

# Briefing Document

## Assessment of the QT Prolongation Potential of the Phosphodiesterase-5 Inhibitor Vardenafil

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## 1. Abbreviations

ANCOVA	analysis of covariance
bpm	beats per minute
CI	confidence interval
C <sub>max</sub>	maximum concentration
CYP	cytochrome P450
EC <sub>50</sub>	concentration producing 50% effect
ECG	electrocardiogram
ED	erectile dysfunction
E <sub>max</sub>	maximum effect
FDA	Food and Drug Administration
hERG	human ether-à-go-go-related gene
HR	heart rate
HPLC	high performance liquid chromatography
IIEF	International Index of Erectile Function
I <sub>kr</sub>	inhibition of the rapidly-activating delayed rectifier potassium current
IC <sub>50</sub>	concentration required for 50% inhibition
LLQ	lower limits of quantification
MiRP	MinK-related peptides
MTD	maximum tolerated dose
NDA	New Drug Application
PDE5	phosphodiesterase type 5
PVC	premature ventricular complexes
QT	QT interval of the cardiac cycle
QTc	corrected QT interval
QTcF	Fridericia's corrected QT interval
QTcB	Bazett's corrected QT interval
QTci	individual-based corrected QT interval
SD	standard deviation
TdP	Torsades de Pointes
T <sub>max</sub>	time to maximum concentration

## 2. Introduction and Organization of the Document

This briefing document on vardenafil has been prepared in relation to the May 29, 2003 meeting of the FDA Cardiovascular and Renal Drugs Advisory Committee convened to discuss QT prolongation. During this Advisory Committee meeting, the discussion is scheduled to focus on:

- clinical trial designs for the assessment of QT prolongation
- approaches to the correction of the QT interval for drugs that affect heart rate (HR)
- the risk of cardiac arrhythmia associated with different degrees of QT prolongation

In recent years there have been a number of reports of drug-induced Torsades de Pointes (TdP) in the market place leading to drug withdrawal. These cases sometimes resulted from unanticipated excess drug exposure and/or misuse in the "real world" setting. As a result of these events, there has been increasingly intense focus on more sensitive, accurate and precise methodologies to detect and evaluate QT interval prolongation of small magnitudes and to provide better assurance of the safety of new drugs with respect to cardiac repolarization effects prior to licensure.

In order to address the questions being posed by FDA concerning optimal study design and data interpretation, this document outlines the generic considerations and those specific to our drug candidate vardenafil in the design, analysis, and interpretation of an optimal intensive QT study.

Vardenafil HCl (LEVITRA<sup>®</sup>) is a potent and selective PDE5 inhibitor that is under review by the FDA as an oral therapy for the treatment of male erectile dysfunction (ED).

To document the effect of vardenafil on cardiac repolarization, Bayer studied the effects of vardenafil on the activity of human ether-à-go-go-related gene (hERG) channels of transfected cells and explored cardiac repolarization in dogs. Furthermore, electrocardiogram (ECG) parameters were assessed in healthy volunteers in standard Phase I studies and patients exposed to vardenafil during a comprehensive Phase II-III clinical development program that included over 5,000 patients.

On 24 Sep 2001 Bayer submitted a new drug application (NDA) that led to an approvable letter dated 23 July 2002. In the approvable letter, the FDA requested additional clinical pharmacology studies. One study was designed to describe the effect of vardenafil on the QT interval under normal dosing and also following suprathreshold drug exposure, encompassing potent metabolic inhibition. This study, a randomized, double-blind, placebo-controlled trial to evaluate the effect of a range of single oral doses of vardenafil on cardiac repolarization has been completed. In discussions with the FDA concerning study design, it was agreed to use vardenafil 10 and 80 mg to cover therapeutic and suprathreshold concentrations of vardenafil. The suprathreshold dose was selected to ensure coverage for a maximum potential exposure to vardenafil that might occur during potent metabolic inhibition (e.g., during concurrent therapy with CYP 3A4 inhibitor, ritonavir). It was also agreed that the study design would include a control (sildenafil) belonging to the same therapeutic class (PDE5 inhibitors), and a well-studied positive control (the fluoroquinolone, moxifloxacin) at a dose previously shown to produce a 5-10 msec effect on QTc duration as a means of providing assay sensitivity.

The present document comprises the following sections:

- a. Brief overview of the efficacy and safety profile of vardenafil.
- b. General consequences of QT prolongation and TdP.
- c. Review of guidances and concepts on the assessment of the QT prolongation potential of non-antiarrhythmic drugs.
- d. Presentation of the effects of vardenafil on cardiac repolarization in:
  - Preclinical studies
  - Initial clinical pharmacology studies
  - Definitive QT study

e. Discussion

f. Conclusions

### **3. Brief Overview of the Efficacy and Safety Profile of Vardenafil**

Bayer selected vardenafil for development because of its in vitro potency and selectivity for PDE5 inhibition, and its favorable toxicity profile in pre-clinical studies. Presently, vardenafil is approved in more than 26 countries including the European Union, Australia, New Zealand and several Latin American countries.

