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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

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/QTc 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 QTc interval. The QTc interval is intended to represent the QT interval at a standardized heart rate of 60 bpm. 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. 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 (hereafter called QT/QTc). The combination of QT/QTc 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/QTc 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/QTc 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/QTc interval as well as the collection of cardiovascular adverse events. 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 use.

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

1.3 Scope

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

2.0 CLINICAL TRIALS

2.1 Design Considerations

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

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

- A negative ‘thorough QT/QTc study’, even in the presence of non-clinical data of concern, will almost alwaysallow the collection of on-therapy ECGs in accordance 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.

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

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

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

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

[1] Comment is requested on the choice of the 5 ms as a threshold for clinical and regulatory concern.

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

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

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

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

Parallel group studies might be preferred under certain circumstances:

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

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

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

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

[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'.

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

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

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

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

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

2.2 Collection, Assessment and Submission of Electrocardiographic Data

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

2.2.1 Collection of Standard 12-Lead Electrocardiograms (ECGs)

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

2.2.2 Assessment of Standard 12-Lead ECGs

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

The quality of the ECG database can 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.

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

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

2.2.3 Ambulatory ECG Monitoring

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

2.2.4 Submission of Interval and Waveform Data

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

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.

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

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

3.1.2 Correction Formulae Derived from Within-Subject Data

Corrections for heart rate using individual subject data have been developed, applying regression analysis techniques to individual pre-therapy QT and RR interval data over a range of heart rates, then applying this correction to on-treatment QT values. These approaches are considered most suitable for the 'thorough QT/QTc study' and early clinical studies, 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 rapid heart rate changes due to this QT/RR hysteresis effect.

3.2 Analysis of QT/QTc Interval Data

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 (for example, 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 almost invariably cause an apparent change from any single baseline value, a phenomenon found in both drug and placebo-treated groups.

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

3.2.1 Analyses of Central Tendency

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

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 might 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.

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

- Absolute QTc interval prolongation:
    - QTc interval > 450
    - QTc interval > 480
    - QTc interval > 500
- Change from baseline in QTc interval:
    - QTc interval increases from baseline ≥30
    - QTc interval increases from baseline ≥60

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 ms. Absolute values of ≥100 ms 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, and 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 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 subjects in each treatment group having changes from baseline that represent the appearance or worsening of the morphological abnormality. Typically these data will be obtained as a part of the ‘thorough QT/QTc study’.

4.0 ADVERSE EVENTS

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

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

4.1 Clinical Trial Adverse Events

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, particularly when there is evidence of an effect on the QT/QTc interval:

- Torsade de pointes*;*
- Sudden death;
- Ventricular tachycardia;
- Ventricular fibrillation and flutter;
- Syncope;
- Dizziness;
- Seizures.

Torsade de pointes (TdP) is infrequently captured in most clinical databases, even those for drugs known to have significant proarrhythmic effects. Given this, the failure to observe an episode of TdP in a drug application database is not considered 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 above, while less specific for an effect on cardiac repolarization, are more commonly captured in clinical trials, and an imbalance in their frequency between study groups can signal a potential proarrhythmic effect of the investigational agent. Sub-group analyses should be conducted in terms of age, gender, pre-existing cardiac disease, electrolyte disturbances, and concomitant medications. 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 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/QTc interval prolongation should not be dismissed on the basis of normal on-therapy ECG measurements performed prior to, or near the time of the adverse event. In addition to an appropriate adverse reaction report, patients with marked QT/QTc prolongation or an episode of TdP might provide useful information on risk management. When identified, they should therefore be examined closely for other risk factors (*e.g.*, genetic predisposition, see section 4.3). Rechallenge with the investigational drug under appropriately monitored conditions can provide useful information on dose- and concentration-response relationships.

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 might 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 evaluation by a cardiac specialist is recommended, both for the 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 are discontinued from clinical trials due to QT/QTc interval prolongation. Information should be provided on the basis for premature discontinuation 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 risk factors for arrhythmia.

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

4.3 Pharmacogenetic Considerations

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

4.4 Post-Marketing Adverse Event Reports

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

5.0 REGULATORY IMPLICATIONS, LABELLING, 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, could 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 can likewise be justification to delay or deny marketing authorization. For non-antiarrhythmic drugs, the outcome of the risk benefit assessment will generally 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 be considered 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 could usefully 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 positive control groups.

It is difficult to determine whether there is an effect on the mean QT/QTc interval that is so small as to be inconsequential, but the risk of arrhythmias appears to increase with the extent of QT/QTc prolongation. Drugs that prolong the mean QT/QTc interval by around 5 ms or less do not appear to cause TdP. 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. The data on drugs that prolong the mean QT/QTc interval by more than around 5 and less than 20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk. Drugs that prolong the mean QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic, and might have clinical arrhythmic events captured during drug development.[3]

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, or have a labeled contraindication to, 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.

[3] Comment is requested on the risk categorization described in this paragraph.

Some factors have been proposed that can modify the risk of QT/QTc prolongation. For instance, 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, although this has not been demonstrated adequately to date. It has also been suggested that proarrhythmic risk might be influenced by other pharmacologic effects (*e.g.*, other channel effects). In any case, it is important to identify the "worst case scenario" for drugs that have demonstrated effects on QT/QTc interval as a part of risk assessment (*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).

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

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

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

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 TdP 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.