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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1.0 INTRODUCTION

1.1 Background

Certain drugs have the ability to delay cardiac repolarization, an effect that is manifested on the surface electrocardiogram (ECG) as prolongation of the QT interval. The QT interval represents the duration of ventricular depolarization and subsequent repolarization, beginning at the initiation of the Q wave of the QRS complex and ending where the T wave returns to isoelectric baseline. QT interval prolongation creates an electrophysiological environment that favours 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 sinus beats preceding the arrhythmia. TdP can degenerate into life-threatening cardiac rhythms, such as ventricular fibrillation, which can result in sudden death.

Delayed cardiac repolarization is an undesired side-effect when caused by non-antiarrhythmic drugs such as pimozide, thioridazine, bepridil, lidoflazine, terfenadine, astemizole, and cisapride. Even when the effect is part of the therapeutic mechanism of an anti-arrhythmic drug, excessive QT interval prolongation can lead to new arrhythmias with potentially fatal consequences.

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 QTc interval. The QTc interval is thus intended to represent the QT interval at a standardized heart rate (essentially the QT interval at a heart rate of 60 bpm). 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 (QTc). Most drugs that have caused TdP clearly increase both the absolute QT and the QTc.

The combination of a drug's effect to prolong QT/QTc interval and documented cases of TdP (fatal and non-fatal) associated with the drug's use has resulted in a substantial number of regulatory actions, including withdrawal from the market (terfenidine, cisapride, astemizole, grepafloxacin), relegation to second-line status (bepridil, thioridazine), and denial of marketing authorization (lidoflazine). Because prolongation of the QT/QTc interval is the electrocardiographic 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/QTc interval, as well as systematic collection of clinical adverse event data that might represent cardiac arrhythmias.

This document provides recommendations to drug developers concerning the design, conduct, and interpretation of clinical studies intended to assess the effects of new agents on the QT/QTc interval. The study, measurement, and interpretation of QT/QTc interval effects are the subject of intense evaluation and discussion.

1.2 Scope

The recommendations contained in this document are generally applicable to new pharmaceuticals having systemic bioavailability. The focus is on agents being developed for uses other than the control of arrhythmias, as anti-arrhythmic drugs may prolong the QT/QTc interval as a part of their mechanism of clinical efficacy. The investigational approach used for a particular drug should be individualized, depending on the pharmacodynamic, pharmacokinetic, and safety characteristics of the product, as well as on its proposed clinical application.

While this document is concerned primarily with the development of novel agents, the recommendations may also be applicable to approved drugs when a new dose or route of administration is being developed that may result in higher C_{max} or AUC values. Additional ECG data may also be appropriate if a new indication or patient population is being pursued. The availability of a comprehensive evaluation of QT/QTc interval effects in the supplemental submission will be particularly important if the drug or members of its therapeutic class have been associated with QT/QTc interval prolongation, torsade de pointes, or sudden cardiac death over the course of clinical trials or during post-marketing surveillance.

2.0 CLINICAL TRIALS

2.1 General

All drugs should receive a systematic electrocardiographic evaluation during the early stages of clinical development, whether or not positive findings were noted in non-clinical electrophysiology studies. A suspicion of delayed cardiac repolarization on the basis of non-clinical studies should, however, lead to a more rigorous ECG assessment program with larger sample sizes, higher systemic concentrations, and more frequent ECG measurements. Because initial clinical trials are generally limited to a relatively small number of healthy volunteers, negative findings in these studies cannot necessarily be extrapolated to the intended patient population, in which additional, population-specific, risk factors may be present.

As with other routine safety variables such as vital signs or laboratory tests, the ECG should be monitored in phase 2 and phase 3 clinical trials, even in the absence of a positive signal of repolarization impairment in non-clinical or earlier clinical studies. If the earlier clinical trials provide evidence of QT/QTc interval prolongation, a more intensive phase 3 evaluation will be needed.

2.2 Design Issues

Clinical studies assessing QT/QTc interval prolongation should be randomized and double-blinded, with concurrent placebo control groups. In addition to the use of a placebo control, a concurrent active control group is very valuable to verify the ability of a particular study to detect a relevant change in the QT/QTc interval. The active control should be selected for its ability to produce an effect that has a magnitude corresponding to the smallest change in the QT/QTc interval that the trial is designed to detect (generally about 5 msec). The control should be very well-characterized, so that it can be expected to produce a consistent effect at the dose used. If an investigational drug belongs to a therapeutic class that has been associated with QT/QTc interval prolongation, active controls should be selected from other members of the same class to permit a comparison of effect sizes, preferably at equipotent therapeutic doses.

Crossover or parallel group study designs may be suitable for trials addressing the potential of a drug to cause QT/QTc interval prolongation. Crossover studies can use smaller numbers of subjects than parallel group studies, as the subjects serve as their own controls. They may also reduce variability compared to parallel design studies and provide greater statistical power. Crossover designs also facilitate heart rate correction approaches based on individual subject data. Moreover, potential diurnal variation can be taken into account by comparing ECGs in the treatment phase with time-matched ECGs for the same subject in the placebo phase.

Parallel group studies may be preferred for drugs with long elimination half-lives for which lengthy time intervals would be required to achieve steady-state or complete washout or if carryover effects are prominent for other reasons, such as irreversible receptor binding. Parallel group studies may also be more practical if multiple doses or treatment groups are to be compared.

Measurement of the baseline value is another factor that critically influences the observed variability in the mean QT/QTc interval. Use of baseline values from single ECGs is a practice to be discouraged; baseline QT/QTc values should be computed as the mean or median of multiple ECGs ($n \geq 3$) to enhance the precision of the measurement. The collection of drug-free ECGs on two or three different days will help document inter-day variability in the baseline. Baseline values will, as noted later, almost always be smaller than the maximum QT/QTc intervals observed among multiple subsequent on-treatment measurements. While maximum values can be compared to a concurrent placebo group, comparison of maximum values with "baseline placebo" will not be useful.

Regardless of the trial design used, baseline ECGs should be collected at similar times of the day to minimize the possible effects of diurnal fluctuation and food. In addition, posture and activity levels at the time of the ECGs should be standardized to the extent possible for all recording periods.

