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

84  
85 **1.0 INTRODUCTION**

86  
87 **1.1 Background**  
88

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

100  
101 While the degree of QT prolongation is recognized as an imperfect biomarker for proarrhythmic  
102 risk, there is a qualitative relationship between QT prolongation and the risk of TdP, especially for  
103 drugs that cause substantial prolongation of the QT/QTc interval.

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

121  
122 **1.2 Objectives**  
123

124 This document provides recommendations to sponsors concerning the design, conduct, analysis,  
125 and interpretation of clinical studies to assess the potential of a drug to delay cardiac  
126 repolarization. This assessment should include testing the effects of new agents on the QT/QTc  
127 interval as well as the collection of cardiovascular adverse events. The investigational approach

128 used for a particular drug should be individualized, depending on the pharmacodynamic,  
129 pharmacokinetic, and safety characteristics of the product, as well as on its proposed clinical use.

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

### 134 135 **1.3 Scope**

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

## 148 149 **2.0 CLINICAL TRIALS**

### 150 151 **2.1 Design Considerations**

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

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

- 169  
170 • A negative 'thorough QT/QTc study', even in the presence of non-clinical data of  
171 concern, will almost always allow the collection of on-therapy ECGs in accordance  
172 with the current practices in each therapeutic area to constitute sufficient evaluation  
173 during subsequent stages of drug development (see section 2.1.3);

- 174 • A positive ‘thorough QT/QTc study’ will almost always call for an expanded ECG  
175 safety evaluation during later stages of drug development (see section 2.1.3).  
176

177 *2.1.1 Subject Enrollment, Safety Monitoring, and Discontinuation Criteria*  
178

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

183 Regarding subject enrollment, until the effects of the drug on the QT/QTc interval have been  
184 characterized, the following exclusion criteria are suggested:  
185

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

192 If supported by the QT/QTc interval safety data from the early studies, later clinical trials could  
193 expand the eligibility criteria to include a broader spectrum of patients who are likely to receive  
194 the drug once approved.  
195

196 Regarding safety monitoring, the procedures to follow if a patient experiences an adverse event  
197 suggestive of TdP should be specified in the clinical trial protocol.  
198

199 Discontinuation of a subject from a clinical trial should be considered if there is a marked  
200 prolongation of the QT/QTc interval during treatment with the study drug, especially if the  
201 measurement is obtained from more than one ECG. While increases in QT/QTc to >500 ms or of  
202 >60 ms over baseline are commonly used as thresholds for potential discontinuation, the exact  
203 criteria chosen for a given trial will depend on the risk-tolerance level considered appropriate for  
204 the indication and patient group in question.  
205

206 *2.1.2 The ‘Thorough QT/QTc Study’: Dose-Effect and Time Course Relationships*  
207

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

220

221 The ‘thorough QT/QTc study’ is intended to determine whether the drug has a threshold  
222 pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation. The study is  
223 typically carried out in healthy volunteers (as opposed to individuals at increased risk of  
224 arrhythmias) and is used to determine whether or not the effect of a drug on the QT/QTc interval  
225 in target patient populations need to be studied intensively during later stages of drug  
226 development. Although data are limited, it is expected that the results of the ‘thorough QT/QTc  
227 study’ would not be affected by ethnic factors.

228

229 The ‘thorough QT/QTc study’ would typically be conducted early in clinical development to  
230 provide maximum guidance for later trials, although the precise timing will depend on the  
231 specifics of the drug under development. It would usually not be the first study, as it is important  
232 to have basic clinical data for its design and conduct, including tolerability and pharmacokinetics.  
233 It would often be conducted in healthy volunteers. Some drugs might not be suitable for study in  
234 healthy volunteers because of issues related to tolerability (e.g., neuroleptic agents,  
235 chemotherapeutics).

