~ the ECG recordings from a  
379 given ~~subject~~ trial. The degree of inter- and intra-reader variability should be established by  
380 having the assessors reread a subset of the data (both normal and abnormal) under blinded  
381 conditions. Criteria for ECG diagnoses and for identification of adverse events should be pre-  
382 defined by the sponsor. If well-characterized data validating the use of fully-automated  
383 technologies become available, the recommendations in the guidance for the measurement of ECG  
384 intervals could be modified. In the absence of a concern in the early clinical trial(s), automated  
385 ECG readings may have a role in the rapid assessment of ECGs for safety.

386  
387 The quality of the ECG database can depend on the use of modern equipment with the capacity for  
388 digital signal processing. Such equipment should be recently serviced and calibrated. Machine  
389 calibration records and performance data should be maintained on file. In the case of multicentre  
390 trials, training sessions are encouraged to ensure consistency of operator technique (e.g., skin  
391 preparation, lead placement, patient position) and data acquisition practices.

392  
393 While the most appropriate lead(s) and methodology to measure the QT interval have not been  
394 established, lead II is often used. A consistent approach should be used for a given trial.

395  
396 Morphological changes in the T-U complex might occur. Information should be provided on  
397 changes in T and U wave morphologies (see section 3.3). Discrete U waves should be excluded  
398 from the QT/QTc interval measurement

### 399 400 2.2.3 Ambulatory ECG Monitoring

401  
402 While ambulatory ECG monitoring has historically not been sufficiently validated to be  
403 considered as the primary assessment ECG for QT/QTc interval effects, newer systems that allow  
404 for the collection of all 12 ~~multiple~~ leads simultaneously, with technical specifications identical to  
405 standard 12 lead ECG devices ~~that more closely approximate a surface ECG have potential value~~  
406 ~~to collect interval data~~ have value in collecting interval data, especially in thorough QT studies.  
407 The use of ambulatory ECG monitors might additionally allow detection of extreme QT/QTc  
408 interval events that occur infrequently during the day and asymptomatic arrhythmias. Data on the  
409 QT/RR from ambulatory ECG monitoring can also prove useful in the calculation of  
410 individualized QT corrections. ~~However, as QT/QTc intervals measured by this methodology~~  
411 ~~might not correspond quantitatively to those from standard surface ECGs, data obtained from the~~  
412 ~~two methodologies might not be suitable for direct comparison, pooling, or interpretation using the~~  
413 ~~same thresholds of concern.~~

414

2.2.4 Submission of Interval and Waveform Data

415  
416  
417 Regional guidance should be sought for information on the submission of ECG interval data  
418 measurements and interpretations ~~overall assessments~~.

3.0 ANALYSIS OF ECG DATA FROM CLINICAL TRIALS

421  
422 Evaluation of the effects of a drug on the standard ECG intervals and waveforms is considered a  
423 fundamental component of the safety database of any new drug application.

424  
425 Regardless of the outcome of the ‘thorough QT/QTc study’, on treatment ECG abnormalities not  
426 noted at baseline ~~changes recorded as adverse events~~ should be pooled from all studies for  
427 analysis. ECG interval data from the ‘thorough QT/QTc study’ should only be pooled with  
428 subsequent trials of similar rigor with regard to ECG data collection and analysis, but should not  
429 be pooled with trials using less rigorous ECG collection. Standardization of ECG collection for  
430 similar studies within a clinical trial programme will facilitate pooled analyses.

3.1 QT Interval Correction Formulae

431  
432  
433  
434 As the QT interval has an inverse relationship to heart rate, the measured QT intervals are  
435 generally corrected for heart rate in order to determine whether they are prolonged relative to  
436 baseline. Various correction formulae have been suggested, of which Bazett’s and Fridericia’s  
437 corrections are the most widely used. In early trials evaluating the effects of a new drug on the  
438 QT/QTc interval in healthy volunteers, designed to detect relatively small effects (e.g., 5 ms), it is  
439 important to apply the most accurate correction available (e.g., methods using individually-derived  
440 relationships between RR and QT intervals). For later trials, where less ECG information is  
441 available, population-derived corrections, including standard correction formulae, can provide  
442 useful information.