For drugs with non-clinical or clinical signals consistent with delayed repolarization, the Investigator's Brochure should contain a detailed account of the nature and implications of the findings. The Patient Informed Consent Form should also provide an explanation of the potential risk associated with QT/QTc interval prolongation in language that can be understood by the patients.

2.2.1 Phase 1 Evaluation: Dose-Effect and Time Course Relationships

All drugs should be thoroughly evaluated for possible effects on the QT/QTc interval in phase 1 trials, whether or not the non-clinical data yield a positive signal for repolarization impairment. An adequate drug development programme should ensure that the dose-response or concentration-response relationship for QT/QTc interval prolongation has been characterized, with exploration of the full proposed dose range. If not precluded by considerations of safety or tolerability due to adverse effects, doses substantially in excess of the projected therapeutic dose should be tested, so that the consequences of overdosage are known. If the metabolism of the drug can be inhibited by concomitant medication, the concentrations studied should include those attainable under conditions of maximum inhibition, whether produced by the drug administered alone or in combination with a metabolic inhibitor. If non-clinical studies have provided evidence of repolarization impairment, low initial doses and conservative dose-escalation steps should be used in early clinical trials.

For phase 1 studies and in phase 2/3 studies when there is a non-clinical or phase 1 signal, collection of plasma samples near the time of the ECG measurement is encouraged to permit an exploration of the relationship between parent drug and active metabolite concentrations and any resulting ECG changes. Important considerations in characterizing the dose- or concentration-response relationship include the following:

- the maximal extent of the QT/QTc interval prolongation at therapeutic and supratherapeutic serum concentrations, and following metabolic inhibition (if applicable),
- the steepness of the relationship between the dose/concentration of the drug and QT/QTc interval prolongation,
- the linearity or nonlinearity of the dose/concentration-effect dependency, and
- the time course of QT/QTc interval prolongation in relation to plasma levels of the parent drug and any active metabolites.

In initial studies, multiple ECGs should be collected at baseline (preferably for > 1 day), at time points throughout the duration of the dosing interval, and prior to release from the clinic. Particular attention should be directed to the time of peak effect. This time point may or may not correspond to the time of peak plasma concentrations. While ECGs should always be performed at the anticipated time of peak plasma concentrations (Tmax) for the parent drug and its major metabolites, this is not sufficient and other time points should be examined as well. As drug-induced QT/QTc interval prolongation may, in some cases, be related to long-term accumulation in myocardial tissue, the time course of the effects on QT/QTc should be adequately addressed (*e.g.*, first dose effect, effect of increasing doses at steady-state, long-term effects, return to baseline following discontinuation of treatment). Studies should be of sufficient duration to allow detection of delayed effects.

2.2.2 Phase 2/3 Clinical Trial Evaluation

In phase 2/3 clinical trials, routine evaluation should include ECGs obtained during baseline and treatment, generally at time points anticipated to coincide with the maximal blood level or maximal effect on the QT/QTc interval, if known from earlier trials. (For relatively long half-life drugs, it is not essential to measure at precisely T_{max}, but measurements should be scheduled to be reasonably close to that time.) Drugs that are associated with any QT/QTc interval prolongation in preclinical studies or phase 1 clinical trials should have more rigorous ECG monitoring in phase 2 studies, with ECG recordings performed during the initial stages of treatment and after dosage increases, as well as under steady-state conditions, with focus both on mean or median QT/QTc interval changes and on outlier values. The collection of ECGs and blood samples should be coordinated for use in exploring the population pharmacokinetic-pharmacodynamic relationships of the drug's effects on the QT/QTc interval. Any patient developing marked QT/QTc prolongation (≥500 msec) should be examined closely for risk factors that may have contributed to this event, including genotyping for hereditary long QT Syndromes.

Figure 1 provides a schematic representation of the roles played by non-clinical assessments and phase 1 clinical trials in determining the extent of the ECG safety evaluation in subsequent phases of the drug development process. The major differences between routine and intensive phase 2/3 evaluation are shown in Table 1. As a general matter, any evidence of QT interval prolongation in human studies will lead to an intensive phase 3 evaluation. A positive non-clinical finding can be "rebutted" by failure to observe an effect in phase 1 and 2 studies. The findings in phase 3 (magnitude of effect, steepness of dose-response relationship, etc.), will determine the need for further studies and will affect the ultimate risk/benefit conclusion.

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	Routine	Intensive (routine plus)
Phase 1	-	See Text (Section 2.2.1)
Phase 2, 3	ECGs at baseline and periodic on-therapy visits, including values at T_{max} and late values Intensive evaluation of any patients with marked QT/QTc prolongation (≥500 msec) or TdP	Complete assessment of dose- and concentration-response relationships. Explore maximum doses in longer studies. Fully assess time course of effect. Population pharmacokinetics to interpret outliers.