236

237 The timing of the collection of ECGs and the study design (e.g., single or multiple dose, duration)  
238 of the ‘thorough QT/QTc study’ should be guided by the available information about the  
239 pharmacokinetic profile of the drug. For drugs with short half-lives and no metabolites, a single  
240 dose study might be sufficient. Studies should characterize the effect of a drug on the QT/QTc  
241 throughout the dosing interval. While the peak serum concentration does not always correspond  
242 to the peak effect on QT/QTc interval, care should be taken to perform ECG recordings at time  
243 points around the C<sub>max</sub>. As one intent of a positive control is to establish assay sensitivity, in  
244 multiple dose studies of new drugs a positive control only needs to be used long enough to have its  
245 expected effect.

246

247 The ‘thorough QT/QTc study’ should be adequate and well-controlled, with mechanisms to deal  
248 with potential bias, including use of randomization, appropriate blinding, and concurrent placebo  
249 control group. As this study has a critical role in determining the intensity of data collection  
250 during later stages of drug development, it is important to have a high degree of confidence in the  
251 ability of the study to detect differences of clinical significance. The confidence in the ability of  
252 the study to detect QT/QTc prolongation can be greatly enhanced by the use of a concurrent  
253 positive control group to establish assay sensitivity. Absence of a positive control should be  
254 justified and alternative methods to establish assay sensitivity provided. It is difficult to determine  
255 whether there is an effect on the mean QT/QTc interval that is so small as to be of no  
256 consequence. However, drugs that prolong the mean QT/QTc interval by around 5 ms or less do  
257 not appear to cause TdP. On that basis, the positive control (whether pharmacological or non-  
258 pharmacological) should be well-characterized and consistently produce an effect corresponding  
259 to the largest change in the QT/QTc interval that is currently viewed as clinically not important to  
260 detect (a mean change of around 5 ms or less)<sup>1</sup>.

261

---

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

262 Based on similar considerations, a negative ‘thorough QT/QTc study’ is one where the largest  
263 time-matched mean difference between the drug and placebo (baseline-subtracted) for the QTc  
264 interval is around 5 ms or less, with a one-sided 95% confidence interval that excludes an effect  
265  $>8.0 \text{ ms}^2$ . This upper bound was chosen to reflect the uncertainty related to the variability of  
266 repeated measurements. As with other data, the presence of outliers (see section 3.2.2) should also  
267 be explored.

268

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

272

273 Crossover or parallel group study designs can be suitable for trials assessing the potential of a drug  
274 to cause QT/QTc interval prolongation. Crossover studies at least have two potential advantages:

275

- 276 • They usually call for smaller numbers of subjects than parallel group studies, as the  
277 subjects serve as their own controls and hence reduce variability of differences related  
278 to diurnal variations and inter-subject variability;
- 279 • They might facilitate heart rate correction approaches based on individual subject data.

280

281 Parallel group studies might be preferred under certain circumstances:

282

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

288

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

294

### 295 *2.1.3 Clinical Trial Evaluation After the ‘Thorough QT/QTc Study’*

296

297 In the absence of QT/QTc interval prolongation in the ‘thorough QT/QTc study’ (see section  
298 2.1.2), the collection of baseline and periodic on-therapy ECGs in accordance with the current  
299 investigational practices in each therapeutic field is, in general, considered appropriate.

300

---

<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’.

301 If the ‘thorough QT/QTc study’ is positive, additional evaluation in subsequent clinical studies  
302 should be performed. One objective of this evaluation should be to fully characterize the dose-,  
303 concentration-, and time- relationships of the drug on the QT/QTc interval in the target patient  
304 population(s) at therapeutic and suprathreshold serum concentrations. The latter can be achieved  
305 in two ways: through administration of high doses or use of metabolic inhibitors (if applicable).  
306

307 Another objective of this evaluation should be to collect information on the adverse events that  
308 occur in the trials following the positive ‘thorough QT/QTc study’. This would include patients  
309 who develop marked QT/QTc prolongation (*e.g.*, >500 ms) or experience a serious cardiovascular  
310 adverse event that suggests an arrhythmia (*e.g.*, TdP). Such patients should be evaluated closely  
311 for risk factors that might have contributed to this event (*e.g.*, genotyping for Long QT  
312 Syndromes, see section 4.3).  
313

