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

PRELIMINARY CONCEPT PAPER

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

1.0 INTRODUCTION

1.1 Background

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

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

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

1.2 Objectives

This document provides recommendations to sponsors concerning the design, conduct, analysis, and interpretation of clinical studies to assess the potential of a drug to delay cardiac repolarization. This assessment should include testing the effects of new agents on the QT/QT_c 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
- 171 • A negative 'thorough QT/QTc study', even in the presence of non-clinical data of
172 concern, will almost always allow the collection of on-therapy ECGs in accordance
173 with the current practices in each therapeutic area to constitute sufficient evaluation
during subsequent stages of drug development (see section 2.1.3);

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

2.1.1 Subject Enrollment, Safety Monitoring, and Discontinuation Criteria

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

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

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

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

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

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

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

An adequate drug development programme should ensure that the dose-response and generally the concentration-response relationship for QT/QTc prolongation have been characterized, including exploration of concentrations that are higher than those achieved following the anticipated therapeutic doses. Data on the drug concentrations around the time of ECG assessment would aid this assessment. If not precluded by considerations of safety or tolerability due to adverse effects, the drug should be tested at substantial multiples of the anticipated maximum therapeutic exposure. Alternatively, if the concentrations of a drug can be increased by drug-drug or drug-food interactions involving metabolizing enzymes (*e.g.*, CYP3A4, CYP2D6) or transporters (*e.g.*, P-glycoprotein), these studies can be performed under conditions of maximum inhibition. This approach calls for a detailed understanding of the absorption, distribution, metabolism and excretion of the drug. In general, the duration of dosing or dosing regimen should be sufficient to 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_{max}. 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)¹.

261

¹ 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 ms². 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

² 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

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.

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3.0 ANALYSIS OF ECG DATA FROM CLINICAL TRIALS

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

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

3.1 QT Interval Correction Formulae

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

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

3.1.1 Population-Derived Correction Formulae

Examples of such corrections include the following:

- 1) Bazett’s correction: $QTc = QT/RR^{0.5}$
- 2) Fridericia’s correction: $QTc = QT/RR^{0.33}$

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

- 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_c 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_c 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_c Interval Data**

454

455 Although increases from baseline in the QT/QT_c 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_c 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_c 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_c 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_c intervals or analysis of changes
476 occurring at the C_{max} 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 ≥ 30
 - 504 • QTc interval increases from baseline ≥ 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 ≥ 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 3.3 Morphological Analyses of ECG Waveforms

518
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.

584 585 **4.2 Premature Discontinuations or Dosage Reductions**

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

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

595 596 **4.3 Pharmacogenetic Considerations**

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

604 605 **4.4 Post-Marketing Adverse Event Reports**

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

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.³

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

³ 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