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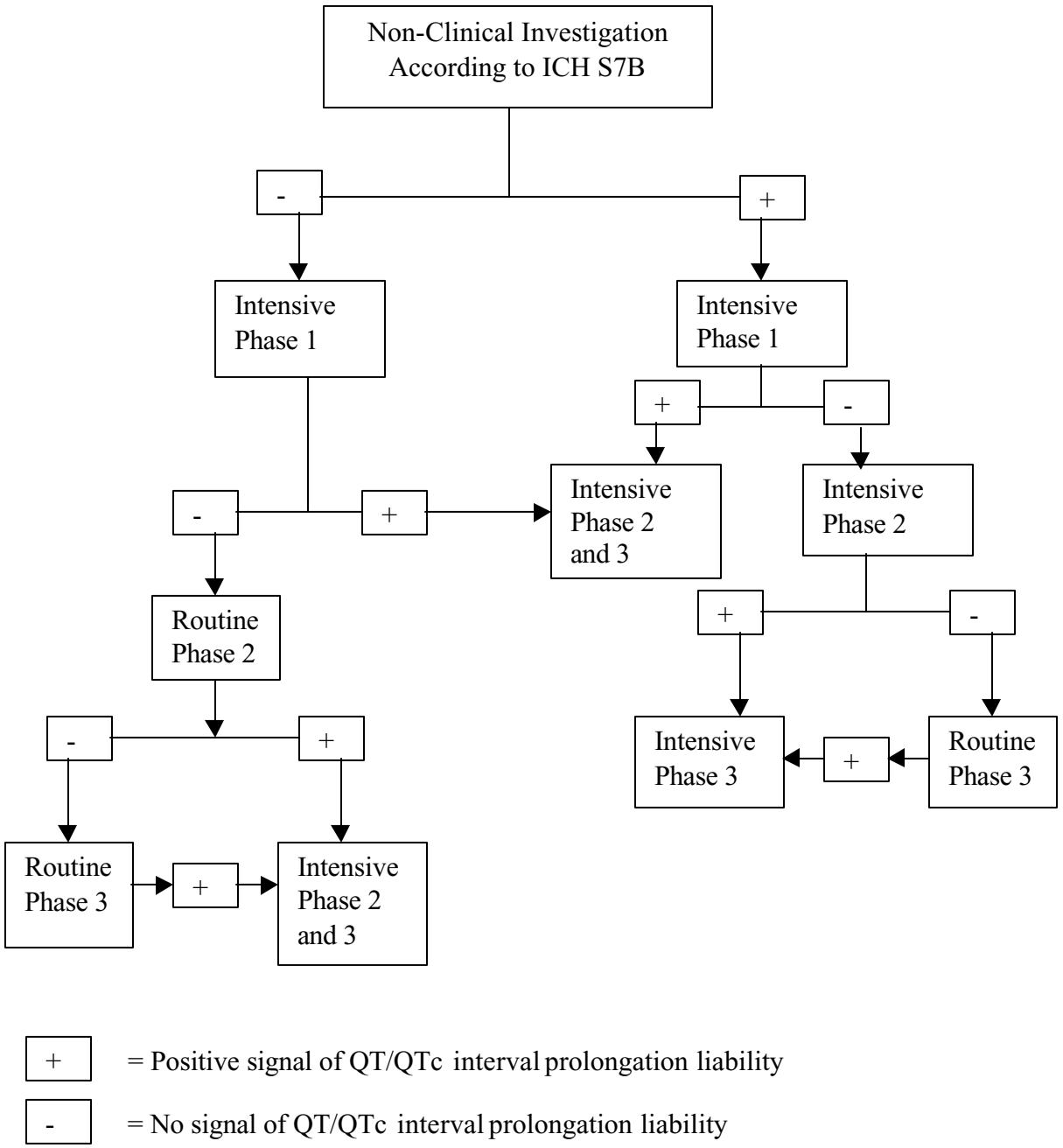

If there is no evidence of QT/QTc interval prolongation liability in non-clinical studies or the phase 1 clinical trials, a routine phase 2 evaluation of ECG safety may be performed, with baseline and periodic on-therapy ECG recordings throughout the treatment phase, the latter performed at time points anticipated to coincide with the C_{max}. If treatment-emergent QT/QTc interval prolongation is observed in these routine phase 2 studies, an intensive phase 2 ECG evaluation would be necessary with complete assessment of dose-response, concentration-reponse, and time course relationships in a patient population. An intensive phase 3 ECG evaluation would also be warranted.

Evidence of repolarization impairment potential in the non-clinical studies would call for an intensive phase 2 clinical investigation of ECG safety, even in the absence of a QT/QTc interval prolongation effect in phase 1 trials. If the results of both the phase 1 and 2 clinical trials do not provide evidence of QT/QTc interval prolongation, these would supersede the positive non-clinical findings and qualify the drug for a routine ECG safety assessment in the phase 3 clinical trials. If the phase 2 clinical trials have findings consistent with repolarization impairment, then an intensive ECG safety evaluation would be required in the phase 3 clinical trials.

2.2.3 Demographic Considerations

The following patient groups are of particular interest in relation to an agent's effects on the QT/QTc interval:

- Patients with electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia)
- Patients with congestive heart failure
- Phenotypic poor metabolizers, for drugs cleared by CYP 450 enzymes that are subject to genetic polymorphisms
- Females
- Patients aged <16 and over 65 years
- Patients with renal or hepatic impairment, depending on the routes of excretion of the drug

Particular attention should be directed to subset analyses for sex, as female gender is recognized to be a predisposing factor for drug-induced QT/QTc interval prolongation and torsade de pointes. Many cardiac co-morbidities, notably congestive heart failure, are also considered to be risk factors.

All applications should include QT/QTc interval subset analyses for the above population groups, derived from phase 2/3 clinical trials. If sufficient numbers of patients are available, a subset analysis may sufficiently address a drug-population interaction while, in other cases, the analyses may suggest the need for studies specifically designed to explore the influence of the covariate of interest.

2.2.4 Drug-Drug Interactions

If the blood levels of a drug that prolongs the QT/QTc interval can be increased by a drug-drug or drug-food interactions involving metabolizing enzymes (*e.g.*, CYP3A4, CYP2D6) or transporters (*e.g.*, P-glycoprotein), systematic clinical pharmacology studies of these interactions should be

conducted, with ECG recordings performed to coincide with blood sampling for pharmacokinetic determinations. These studies should involve co-administration of the test drug with metabolic inhibitors/inducers and/or inhibitors of the P-glycoprotein transporter and comparison of co-administration with test drug alone. These studies should generally employ maximum doses of the enzyme- or transport-altering drug and have a sufficient duration to allow the test drug to achieve steady-state levels, unless such dosing practices are expected to result in QT/QTc interval prolongation of a magnitude that would endanger the study participants, in which case lower doses and/or single dose administration may be more appropriate.

Population pharmacokinetic-pharmacodynamic analyses may have a useful role in the identification of unsuspected drug-drug interactions leading to cases of marked QT/QTc interval prolongation in the pivotal clinical trials.

2.2.5 Eligibility and Discontinuation Criteria

If QT/QTc interval prolongation is anticipated on the basis of non-clinical studies or preliminary clinical trial data, the following exclusion criteria should be used for early clinical trials, especially those enrolling healthy volunteers:

- A marked baseline prolongation of QT/QTc interval (see below).
- A history of additional risk factors for torsade de pointes (*e.g.*, heart failure, hypokalemia).
- The use of concomitant medications that prolong the QT/QTc interval.