314 If the ‘thorough QT/QTc study’ is positive, analyses of the ECG and adverse event data from  
315 certain patient sub-groups are of particular interest, such as:  
316

- 317 • Patients with electrolyte abnormalities (*e.g.*, hypokalemia);
- 318 • Patients with congestive heart failure;
- 319 • Patients with impaired drug metabolizing capacity or clearance (*e.g.*, renal or hepatic  
320 impairment, drug interactions);
- 321 • Female patients;
- 322 • Patients aged <16 and over 65 years.

323  
324 Even if the ‘thorough QT/QTc study’ is negative, if other evidence of an effect in a patient  
325 population from subsequent studies (*e.g.*, marked QT/QTc interval prolongation, TdP) were to  
326 emerge, then additional investigation would be needed.  
327

## 328 **2.2 Collection, Assessment and Submission of Electrocardiographic Data**

329  
330 The recommendations below are most relevant to the ‘thorough QT/QTc study’ and to any studies  
331 investigating a drug with a known effect on cardiac repolarization.  
332

### 333 *2.2.1 Collection of Standard 12-Lead Electrocardiograms (ECGs)*

334  
335 Until better ways are established to assess proarrhythmic risk during drug development, the  
336 measurement of the QT/QTc interval on the surface ECG is central to the detection of that risk.  
337 The clinical ECG database is typically derived from the collection of 12-lead surface ECGs,  
338 although ambulatory ECG techniques show promise (see section 2.2.3).  
339

### 340 *2.2.2 Assessment of Standard 12-Lead ECGs*

341

*Draft— Not for Implementation  
For Discussion Purposes Only*

342 Several methods for measuring ECG intervals have been used in clinical trials, and for a given  
343 trial, the sponsor should describe the accuracy and precision of QT/QTc interval measurements  
344 using the selected system. The method chosen will depend on the level of precision needed for a  
345 given trial. For example, the ‘thorough QT/QTc study’ would warrant particularly careful  
346 attention to interval measurement. At present, this would usually involve the measurement by a  
347 few skilled readers operating from a centralized ECG laboratory, although other methods (e.g.,  
348 semi-automated ECG reading) can be acceptable when appropriately supported. Readers of ECGs  
349 should be blinded to time, treatment and subject identifier, and one reader should read all the ECG  
350 recordings from a given subject. The degree of inter- and intra-reader variability should be  
351 established by having the assessors reread a subset of the data (both normal and abnormal) under  
352 blinded conditions. Criteria for ECG diagnoses and for identification of adverse events should be  
353 pre-defined by the sponsor. If well-characterized data validating the use of fully-automated  
354 technologies become available, the recommendations in the guidance for the measurement of ECG  
355 intervals could be modified. In the absence of a concern in the early clinical trial(s), automated  
356 ECG readings have a role in the rapid assessment of ECGs for safety.

357  
358 The quality of the ECG database can depend on the use of modern equipment with the capacity for  
359 digital signal processing. Such equipment should be recently serviced and calibrated. Machine  
360 calibration records and performance data should be maintained on file. In the case of multicentre  
361 trials, training sessions are encouraged to ensure consistency of operator technique (e.g., skin  
362 preparation, lead placement, patient position) and data acquisition practices.

363  
364 While the most appropriate lead(s) and methodology to measure the QT interval have not been  
365 established, lead II is often used. A consistent approach should be used for a given trial.