443  
444 Because the best correction approach is a subject of controversy, uncorrected QT and RR interval  
445 data, heart rate data, as well as QT interval data corrected using Bazett’s and Fridericia’s  
446 corrections should be submitted in all applications, in addition to QT interval data corrected using  
447 any other formulae. The sponsor should pre-specify the primary correction method. A concurrent  
448 positive control group is strongly encouraged to support the use of newer correction approaches  
449 (e.g., individual subject correction) in order to demonstrate the ability of the correction method to  
450 allow detection of relevant effects on the QT/QTc interval.

3.1.1 Population-Derived Correction Formulae

451  
452  
453  
454 Examples of such corrections include the following:

455  
456 | 1) Bazett’s correction:  $QTc = QT/RR^{0.5}$

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457  
458 | 2) Fridericia’s correction:  $QTc = QT/RR^{0.33}$

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459  
460 Bazett's correction is frequently used in clinical practice and in the medical literature. In general,  
461 however, Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates  
462 below 60 bpm and hence is not an ideal correction. Fridericia's correction is more accurate than  
463 Bazett's correction in subjects with such altered heart rates.

464  
465 3) Corrections based on linear regression techniques  
466 Application of linear regression techniques to plots of QT/RR data for the placebo or baseline  
467 study population allows for the estimation of the slope (b), which can be used for standardizing the  
468 data from both the drug and control groups to a normalized heart rate of 60 beats per minute, using  
469 the equation  $QT = a + b(RR)$ . The Framingham correction [ $QT_c = QT + 0.154(1-RR)$ ] is one  
470 example of a correction derived by linear regression.

471  
472 4) Corrections using linear or non-linear regression modeling on pooled data from large databases  
473

### 474 3.1.2 Correction Formulae Derived from Within-Subject Data

475  
476 Corrections for heart rate using individual subject data have been developed, applying regression  
477 analysis techniques to individual pre-therapy QT and RR interval data over a range of heart rates,  
478 then applying this correction to on-treatment QT values. These approaches are considered most  
479 suitable for the 'thorough QT/QTc study' and early clinical studies, where it is possible to obtain  
480 many QT interval measurements for each study subject. As adaptation of the QT/QTc interval to  
481 changes in heart rate is not instantaneous, care should be taken to exclude ECG recordings  
482 collected during times of rapid heart rate changes due to this QT/RR hysteresis effect.

## 483 3.2 Analysis of QT/QTc Interval Data

484  
485 Although increases from baseline in the QT/QTc interval constitute signals of interest,  
486 interpretation of these differences is complicated by the potential for changes not related to drug  
487 therapy, including regression toward the mean and choice of extreme values. Regression toward  
488 the mean refers to the tendency of subjects with high baseline values to have lower values at later  
489 time points, while subjects with low baseline values tend to experience increases. The direction  
490 of regression depends on initial selection criteria (for example, if subjects with high baseline  
491 QT/QTc interval values are excluded from the trial, values recorded during treatment will tend to  
492 rise relative to baseline levels). The process of choosing the highest of multiple observed values  
493 will also almost invariably cause an apparent change from any single baseline value, a  
494 phenomenon found in both drug and placebo-treated groups.

495  
496 The QT/QTc interval data should be presented both as analyses of central tendency (e.g., means,  
497 medians) and categorical analyses. Both can provide relevant information on clinical risk  
498 assessment.

### 500 3.2.1 Analyses of Central Tendency

501  
502 The effect of an investigational drug on the QT/QTc interval is most commonly analyzed using the  
503 ~~largest time-matched~~ mean difference between the drug and placebo (baseline-subtracted) over the  
504

505 relevant times of the collection period (e.g., hourly, weekly, monthly). Additional approaches to  
506 the assessment of central tendency could include analysis of time-averaged QT/QTc intervals or  
507 analysis of changes occurring at the C<sub>max</sub> for each individual. Changes from baseline can be  
508 calculated using a time-averaged approach or potentially by exploring a time-matched approach  
509 taking into consideration a drug's pharmacokinetics, pharmacodynamics and considerations to  
510 reduce variability and effects of regression to the mean. Additional approaches to the assessment  
511 of central tendency should include the overall or mean effect over the dosing interval, the effect at  
512 peak plasma or tissue concentration, and the effect at peak pharmacodynamic activity.

### 513 3.2.2 Categorical Analyses

514 Categorical analyses of QT/QTc interval data are based on the number and percentage of patients  
515 meeting or exceeding some predefined upper limit value. Clinically noteworthy QT/QTc  
516 interval signals might be defined in terms of absolute QT/QTc intervals or changes from  
517 baseline. Absolute interval signals are QT/QTc interval readings in excess of some specified  
518 threshold value. Separate analyses should be provided for patients with normal and elevated  
519 baseline QT/QTc intervals. As with all QT/QTc interval analyses, categorical analyses are most  
520 informative when it is possible to compare the rate of supra-threshold readings in the treatment  
521 and control groups.