A commonly-used definition of baseline prolongation of the QT/QTc interval is repeated demonstration of a QT/QTc interval of >450 msec on a baseline ECG. If supported by the QT/QTc interval safety data from the early studies, later clinical trials should expand the eligibility criteria to include a fuller spectrum of patients who are likely to receive the drug once approved. Depending on the population, this could include patients with prolonged QT/QTc intervals at baseline or additional risk factors for arrhythmia.

If a clinical trial subject experiences a significant, treatment-emergent increase in the QT/QTc interval, procedures for more intensive cardiac monitoring of that individual should be implemented immediately; these should be considered before the trial and specified in the clinical trial protocol. In the event of overdosage with a QT/QTc interval-prolonging drug, ECG monitoring is recommended until plasma concentrations of the drug have declined to the therapeutic range and the QT/QTc interval has returned to normal. Discontinuation of a subject from a clinical trial should be considered if there is a prolongation of the QT/QTc interval during treatment with the study drug. While an increase in QT/QTc to >500 msec or an increase of >60 msec 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.

2.3 Assessment and Submission of Electrocardiographic Data

2.3.1 Standard 12-Lead Electrocardiograms (ECGs)

The clinical ECG database should be derived primarily from the collection of standard 12-lead ECGs. The ECG should be recorded and stored as a digital signal, but the assessment of intervals and the overall interpretation may be made from the digital record or from a printed record.

If the analysis will be based on a paper record and the resolution for QT/QTc interval verification is within the desired range of <5.0 msec, a paper speed of 25 mm/sec is preferred, as higher speeds (*e.g.* 50 mm/sec) may lead to distortion of low amplitude waves such as U waves.

The QT/QTc interval should be determined as a mean value derived from at least 3-5 cardiac cycles (heart beats). Historically, lead II has been preferred for QT/QTc interval measurements, as the end of the T wave is usually most clearly discerned in this lead. Restricting measurements to a single lead may, however, limit sensitivity, as the lead with the longest QT/QTc interval may vary. The multi-channel recorder is an evolving technology, providing an alternative that enables simultaneous recording of limb and precordial leads and selection of the longest QT/QTc interval in any lead.

While a description of morphological changes in the T-U complex is important, a discrete U wave of small amplitude should be excluded from the QT/QTc interval measurement. If the size of the U wave and the extent of T-U overlap are such that the end of the T wave cannot be determined, inclusion of the U wave in the QT/QTc interval measurement may be necessary and should be discussed with the regulatory authority. Every effort should be made to find a lead that does allow accurate measurement of the QT/QTc by allowing a clear separation of the T wave from the U wave, as the implications of a prolonged QTU complex are not clear.

Pending improvements in automated technologies, the ECG readings should be performed manually. Although automated ECG recorders can be programmed to calculate many ECG intervals (RR, QRS, QT, QTc, and PR) from digital data signals, automated measurements of low amplitude wave forms, such as the P, T, and U waves, can result in inaccurate PR and QT interval measurements. While these automated recordings have a useful role in the rapid assessment of ECGs for safety, manual recalculation of the intervals ("over-read") is needed for the clinical trial database. Inconsistency between manufacturers in terms of the algorithms used for calculation of the intervals is another problem in the interpretation of computerized readings.

Manual ECG readings are performed using visual determinations ("eyeball"/caliper techniques), digitizing methods, and/or on-screen computerized methods. Visual determinations/caliper techniques are considered less accurate than digitizing methods. Some digitizing methods employ a digitizing pad, magnifying lamp, and pointing device to identify the beginning and end of the QT/QTc interval for automatic recording in the ECG database. A more technologically advanced option is to display digitally recorded ECGs on a computer screen, where they can be measured using computer-driven, on-screen calipers. Scanned paper-recorded ECGs can also be subjected to on-screen measurements. For a given trial, the sponsor should describe the accuracy and precision of QT/QTc interval measurements using the selected system.

All ECG readings should be performed by a few designated cardiologists operating from a centralized (core) ECG laboratory who are blinded to time, treatment and patient identity. The generation of multiple databases should be discouraged. Inter-reader variability can be minimized by having one or two cardiologists serve as readers for the entire database. The degree of inter- and intra-reader reliability should be established by having the cardiologist(s) reread a subset of the data under blinded conditions. The participation of cardiology specialists is also valuable for diagnostic evaluation of the ECG recordings. Criteria to assess ECG diagnoses and identify adverse events should be pre-defined by the sponsor. If it proves impractical to have a small number of readers, at a minimum any ECGs that pose reading problems or are above some threshold (*e.g.*, 440 msec) should be over-read by a single or small number of readers.

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

2.3.2 Holter Monitoring

Holter monitoring is an ambulatory ECG recording obtained from one (usually) or multiple (up to 12) leads. Although Holter monitoring is not sufficiently well standardized to serve as the primary assessment ECG for QT/QTc interval effects, it has clear potential value. It may, for example, allow detection of extreme QT/QTc interval events that occur infrequently during the day. If a lead with a well-defined T wave can be found, Holter monitoring allows measurement of the QT/QTc interval over an extended period (up to 72 h) so that the effects of diurnal fluctuation and variations of heart rate during exercise and rest can be explored. QT/RR data from Holter monitoring can be used in the calculation of individualized QT corrections. However, as QT/QTc intervals measured by Holter methodology do not correspond quantitatively to those for standard ECGs, data obtained from the two methodologies are not suitable for direct comparison or pooling.

2.3.3 Submission of Interval Data and Overall Assessments

In general, intervals and overall interpretations of all ECGs recorded throughout the drug development program should be submitted as part of the full study reports. For guidance on the submission of ECG interval data and overall assessments, see "Regulatory Submissions in Electronic Format; General Considerations."

2.3.4 Submission of Annotated Waveform Data

For the purpose of validating assessments of ECG intervals and overall interpretations, it is necessary to review the placement of fiduciary marks on the ECG waveform. A standard format for the submission of annotated ECG waveforms is being developed in cooperation with the HL7 standards organization. When such a standard is available, annotated ECG waveform data may be submitted to supplement ECG interval and overall assessment datasets for any study, according to

applicable guidance. However, it will be critical to have annotated ECG waveform data for those studies intended to definitively address the effects of a drug on ventricular repolarization.