366  
367 Morphological changes in the T-U complex might occur. Information should be provided on  
368 changes in T and U wave morphologies (see section 3.3). Discrete U waves should be excluded  
369 from the QT/QTc interval measurement

370  
371 *2.2.3 Ambulatory ECG Monitoring*

372  
373 While ambulatory ECG monitoring has historically not been sufficiently validated to be  
374 considered as the primary assessment ECG for QT/QTc interval effects, newer systems that allow  
375 for the collection of multiple leads that more closely approximate a surface ECG have potential  
376 value to collect interval data. The use of ambulatory ECG monitors might additionally allow  
377 detection of extreme QT/QTc interval events that occur infrequently during the day and  
378 asymptomatic arrhythmias. Data on the QT/RR from ambulatory ECG monitoring can also prove  
379 useful in the calculation of individualized QT corrections. However, as QT/QTc intervals  
380 measured by this methodology might not correspond quantitatively to those from standard surface  
381 ECGs, data obtained from the two methodologies might not be suitable for direct comparison,  
382 pooling, or interpretation using the same thresholds of concern.

383  
384 *2.2.4 Submission of Interval and Waveform Data*

385  
386 Regional guidance should be sought for information on the submission of ECG interval data and  
387 overall assessments.

388

### 389 3.0 ANALYSIS OF ECG DATA FROM CLINICAL TRIALS

390

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

393

394 Regardless of the outcome of the ‘thorough QT/QTc study’, ECG changes recorded as adverse  
395 events should be pooled from all studies for analysis. ECG interval data from the ‘thorough  
396 QT/QTc study’ should only be pooled with subsequent trials of similar rigor with regard to ECG  
397 data collection and analysis, but should not be pooled with trials using less rigorous ECG  
398 collection. Standardization of ECG collection for similar studies within a clinical trial programme  
399 will facilitate pooled analyses.

400

#### 401 3.1 QT Interval Correction Formulae

402

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

412

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

420

##### 421 3.1.1 Population-Derived Correction Formulae

422

423 Examples of such corrections include the following:

424

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

426

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

428

429 Bazett’s correction is frequently used in clinical practice and in the medical literature. In general,  
430 however, Bazett’s correction overcorrects at elevated heart rates and under corrects at heart rates  
431 below 60 bpm and hence is not an ideal correction. Fridericia’s correction is more accurate than  
432 Bazett’s correction in subjects with such altered heart rates.

433

- 434 3) Corrections based on linear regression techniques  
435 Application of linear regression techniques to plots of QT/RR data for the placebo or baseline  
436 study population allows for the estimation of the slope (b), which can be used for standardizing the  
437 data from both the drug and control groups to a normalized heart rate of 60 beats per minute, using  
438 the equation  $QT = a + b(RR)$ . The Framingham correction [ $QT_c = QT + 0.154(1-RR)$ ] is one  
439 example of a correction derived by linear regression.  
440
- 441 4) Corrections using linear or non-linear regression modeling on pooled data from large databases  
442

### 443 *3.1.2 Correction Formulae Derived from Within-Subject Data*

444

445 Corrections for heart rate using individual subject data have been developed, applying regression  
446 analysis techniques to individual pre-therapy QT and RR interval data over a range of heart rates,  
447 then applying this correction to on-treatment QT values. These approaches are considered most  
448 suitable for the ‘thorough QT/QT<sub>c</sub> study’ and early clinical studies, where it is possible to obtain  
449 many QT interval measurements for each study subject. As adaptation of the QT/QT<sub>c</sub> interval to  
450 changes in heart rate is not instantaneous, care should be taken to exclude ECG recordings  
451 collected during times of rapid heart rate changes due to this QT/RR hysteresis effect.  
452

## 453 **3.2 Analysis of QT/QT<sub>c</sub> Interval Data**

454

455 Although increases from baseline in the QT/QT<sub>c</sub> interval constitute signals of interest,  
456 interpretation of these differences is complicated by the potential for changes not related to drug  
457 therapy, including regression toward the mean and choice of extreme values. Regression toward  
458 the mean refers to the tendency of subjects with high baseline values to have lower values at later  
459 time points, while subjects with low baseline values tend to experience increases. The direction  
460 of regression depends on initial selection criteria (for example, if subjects with high baseline  
461 QT/QT<sub>c</sub> interval values are excluded from the trial, values recorded during treatment will tend to  
462 rise relative to baseline levels). The process of choosing the highest of multiple observed values  
463 will also almost invariably cause an apparent change from any single baseline value, a  
464 phenomenon found in both drug and placebo-treated groups.  
465