522 There is no consensus concerning the choice of upper limit values for absolute interval signals  
523 and change from baseline signals. While lower limits increase the false-positive rate, higher  
524 limits increase the risk of failing to detect a signal. In clinical trials, a prolongation of QTc > 500  
525 ms during therapy has been a threshold of particular concern. Multiple analyses using different  
526 signal values are a reasonable approach to this uncertainty, including:

- 527 • Absolute QTc interval prolongation:
  - 528 • QTc interval > 450
  - 529 • QTc interval > 480
  - 530 • QTc interval > 500

- 537 • Change from baseline in QTc interval:
- 538
- 539 • QTc interval increases from baseline  $\geq 30$
- 540 • QTc interval increases from baseline  $\geq 60$
- 541

### 542 ~~3.2.3 QT/QTc Interval Dispersion~~

543  
544 ~~QT/QTc interval dispersion, defined as the difference between the shortest and the longest~~  
545 ~~QT/QTc interval measured on the 12-lead ECG, has been thought to reflect the regional~~  
546 ~~heterogeneity of cardiac repolarization. Normal values are typically in the range of 40-60 ms.~~  
547 ~~Absolute values of  $\geq 100$  ms and changes from baseline of  $>100\%$  have been suggested as~~  
548 ~~clinically noteworthy signals for categorical analyses. The value of assessment of QT/QTc~~  
549 ~~interval dispersion as a measure of proarrhythmic risk of a drug is, however, the subject of debate,~~  
550 ~~and the predictive value of this parameter has yet to be demonstrated. Analyses of QT/QTc~~  
551 ~~dispersion should therefore be used, if at all, to supplement more standard analyses of QT/QTc~~  
552 ~~interval duration. [Comment: It is well recognized that QT dispersion is not a reliable nor a precise~~  
553 ~~measure of proarrhythmic risk, therefore this section can be deleted from the document.]~~  
554

### 555 3.3 Morphological Analyses of ECG Waveforms

556  
557 While the predictive value of changes in ECG morphology, such as the development of U waves,  
558 has not been established, morphological abnormalities should be described and the data presented  
559 in terms of the number and percentage of subjects in each treatment group having changes from  
560 baseline that represent the appearance ~~or worsening~~ of the morphological abnormality. Typically  
561 these data will be obtained as a part of the 'thorough QT/QTc study'.  
562

## 563 4.0 ADVERSE EVENTS

564  
565 In addition to data on changes in ECG intervals, adverse event data can be another source of  
566 information on proarrhythmic potential, including:

- 567 • Premature discontinuations and dosage adjustments during clinical studies;
- 568 • Post-marketing adverse event reports if available.

### 569 4.1 Clinical Trial Adverse Events

570  
571 Although drug-induced prolongation of the QT/QTc interval is usually asymptomatic, an  
572 increased rate of certain adverse events in patients taking an investigational agent can signal  
573 potential proarrhythmic effects. The rates of the following clinical events should be compared in  
574 the treated and control patients, particularly when there is evidence of an effect on the QT/QTc  
575 interval:  
576

- 577 • Torsade de pointes;
- 578 • Sudden death;
- 579 • Ventricular tachycardia;
- 580 • Ventricular fibrillation and flutter;
- 581 • Syncope;
- 582 • Dizziness;

- 583 • Seizures.

584  
585 Torsade de pointes (TdP) is infrequently captured in most clinical databases, even those for drugs  
586 known to have significant proarrhythmic effects. Given this, the failure to observe an episode of  
587 TdP in a drug application database is not considered sufficient grounds for dismissing the possible  
588 arrhythmogenic risks of a drug when these are suspected on the basis of ECG and other clinical  
589 data. The other adverse events listed above, while less specific for an effect on cardiac  
590 repolarization, are more commonly captured in clinical trials, and an imbalance in their frequency  
591 between study groups can signal a potential proarrhythmic effect of the investigational agent.  
592 Sub-group analyses should be conducted in terms of age, gender, pre-existing cardiac disease,  
593 electrolyte disturbances, and concomitant medications. Comparing cause-specific rates of death is  
594 difficult, but a difference in the fraction of total deaths qualifying as “sudden” has also been  
595 proposed as a marker for proarrhythmic potential.