3.0 ANALYSIS OF ECG DATA FROM CLINICAL TRIALS

Evaluation of a drug's effects on the standard ECG intervals and waveforms is a standard part of the required safety database, and the results of these analyses should be submitted in support of any new drug application.

As is true for most safety analyses, it is generally useful to integrate QT/QTc interval findings from all studies and, in some cases, to pool study results. Critical considerations include the adequacy of the size of the safety database (the total number of patients receiving ECG recordings and the number of patients at each dosage receiving ECG recordings) and the estimates of QT/QTc interval effects based on pooled data (*i.e.*, estimates of mean effect size and the incidence of clinically noteworthy changes). Analyses of pooled ECG data from several clinical trials may increase the ability to detect a drug effect; the clinical trials used in the generation of such analyses should be clearly identified, however, and their inclusion justified. The data from certain trials may be inappropriate for pooling, if the study conditions under which they were collected were not representative of the proposed clinical use. For example, if the pooling results in inclusion of data from many patients receiving sub-therapeutic doses of the drug, the calculated means and incidence values may underestimate the magnitude and frequency of the QT/QTc interval prolonging effect at the recommended doses.

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.

Bazett's correction (exponential square root)

$$QTc = \frac{QT}{RR^{1/2}}$$

Fridericia's correction (exponential cube root)

$$QTc = \frac{QT}{RR^{1/3}}$$

Bazett's formula has been more frequently used in the medical literature than Fridericia's formula, so that most reported criteria for normal and abnormal values are derived from Bazett's formula[1]:

[1] Moss AJ. The QT interval and torsade de pointes. *Drug Safety* 1999; 21(1):5-10.

Rating	Adult Male (msec)	Adult Female (msec)
Normal	<430	<450
Borderline	430-450	450-470
Prolonged	>450	>470

Bazett's correction, however, overcorrects at elevated heart rates and undercorrects at rates below 60 bpm. Fridericia's formula may therefore be more accurate in subjects with extreme heart rate values.

Correction formulae based on linear regression techniques have also been proposed. In such a method, one would fit a linear model of QT = a + b x RR to the placebo/unexposed (baseline) study population. Using this estimated slope "b," one could standardize the data for both drug and control treatment groups to a normalized heart rate of 60 bpm using the following equation: observed QT(in msec) + [slope ((1-RR)] = standardized QT. The Framingham formula, [QTc= QT + 0.154(1-RR)] is one example of a correction formula derived by linear regression.

Linear or non-linear regression modeling has also been used to analyze pooled data from large databases to derive population-based heart rate corrections.

Finally, heart rate corrections using individual patient data have been proposed, applying regression analysis techniques to obtain individual pre-therapy QT/RR interval data over a range of heart rates, then looking for a change in regression line with treatment[2]. This approach is most suitable for phase 1 and early phase 2 studies of crossover design, where it is possible to obtain many QT interval measurements for each study subject. As adaptation of the QT/QTc interval to changes in heart rate is not instantaneous, care should be taken to exclude ECG recordings collected during times of heart rate instability (*e.g.*, during exercise protocols) due to this QT/RR hysteresis effect.

As the optimal correction approach is a subject of controversy, uncorrected QT interval data, along with QT interval data corrected using Bazett's and Fridericia's corrections, should be submitted in all applications, as should corrected QT intervals using less standard corrections. Concurrent active control groups are strongly encouraged to support the use of novel correction approaches (*e.g.*, individual patient correction, Holter-based correction) in order to demonstrate the ability of the correction method to allow detection of relevant effects on the QT/QTc interval. The sponsor should attempt to explain any discrepancy between the results obtained by application of different correction formulae.

[2] Malik M, Camm AJ. Evaluation of drug-induced QT interval prolongation. *Drug Safety* 2001; 25(5):323-351.

3.2 Analysis of QT/QTc Interval Data

Data on QT/QTc intervals should always be presented both as analyses of central tendency (means, medians, ranges, etc.) and categorical analyses (proportion of individual subjects in each treatment group experiencing specified degrees of abnormality *i.e.* outlier analyses). As the QT/QTc interval is subject to considerable inter- and intra-individual variation, non-comparative data are very difficult to interpret.

3.2.1 Analyses of Central Tendency

For analyses of central tendency, the effect of an investigational drug on the QT/QTc interval can be characterized in a number of ways, including the following:

- **Maximum Change in the QT/QTc Interval:** The maximum observed difference between on-treatment and baseline QT/QTc values should be expressed both as mean and median changes in the population. This value is meaningful only as a comparison with placebo or a non-QT prolonging drug, as selection of the highest of many on-treatment values will invariably show an increase from baseline.

- **Time-matched QT/QTc Intervals:** Mean changes from baseline in the observed QT/QTc interval can be presented as time-matched control and treatment group values (e.g. hourly, weekly, monthly, etc.). Although these values may show regression to the mean, they do not have the same upward bias as the maximum change.

- **Time-averaged QT/QTc Intervals:** The mean time-averaged change from baseline in the QT/QTc interval (mean based on averages of all on-therapy QT/QTc changes for each individual) is acceptable only as an auxiliary to more commonly used analyses. Time-averaging of changes in the QT/QTc intervals ignores the possible influence of concentration-effect relationships and circadian variations on intra-subject variation and thus has a tendency to underestimate the magnitude of a drug effect.

- **Area Under the QT/QTc Interval Time Curve (QT/QTc AUC):** Use of the QT/QTc AUC as the dependent variable requires the collection of multiple data points for each subject during the placebo and treatment phases. Experience with this approach is limited and interpretation is complicated by the lack of well recognized criteria for distinguishing clinically relevant changes. For the purpose of drug submissions, summary statistics based on QT/QTc AUC computations should be used only as an auxiliary to more established data analyses.

As the absence of statistically or clinically significant differences between the test drug and comparator groups does not preclude the possibility of marked QT/QTc interval prolongation occurring in individual subjects, analyses of central tendency should always be accompanied by appropriate categorical analyses.