466 The QT/QT<sub>c</sub> interval data should be presented both as analyses of central tendency (*e.g.*, means,  
467 medians) and categorical analyses. Both can provide relevant information on clinical risk  
468 assessment.  
469

### 470 *3.2.1 Analyses of Central Tendency*

471

472 The effect of an investigational drug on the QT/QT<sub>c</sub> interval is most commonly analyzed using the  
473 largest time-matched mean difference between the drug and placebo (baseline-subtracted) over the  
474 collection period (*e.g.*, hourly, weekly, monthly). Additional approaches to the assessment of  
475 central tendency could include analysis of time-averaged QT/QT<sub>c</sub> intervals or analysis of changes  
476 occurring at the C<sub>max</sub> for each individual.  
477

### 478 *3.2.2 Categorical Analyses*

479

480 Categorical analyses of QT/QTc interval data are based on the number and percentage of patients  
481 meeting or exceeding some predefined upper limit value. Clinically noteworthy QT/QTc  
482 interval signals might be defined in terms of absolute QT/QTc intervals or changes from  
483 baseline. Absolute interval signals are QT/QTc interval readings in excess of some specified  
484 threshold value. Separate analyses should be provided for patients with normal and elevated  
485 baseline QT/QTc intervals. As with all QT/QTc interval analyses, categorical analyses are most  
486 informative when it is possible to compare the rate of supra-threshold readings in the treatment  
487 and control groups.  
488

489 There is no consensus concerning the choice of upper limit values for absolute interval signals  
490 and change from baseline signals. While lower limits increase the false-positive rate, higher  
491 limits increase the risk of failing to detect a signal. In clinical trials, a prolongation of QTc > 500  
492 ms during therapy has been a threshold of particular concern. Multiple analyses using different  
493 signal values are a reasonable approach to this uncertainty, including:  
494

- 495 • Absolute QTc interval prolongation:
  - 496
  - 497 • QTc interval > 450
  - 498 • QTc interval > 480
  - 499 • QTc interval > 500
  - 500
- 501 • Change from baseline in QTc interval:
  - 502
  - 503 • QTc interval increases from baseline  $\geq 30$
  - 504 • QTc interval increases from baseline  $\geq 60$
  - 505

### 506 3.2.3 QT/QTc Interval Dispersion

507

508 QT/QTc interval dispersion, defined as the difference between the shortest and the longest  
509 QT/QTc interval measured on the 12-lead ECG, has been thought to reflect the regional  
510 heterogeneity of cardiac repolarization. Normal values are typically in the range of 40-60 ms.  
511 Absolute values of  $\geq 100$  ms and changes from baseline of  $>100\%$  have been suggested as  
512 clinically noteworthy signals for categorical analyses. The value of assessment of QT/QTc  
513 interval dispersion as a measure of proarrhythmic risk of a drug is, however, the subject of debate,  
514 and the predictive value of this parameter has yet to be demonstrated. Analyses of QT/QTc  
515 dispersion should therefore be used, if at all, to supplement more standard analyses of QT/QTc  
516 interval duration.  
517

## 518 3.3 Morphological Analyses of ECG Waveforms

519

520 While the predictive value of changes in ECG morphology, such as the development of U waves,  
521 has not been established, morphological abnormalities should be described and the data presented  
522 in terms of the number and percentage of subjects in each treatment group having changes from  
523 baseline that represent the appearance or worsening of the morphological abnormality. Typically  
524 these data will be obtained as a part of the 'thorough QT/QTc study'.  
525

## 526 4.0 ADVERSE EVENTS

527

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

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

532

### 533 4.1 Clinical Trial Adverse Events

534

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

- 540 • Torsade de pointes;
- 541 • Sudden death;
- 542 • Ventricular tachycardia;
- 543 • Ventricular fibrillation and flutter;
- 544 • Syncope;
- 545 • Dizziness;
- 546 • Seizures.