596  
597 Detailed patient narratives should be provided for all serious cardiac adverse events, as would be  
598 the case for any serious event or events leading to discontinuation. In assessing the possible  
599 causal relationship of drug-induced QT/QTc interval prolongation to the event, attention should be  
600 directed to considerations such as temporal relationship and ECG results collected at the time of  
601 the event. As the QT/QTc interval is subject to considerable fluctuation, a possible role for  
602 QT/QTc interval prolongation should not be dismissed on the basis of normal on-therapy ECG  
603 measurements performed prior to, or near the time of the adverse event. In addition to an  
604 appropriate adverse reaction report, patients with marked QT/QTc prolongation or an episode of  
605 TdP might provide useful information on risk management. When identified, they should  
606 therefore be examined closely for other risk factors (*e.g.*, genetic predisposition, see section 4.3).  
607 Rechallenge with the investigational drug under appropriately monitored conditions can provide  
608 useful information on dose- and concentration-response relationships.

609  
610 In evaluating the safety database of a new drug, consideration should be given to the extent to  
611 which the inclusion and exclusion criteria for patient eligibility might have influenced the study  
612 population with respect to the risk of QT/QTc interval prolongation and associated adverse events  
613 (*e.g.*, exclusion of patients with cardiac co-morbidities or renal/hepatic impairment, prohibition of  
614 diuretics as concomitant medications). Ideally, the major clinical studies should include an  
615 adequate representation of female and elderly patients, as well as patients with co-morbidities and  
616 concomitant medications typical of the expected user population.

617  
618 If a subject experiences symptoms or ECG findings suggestive of an arrhythmia during a clinical  
619 trial, immediate evaluation by a cardiac specialist is recommended, both for the purposes of  
620 treating the patient and for discussions related to continuation/ re-institution of the therapy.

621

622 **4.2 Premature Discontinuations or Dosage Reductions**

623

624 Particular attention should be directed to subjects or patients who are discontinued from clinical  
625 trials due to QT/QTc interval prolongation. Information should be provided on the basis for  
626 premature discontinuation of the patient (e.g., a QT/QTc interval value in excess of a protocol-  
627 defined upper limit, occurrence of QT/QTc interval prolongation in association with symptoms of  
628 arrhythmia), as well as the dose and duration of treatment, plasma levels if available, demographic  
629 characteristics, and the presence or absence of risk factors for arrhythmia.

630

631 Dosage reductions prompted by QT/QTc interval prolongation should also be documented.

632

633 **4.3 Pharmacogenetic Considerations**

634

635 Many forms of Long QT Syndrome are now known to be linked to mutations in genes encoding  
636 cardiac ion channel proteins. Because of incomplete penetrance, not all carriers of mutated ion  
637 channel genes will manifest QT/QTc interval prolongation in screening ECG evaluations.  
638 Common polymorphisms can affect ion channels, leading to an increased sensitivity to drugs that  
639 affect repolarization. When possible, and following informed consent, patients who experience  
640 marked prolongation of the QT/QTc or TdP while on drug therapy should be genotyped.

641

642 **4.4 Post-Marketing Adverse Event Reports**

643

644 Because documented cases of TdP are relatively rare, even for drugs that prolong the QT/QTc,  
645 they are often not reported until large populations of patients have received the agent in post-  
646 marketing settings. The available post-marketing adverse event data should be examined for  
647 evidence of QT/QTc interval prolongation and TdP and for adverse events possibly related to  
648 QT/QTc interval prolongation, such as cardiac arrest, sudden cardiac death and ventricular  
649 arrhythmias (e.g., ventricular tachycardia and ventricular fibrillation). A well-characterized  
650 episode of TdP has a high probability of being related to drug use, whereas the other events that  
651 are reported more commonly would be of particular concern if reported in a population at low risk  
652 for them (e.g., young men experiencing sudden death).