3.2.2 Categorical Analyses

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

Although increases from baseline in the QT/QTc interval constitute signals of interest, interpretation of these differences is complicated by the potential for changes not related to drug therapy, including regression toward the mean and choice of extreme values. Regression toward the mean refers to the tendency of subjects with high baseline values to have lower values at later time points, while subjects with low baseline values tend to experience increases. The direction of regression depends on initial selection criteria; *e.g.*, if subjects with high baseline QT/QTc interval values are excluded from the trial, values recorded during treatment will tend to rise relative to baseline levels. The process of choosing the highest of multiple observed values will also invariably cause an apparent change from any single baseline value, a phenomenon found in both drug and placebo-treated groups. The protection against spurious findings is comparison with the results in the appropriate control group(s), including placebo or a drug with no QT/QTc prolongation effect. A better option may be to compare multiple baseline values with multiple, time-matched on-treatment values, not just the greatest value. This may still show regression to the mean but will not have the upward bias of selecting only extreme values. The on-treatment values could be only those recorded at peak blood levels or other specified times.

Consensus within the scientific community concerning the choice of upper limit values for absolute interval signals and change from baseline signals does not exist. While lower limits increase the false-positive rate, higher limits increase the risk of failing to detect a signal. Multiple analyses using different signal values are a reasonable approach to this controversy:

- Absolute QT/QTc interval signals of interest include the following:
  - QT/QTc ≥450 msec.
  - QT/QTc ≥480 msec.
  - QT/QTc ≥500 msec.
- Change from baseline signals of interest include the following:
  - QT/QTc interval increases from baseline ≥30 msec.
  - QT/QTc interval increases from baseline ≥60 msec.

An increase over control group values in the proportion of subjects experiencing abnormal QT/QTc interval values should be considered a cause for concern, regardless of whether statistically significant differences are present for group mean values. It is possible that treatment

groups could show similar changes in the mean QT/QTc interval, but differ in their ability to promote extreme outliers.

3.2.3 QT/QTc Interval Dispersion

QT/QTc interval dispersion, defined as the difference between the shortest and the longest QT/QTc interval measured on the 12-lead ECG, has been thought to reflect the regional heterogeneity of cardiac repolarization. Normal values are typically in the range of 40-60 msec. Absolute values of ≥100 msec and changes from baseline of >100% have been suggested as clinically noteworthy signals for categorical analyses. The value of assessment of QT/QTc interval dispersion as a measure of proarrhythmic risk of a drug is, however, the subject of debate, as the predictive value of this parameter has yet to be demonstrated. Analyses of QT/QTc dispersion should therefore be used, if at all, to supplement, not to replace, more standard analyses of QT/QTc interval duration.

3.3 Morphological Analyses of ECG Waveforms

While the predictive value of changes in ECG morphology, such as the development of U waves, has not been established, morphological abnormalities should be described and the data presented in terms of the number and percentage of patients in each treatment group having changes from baseline that represent the appearance or worsening of the morphological abnormality.

Attention should be directed to changes in T wave morphology and the occurrence of abnormal U waves as these phenomena may predict torsade de pointes. Similarly, T wave alternans (beat-to-beat variability in the amplitude and/or morphology of the T wave) may be associated with an increased likelihood of ventricular tachyarrhythmias. Other T wave abnormalities that can indicate delayed repolarization include double humps ("notched" T wave), wide bases, indistinct terminations (TU complex), delayed inscription (prolonged isoelectric ST segment), and sinusoidal oscillations.

Principal component analysis is a quantitative approach to assessing increased complexity of the T wave[3]. The roundness of the T loop is quantified by dividing the principal components of its width and length. As experience with this form of analysis is limited, it should be used, if at all, to supplement, not replace, standard analyses of T wave morphology.

[3] Moss AJ, Zareba W, Benhorin J. *et al.* ISHNE guidelines for electrocardiographic evaluation of drug-related QT prolongation and other alterations in ventricular repolarization: Task force summary. *Ann. Noninvas. Electrocardiol.* 2001;6(4):334-341.

3.4 Statistical Considerations

QT/QTc interval data should be presented in terms of means, standard deviations, ranges, and confidence intervals. Clinical trials that investigate the QT/QTc interval prolongation potential of a drug should have sufficient power (*i.e.*, ≥80%) to detect modest mean differences between treatment groups (*e.g.*, 4-5 msec). The power calculation should take into account the expected precision of the QT/QTc interval measurement. The actual precision should be experimentally verified in each study. The most direct way to accomplish this is through the inclusion of a concomitant positive control in the trial design.

4.0 ADVERSE EXPERIENCES

There are three categories of clinical adverse events that are of interest in assessing a drug's potential for proarrhythmia:

- Adverse experiences reported during clinical studies.
- Premature discontinuations and dosage adjustments during clinical studies.
- Post-marketing adverse experience reports.

4.1 Clinical Trial Adverse Experience Reports

Although drug-induced prolongation of the QT/QTc interval is usually asymptomatic, an increased rate of certain adverse events in patients taking an investigational agent can signal potential proarrhythmic effects. The rates of the following clinical events should be compared in the treated and control patients as a part of a product's submission for marketing, particularly when there is evidence that a drug affects the QT/QTc interval.

- Torsade de pointes.
- Ventricular tachycardia.
- Ventricular arrhythmia.
- Ventricular ectopy.
- Ventricular fibrillation and flutter.
- Cardiac arrest.
- Sudden death.
- Syncope.
- Dizziness.
- Palpitations.
- Seizures (a possible consequence of cerebral ischemia resulting from arrhythmia).

The occurrence of torsade de pointes is captured infrequently in most clinical databases, even those for drugs known to have significant proarrhythmic effects (*e.g.*, dofetilide). Given this, the failure to observe an episode of torsade de pointes in a drug application database is not sufficient grounds for dismissing the possible arrhythmogenic risks of a drug when these are suspected on the basis of ECG and other clinical data. The other adverse events listed, while less specific for an

effect on cardiac repolarization, are more commonly captured in clinical trials, and an imbalance in their occurrence between study groups may signal a potential proarrhythmic effect of the investigational agent. Comparing cause-specific rates of death is difficult, but a difference in the fraction of total deaths qualifying as "sudden" has also been proposed as a marker for possible proarrhythmic potential.