The clinical development program of vardenafil studied doses from 2.5 mg to 120 mg and the Phase III program focused on the three dose strengths of 5 mg, 10 mg and 20 mg. Thirty-two single and multiple dose Phase I studies, three Phase IIa pharmacodynamic studies (analyses of penile rigidity by RigiScan<sup>®</sup> methodology in patients with erectile dysfunction), one Phase IIb study, and eight Phase III studies were conducted in more than 5,700 subjects and patients.

The proposed prescribing information for vardenafil recommends a starting dose of 10 mg, taken as needed with a maximum recommended dosing frequency of once per day. The dose may be increased to a maximum recommended dose of 20 mg or decreased to 5 mg based on efficacy and tolerability.

#### **Efficacy**

In the Phase III clinical development program, vardenafil doses of 5 mg, 10 mg, and 20 mg were always statistically significantly better than placebo on the three primary efficacy variables (improvement in the International Index of Erectile Function (IIEF) Erectile Function Domain score and diary questions regarding improved rates of achieving an erection sufficient for penetration and the overall rate of maintenance of erection to successful intercourse). The drug was shown to be effective in the general ED population as well as in special ED populations (e.g., patients with diabetes mellitus and patients with a history of prostatectomy).

Overall, vardenafil was effective in all subgroups, regardless of age, race, severity, duration or etiology of ED, presence of diabetes mellitus, history of prostatectomy, or other comorbid conditions, and concomitant use of antihypertensive or antidepressant medications. The efficacy of all three vardenafil doses evaluated in the vardenafil Phase III clinical program was shown to be consistent, sustained, and reproducible over time in studies up to 12 months in duration.

## Safety

The adverse events that were more common on vardenafil than on placebo and having an incidence  $\geq 2\%$  in vardenafil patients are shown in Table 3-1.

**Table 3-1: Adverse Events Reported By  $\geq 2\%$  of Patients Treated with Vardenafil and More Frequent on Drug than Placebo in Fixed and Flexible Dose Phase III Trials Of 5 mg, 10 mg, or 20 mg Vardenafil**

Adverse Event	Percentage of Patients Reporting Event	
	Placebo n = 1199	Vardenafil n = 2203
Headache	4%	15%
Flushing	1%	11%
Rhinitis	3%	9%
Dyspepsia	1%	4%
Accidental Injury	2%	3%
Sinusitis	1%	3%
Flu Syndrome	2%	3%
Dizziness	1%	2%
Increased Creatine Kinase	1%	2%
Nausea	1%	2%

In the placebo-controlled studies, the incidence of treatment-emergent serious adverse events was 2.5% for both the vardenafil and placebo treatment groups. The overall incidence of serious adverse events and the nature of individual adverse events do not suggest a specific risk pattern for developing serious adverse events during vardenafil treatment.

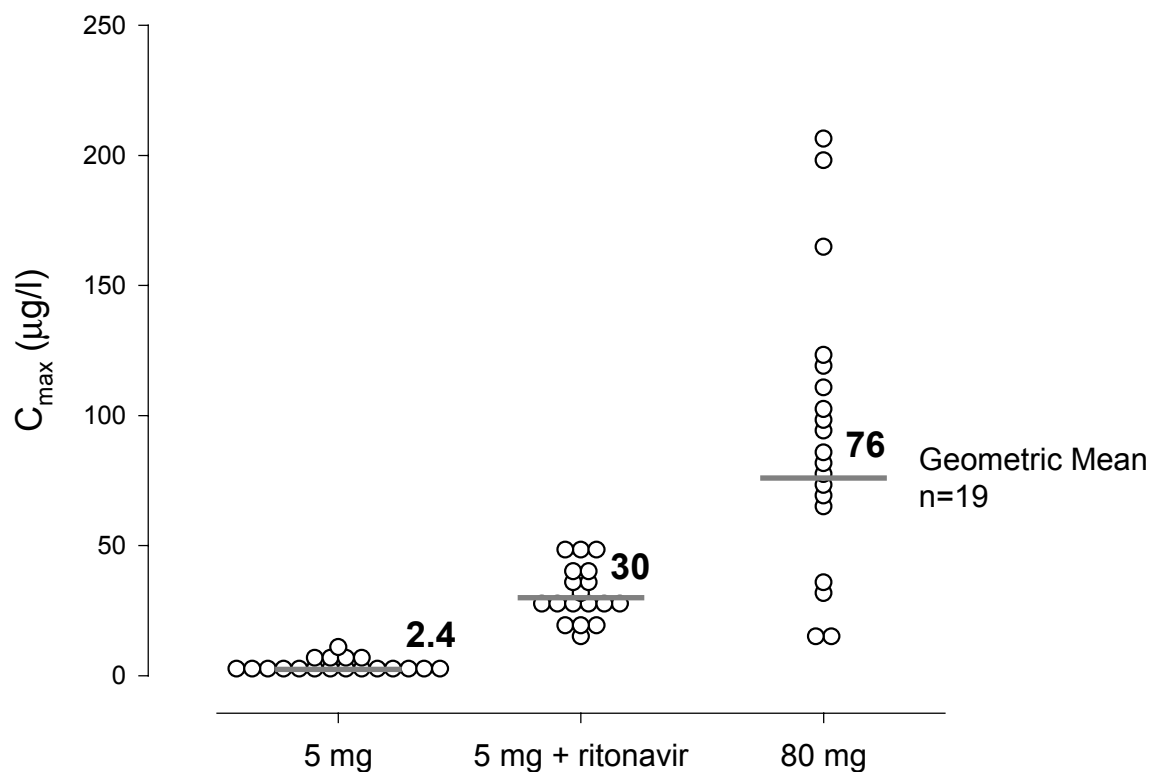
Evaluation of specific cardiovascular adverse events, some of which may be considered as a possible signal for proarrhythmic events (dizziness, syncope,