653

654 **5.0 REGULATORY IMPLICATIONS, LABELLING, AND RISK MANAGEMENT**  
655 **STRATEGIES**

656

657 **5.1 Relevance of QT/QTc Interval Prolonging Effects to the Approval Process**

658

659 Substantial prolongation of the QT/QTc interval, with or without documented arrhythmias, could  
660 be the basis for non-approval of a drug or discontinuation of its clinical development, particularly  
661 when the drug has no clear advantage over available therapy and available therapy appears to meet  
662 the needs of most patients. Failure to perform an adequate non-clinical and clinical assessment of  
663 the potential QT/QTc interval prolonging properties of a drug can likewise be justification to delay  
664 or deny marketing authorization. For non-antiarrhythmic drugs, the outcome of the risk benefit  
665 assessment will generally be influenced by the size of the QT/QTc interval prolongation effect,  
666 whether the effect occurs in most patients or only in certain defined outliers, the overall benefit of  
667 the drug, and the utility and feasibility of risk management options. The inclusion of

668 precautionary material in the prescribing information will not necessarily be considered an  
669 adequate risk management strategy, if implementation of the recommendations in a clinical use  
670 setting is judged to be unlikely.

671  
672 If QT/QTc interval prolongation is a feature shared by other drugs of the therapeutic class in  
673 question, evaluation of the new drug could usefully involve a comparison of the magnitude and  
674 incidence of any QT/QTc interval prolongation effects relative to those of other members of its  
675 class in concurrent positive control groups.

676  
677 It is difficult to determine whether there is an effect on the mean QT/QTc interval that is so small  
678 as to be inconsequential, but the risk of arrhythmias appears to increase with the extent of QT/QTc  
679 prolongation. Drugs that prolong the mean QT/QTc interval by around 5 ms or less do not appear  
680 to cause TdP. Whether this signifies that no increased risk exists for these compounds or simply  
681 that the increased risk has been too small to detect is not clear. The data on drugs that prolong the  
682 mean QT/QTc interval by more than around 5 and less than 20 ms are inconclusive, but some of  
683 these compounds have been associated with proarrhythmic risk. Drugs that prolong the mean  
684 QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic, and  
685 might have clinical arrhythmic events captured during drug development.<sup>3</sup>

686  
687 Regardless of the degree to which a drug prolongs the QT/QTc interval, decisions about its  
688 development and approval will depend upon the morbidity and mortality associated with the  
689 untreated disease or disorder and the demonstrated clinical benefits of the drug, especially as they  
690 compare with available therapeutic modalities. Demonstrated benefits of the drug in resistant  
691 populations or in patients who are intolerant of, or have a labeled contraindication to, approved  
692 drugs for the same disease represent additional relevant clinical considerations that might justify  
693 approval of the drug, if the indication were limited to use in such patients.

694  
695 Some factors have been proposed that can modify the risk of QT/QTc prolongation. For instance,  
696 it has been suggested that some drugs might prolong the QT/QTc interval up to a “plateau” value,  
697 above which there is no dose-dependent increase, although this has not been demonstrated  
698 adequately to date. It has also been suggested that proarrhythmic risk might be influenced by  
699 other pharmacologic effects (*e.g.*, other channel effects). In any case, it is important to identify the  
700 “worst case scenario” for drugs that have demonstrated effects on QT/QTc interval as a part of risk  
701 assessment (*i.e.*, the QT/QTc interval measured in the target patient population at the time of peak  
702 effect and under conditions of the highest blood levels that can be attained during therapy).

## 703 704 **5.2 Labelling Issues for Drugs that Prolong the QT/QTc Interval**

705  
706 It is recognized that there will be regional differences in labelling. However, it is recommended  
707 that the following be considered:

- 708  
709
- A warning/precautionary statement about the risk;
  - A description of the design and results of the trials investigating the effect on the  
710 QT/QTc interval, including the absence of demonstrated effect;
- 711

---

<sup>3</sup> Comment is requested on the risk categorization described in this paragraph.

- 712 • The dosage recommendations;
- 713 • A list of conditions known to increase the proarrhythmic risk (e.g., congestive heart
- 714 failure, Long QT Ssyndrome, hypokalemia);
- 715 • A precautionary statement regarding the concomitant use of two or more QT/QTc
- 716 interval prolonging drugs and other interactions increasing the risk.
- 717 • Recommendations for patient monitoring (ECG and electrolytes) and management of
- 718 patients with QT/QTc prolongation or symptoms suggestive of an arrhythmia.

719

720 **5.3 Post-Marketing Risk Management for Drugs that Prolong the QT/QTc Interval**

721

722 The use of dosing adjustments following institution of therapy appears to materially decrease the  
723 risk of TdP in hospitalized patients receiving an antiarrhythmic drug; no similar data are available  
724 for drugs of other therapeutic classes. For approved drugs that prolong the QT/QTc interval, risk-  
725 management strategies aimed at minimizing the occurrence of arrhythmias associated with their  
726 use have focused on education of the health-care providers and patients.

727