Detailed patient narratives should be provided for all serious cardiac adverse events, as would be the case for any serious event or events leading to discontinuation. In assessing the possible causal relationship of drug-induced QT/QTc interval prolongation to the event, attention should be directed to considerations such as temporal relationship and ECG results collected at the time of the event. As the QT/QTc interval is subject to considerable fluctuation, a possible role for QT/QT interval prolongation cannot be dismissed on the basis of normal on-therapy ECG measurements performed prior to near the time of the adverse event. For adverse events that appear to be dose-related, potential relationships to patient age, gender, pre-existing cardiac disease, electrolyte disturbances, concomitant medications, and the other risk factors listed in section 5.2 should be explored. In addition to an appropriate adverse reaction report, patients with marked QT/QTc prolongation or an episode of torsade de pointes may provide useful information on risk management. When identified, they should therefore be examined closely for other risk factors, including genetic predisposition (see section 4.3). When conducted in a well-monitored environment starting at low doses, exploring the dose and concentration-responses of the drug in these individuals could also prove useful.

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

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

4.2 Premature Discontinuations or Dosage Reductions

Particular attention should be directed to subjects or patients who discontinue clinical trials due to QT/QTc interval prolongation. Information should be provided on the basis for premature termination of the patient (*e.g.*, a QT/QTc interval value in excess of a protocol-defined upper limit, occurrence of QT/QTc interval prolongation in association with symptoms of arrhythmia), as well as the dose and duration of treatment, plasma levels if available, demographic characteristics, and the presence or absence of the other risk factors listed in section 5.2.

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

4.3 Pharmacogenetic Considerations

Many forms of congenital long QT syndrome (LQTS) are now known to be linked to mutations in genes encoding cardiac ion channel proteins. As these disorders are thought to be risk factors for an exaggerated response to QT/QTc interval prolonging drugs, genotyping should be considered for subjects who experience marked QT/QTc interval prolongation or symptoms of arrhythmia in clinical trials. To date, mutations in the following genes have been implicated in congenital long QT syndrome:

Gene	Long QT Syndromes
KCNQ1	LQT1
HERG	LQT2
SCN5A	LQT3
KCNE1	LQT5
KCNE2	LQT6
KCNJ2	LQT7

Because of incomplete penetrance, not all carriers of mutated ion channel genes will manifest QT/QTc interval prolongation in screening ECG evaluations. In addition to mutations, common polymorphisms may result in ion channels that have increased sensitivity to drug-induced effects.

4.4 Post-Marketing Adverse Experience Reports

Owing to their rarity (except with type III anti-arrhythmics), serious ventricular arrhythmias and sudden cardiac death together with evidence of QT/QTc interval prolongation are often not reported until large populations of patients have received the agent in post-marketing settings. If the drug is licensed for sale in other countries, the post-marketing adverse experience data should be examined for evidence of QT/QTc interval prolongation and TdP and for adverse experiences possibly related to QT/QTc interval prolongation, such as cardiac arrest, sudden cardiac death, and ventricular arrhythmias (*e.g.* ventricular tachycardia and ventricular fibrillation). These events are probably of greater significance if seen in a population at low risk (*e.g.*, young women). A well-characterized episode of TdP, in contrast, creates a high probability of a relationship to drug use.

5.0 REGULATORY IMPLICATIONS, LABELING, AND RISK MANAGEMENT STRATEGIES

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

Substantial prolongation of the QT/QTc interval, with or without documented arrhythmias, may be the basis for non-approval of a drug or discontinuation of its clinical development, particularly when the drug has no clear advantage over available therapy and available therapy appears to meet the needs of most patients. Failure to perform an adequate non-clinical and clinical

assessment of the potential QT/QTc interval prolonging properties of a drug may likewise be justification to delay or deny marketing authorization.

Special considerations apply to anti-arrhythmic drugs that utilize delayed repolarization as part of their mechanisms, but in this case, it will be critical to provide outcome data to quantify risk. Whether such a drug could be approved would depend on the nature of its benefit, the size of its effect on the QT/QTc interval, and the potential for managing or reducing risk by dose limitation, monitoring, or other approaches.

For non-antiarrhythmic drugs, the outcome of the risk benefit assessment will be influenced by the size of the QT/QTc interval prolongation effect, whether the effect occurs in most patients or only in certain defined outliers, the overall benefit of the drug, and the utility and feasibility of risk management options. The inclusion of precautionary material in the prescribing information will not necessarily represent an adequate risk management strategy, if implementation of the recommendations in a clinical use setting is judged to be unlikely.

If QT/QTc interval prolongation is a feature shared by other drugs of the therapeutic class in question, evaluation of the new drug will involve a comparison of the magnitude and incidence of any QT/QTc interval prolongation effects relative to those of other members of its class in concurrent active control groups. An excess risk for the new drug relative to approved therapies would, other things being equal, have a negative impact on its risk-benefit assessment.

For drugs that prolong the QT/QTc interval, the mean degree of prolongation has been roughly correlated with the observed risk of clinical proarrhythmic events. Whether there are drugs that cause extreme prolongation (*e.g.*, >500 msec) in a small fraction of patients with only modest mean effects is not clear, but this would seem to be a troublesome property.

It is difficult to determine whether there is an effect on the mean QT/QTc interval that is so small as to be inconsequential, although drugs whose maximum effect is less than 5 msec at high doses and during co-administration of saturating doses of metabolic inhibitors, have not so far been associated with torsade de pointes. Whether this signifies that no increased risk exists for these compounds or simply that the increased risk has been too small to detect is not clear. To date, drugs that prolong the mean QT/QTc interval by 5-10 msec under conditions of maximum effect have also not been clearly associated with risk. Drugs causing a mean 10-20 msec increase under conditions of maximum effect are of concern, but have been approved if they appear to have important therapeutic roles. Drugs that prolong the mean QT/QTc interval by >20 msec have a substantially increased likelihood of being proarrhythmic, and may have clinical arrhythmic events captured during drug development. While it has been suggested that some drugs might prolong the QT/QTc interval up to a "plateau" value, above which there is no dose-dependent increase, this has not been demonstrated adequately to date. As noted, it is critical to identify the "worst case scenario," *i.e.*, the QT/QTc interval measured in the target patient population at the time of peak effect and under conditions of the highest blood levels that can be attained during therapy as a result, *e.g.*, of a drug-drug interaction.