547

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

559

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

572

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

580

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

584

#### **4.2 Premature Discontinuations or Dosage Reductions**

585

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

592

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

594

595

#### **4.3 Pharmacogenetic Considerations**

596

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

603

604

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

605

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

615

616

617 **5.0 REGULATORY IMPLICATIONS, LABELLING, AND RISK MANAGEMENT**  
618 **STRATEGIES**

619

620 **5.1 Relevance of QT/QTc Interval Prolonging Effects to the Approval Process**  
621

622 Substantial prolongation of the QT/QTc interval, with or without documented arrhythmias, could  
623 be the basis for non-approval of a drug or discontinuation of its clinical development, particularly  
624 when the drug has no clear advantage over available therapy and available therapy appears to meet  
625 the needs of most patients. Failure to perform an adequate non-clinical and clinical assessment of  
626 the potential QT/QTc interval prolonging properties of a drug can likewise be justification to delay  
627 or deny marketing authorization. For non-antiarrhythmic drugs, the outcome of the risk benefit  
628 assessment will generally be influenced by the size of the QT/QTc interval prolongation effect,  
629 whether the effect occurs in most patients or only in certain defined outliers, the overall benefit of  
630 the drug, and the utility and feasibility of risk management options. The inclusion of  
631 precautionary material in the prescribing information will not necessarily be considered an  
632 adequate risk management strategy, if implementation of the recommendations in a clinical use  
633 setting is judged to be unlikely.

634

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

639

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

649

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

657

---

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

658 Some factors have been proposed that can modify the risk of QT/QTc prolongation. For instance,  
659 it has been suggested that some drugs might prolong the QT/QTc interval up to a “plateau” value,  
660 above which there is no dose-dependent increase, although this has not been demonstrated  
661 adequately to date. It has also been suggested that proarrhythmic risk might be influenced by  
662 other pharmacologic effects (*e.g.*, other channel effects). In any case, it is important to identify the  
663 “worst case scenario” for drugs that have demonstrated effects on QT/QTc interval as a part of risk  
664 assessment (*i.e.*, the QT/QTc interval measured in the target patient population at the time of peak  
665 effect and under conditions of the highest blood levels that can be attained during therapy).  
666

## 667 **5.2 Labelling Issues for Drugs that Prolong the QT/QTc Interval**

668  
669 It is recognized that there will be regional differences in labelling. However, it is recommended  
670 that the following be considered:  
671

- 672 • A warning/precautionary statement about the risk;
- 673 • A description of the design and results of the trials investigating the effect on the  
674 QT/QTc interval, including the absence of demonstrated effect;
- 675 • The dosage recommendations;
- 676 • A list of conditions known to increase the proarrhythmic risk (*e.g.*, congestive heart  
677 failure, Long QT Ssyndrome, hypokalemia);
- 678 • A precautionary statement regarding the concomitant use of two or more QT/QTc  
679 interval prolonging drugs and other interactions increasing the risk.
- 680 • Recommendations for patient monitoring (ECG and electrolytes) and management of  
681 patients with QT/QTc prolongation or symptoms suggestive of an arrhythmia.

## 682 683 **5.3 Post-Marketing Risk Management for Drugs that Prolong the QT/QTc Interval**

684  
685 The use of dosing adjustments following institution of therapy appears to materially decrease the  
686 risk of TdP in hospitalized patients receiving an antiarrhythmic drug; no similar data are available  
687 for drugs of other therapeutic classes. For approved drugs that prolong the QT/QTc interval, risk-  
688 management strategies aimed at minimizing the occurrence of arrhythmias associated with their  
689 use have focused on education of the health-care providers and patients.  
690