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

QT/QTc interval prolonging drugs having primary metabolic pathways involving enzymes that are subject to genetic polymorphisms (*e.g.*, CYP2D6, CYP2C19) or inhibition by many drugs (CYP3A4) would be regarded with particular concern due to the possibility of markedly elevated plasma levels in those patients who are poor metabolizers or who receive an interacting xenobiotic, unless it has been established that these higher levels do not lead to greater effect on the QT/QTc interval. A susceptibility to drug-drug interactions due to effects on transporter proteins would also have a negative impact on the risk-benefit assessment.

5.2 Labeling Issues for Drugs that Prolong the QT/QTc Interval

If approval is granted to a drug that affects cardiac repolarization to an extent that is considered a clinical concern, sponsors should consider the following prescribing information:

- A warning/precautionary statement about the effects of the drug on cardiac repolarization, appropriate to the risk observed in the development program.
- A clear description of the trials used to obtain QT/QTc interval information, including the numbers and demographics of the patients who received ECG evaluations in clinical trials. Any entry criteria that limited the patient exposure (*e.g.*, excluding the use of antiarrhythmic drugs).
- A description of the effects of the drug on the QT/QTc interval in the relevant patient populations in terms of both the mean change in the QT/QTc interval and the percentage of patients with on-therapy QT/QTc readings in excess of a defined upper limit (*e.g.*, ≥480 msec). Information on the dose-, concentration-, and time-dependency of the QT/QTc interval prolongation effect.
- Where possible, dosage recommendations encouraging the use of the lowest effective dose of the drug and specifying maximum recommended single and total daily doses that should not be exceeded. Restrictions on the size and frequency of incremental dose adjustments. Identification of a time after which the drug should be discontinued if there has not been a satisfactory response. For an intravenously administered QT/QTc interval-prolonging drug, limitations on the injection and/or infusion rates if known.
- A list of the diseases or disorders known to increase the possibility of arrhythmic events. Emphasis should be placed on the need to exercise particular care in patients having these conditions. In some cases, contraindications may be appropriate. Risk factors for drug-induced arrhythmias secondary to QT/QTc interval prolongation include, but are not limited to, the following:

- Congenital long QT interval syndrome (*e.g.* Romano-Ward syndrome, Jervell and Lange-Nielson syndrome, and Andersen syndrome).
- Family history of sudden cardiac death at <50 years.
- Ischemic heart disease or infarction.
- Congestive heart failure.
- Left ventricular hypertrophy.
- Positive history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation).
- Cardiomyopathy.
- Bradycardia.
- Myocarditis.
- Cardiac tumours.
- Valvular heart disease.
- Bundle branch block.
- Sinus node dysfunction.
- Severe hepatic or renal dysfunction, if the drug is excreted renally or hepatically.
- Electrolyte imbalance (*e.g.*, hypokalaemia, hypomagnesaemia, hypocalcaemia, acidosis, intracellular Ca^{2+} loading) or conditions (*e.g.*, chronic vomiting, anorexia nervosa, bulimia nervosa) and drugs (*e.g.*, diuretics) predisposing the patient to electrolyte imbalances .
- Concomitant treatment with other drugs or foods that inhibit the metabolism of the QT/QTc interval prolonging drug.
- Subarachnoid haemorrhage.
- Hypothermia.
- Nutritional deficits (e.g. eating disorders, liquid protein diets).
- Alcoholism.
- Autonomic neuropathy.

- Discouragement (or contraindication of) the concomitant use of two or more QT/QTc interval prolonging drugs. Where available from the clinical trials, information about the concomitant use of such medications. The list of drugs that affect cardiac repolarization and prolong the QT/QTc interval (it would be lengthy and change as new information becomes available). Examples of such agents include, but are not limited to, the following:

  - Class IA antiarrhythmics (*e.g.*, quinidine, procainamide, disopyramide).
  - Class III antiarrhythmics (*e.g.*, amiodarone, dofetilide, sotalol, ibutilide).
  - Tricyclic antidepressants (*e.g.*, amitripyline, imipramine, doxepin, nortriptyline, desipramine).
  - Bepridil.
  - Certain phenothiazine antipsychotics (*e.g.*, thioridazine, mesoridazine, chlorpromazine).
  - Pimozide.
  - Maprotiline.
  - Macrolide antibiotics (*e.g.*, erythromycin, clarithromycin).
  - Certain fluoroquinolone antibiotics (*e.g.*, moxifloxacin, gatifloxacin).

- Pentamidine.
- Antimalarials (*e.g.*, halofantrine, quinine, chloroquine, mefloquine).
- Probucol.
- Droperidol.
- Dolasetron.
- Tamoxifen.
- Tacrolimus (intravenous).
- levo-alpha-acetylmethadol (LAAM).
- Arsenic trioxide.

- Recommendations for screening ECGs, depending on the information available from the clinical trials. In general, a drug that prolongs the QT/QTc interval should not be initiated in patients with abnormally long baseline QT/QTc intervals. Monitoring of the QT/QTc interval during treatment may also be advisable, particularly during the initial stages of treatment, after a dosage increase, or for drugs administered intravenously. Discontinuation of the drug should be considered if an arrhythmic event occurs or if the QT/QTc interval becomes markedly prolonged.
- Warning that serum potassium, calcium, and magnesium levels should be measured prior to initiation of treatment with a QT/QTc interval prolonging drug. Treatment should not be initiated in any patient with uncorrected electrolyte abnormalities. Serum electrolyte levels should be monitored during treatment, with prompt correction and/or discontinuation of the QT/QTc interval-prolonging drug in the event of an electrolyte abnormality.
- Recommendations to physicians who prescribe a drug that prolongs the QT/QTc interval to counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that may represent risk factors, demonstrated and predicted drug-drug interactions, symptoms of possible arrhythmia, and other information relevant to the use of the drug.
- Information for the consumer that explains in lay language the effect of the drug on the electrical activity of the heart and the relationship between this ECG effect and the theoretical or demonstrated risk of arrhythmias and sudden death. Any risk management strategies recommended for a given drug. An alert to patients about the symptoms of possible arrhythmia such as dizziness, palpitations, and fainting and instructions to seek immediate medical attention if these occur.

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

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