palpitation), acute coronary syndrome, stroke, and all deaths indicated an acceptable cardiovascular safety profile for the drug. Cardiovascular clinical events that could signal proarrhythmic events are discussed in Section 7.3 of this document.

### **Pharmacokinetic profile**

Vardenafil is rapidly absorbed after oral administration (median  $T_{max}$  1 hour) and its elimination half-life is approximately 4-5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the feces (91%-95%) and to a lesser extent in the urine (2%-6%). The pharmacokinetic properties of the major (M1) and minor metabolites (M4, M5) of vardenafil in the plasma are comparable to the parent drug with respect to  $T_{max}$  and half-life. There is no accumulation of vardenafil or any of its metabolites with daily dosing. Vardenafil is metabolized predominantly by cytochrome P450 (CYP) 3A4, with some contribution from the CYP3A5 and CYP2C isoenzymes. Concomitant use of potent CYP 3A4 inhibitors can be expected to elevate plasma concentrations of vardenafil. The maximum vardenafil plasma concentrations are increased significantly in the presence of the potent CYP inhibitor ritonavir (Figure 1). However, vardenafil concentrations observed following a 5 mg dose of vardenafil in the presence of ritonavir were lower than those observed in the presence of a single dose of vardenafil 80 mg (four times the maximum recommended dose). The definitive QT study described in Section 6.3 included an 80 mg dose of vardenafil to cover the plasma concentrations that might be reached with 5 mg vardenafil plus concomitant ritonavir therapy.

**Figure 1:  $C_{max}$  Data From a Crossover PK Interaction Study of Vardenafil with Ritonavir**



#### **4. General Consequences of QT Prolongation and Torsades de Pointes**

The QT interval of the ECG reflects the duration of the cardiac ventricular action potential, i.e., the duration of ventricular depolarization and subsequent repolarization. Because of its dependency on HR, the QT interval (absolute QT) is routinely transformed using formulae (corrected QT or QTc) that attempt to compensate for HR variations. However, Fenichel and Koerner stated that “drugs that increase the heart rate pose a special problem, since an apparent QTc difference between drug and placebo might in fact be an artifact of increased heart rate and imperfect correction for rate”.<sup>1</sup> Moreover, a comprehensive review of the epidemiologic literature suggests that the corrected QT interval is an important but imprecise marker of cardiovascular disease.<sup>2</sup>



QT interval prolongation per se is not necessarily harmful. For example, the ability to prolong cardiac repolarization has been clinically exploited to treat cardiac arrhythmias with Class III antiarrhythmic drugs such as amiodarone and bretyllium.

The usual site of action for non-cardiac drugs that prolong the QT interval is the inhibition of the rapidly-activating delayed rectifier potassium current,  $I_{kr}$  by blockade of the hERG potassium channel<sup>6</sup> or the hERG-MiRP complex that transduces an outward repolarizing potassium current across the cardiomyocyte plasma membrane during Phase 3 of the action potential.

For non-antiarrhythmic drugs, prolongation of cardiac repolarization is an undesired side effect, because delayed repolarization may result in ventricular tachyarrhythmias such as TdP. TdP is a potentially life-threatening polymorphic tachycardia associated with prolonged QT duration and has been implicated in the occurrence of sudden cardiac death. Women comprised 70% of a meta-analysis of 332 reported cases of cardiovascular drug-related TdP.<sup>3</sup> A QT threshold of risk for TdP has not been demonstrated, but most reported cases of TdP occurred in individuals with a measured QTc value exceeding 500 msec (92%, 107 of 116 cases).<sup>3</sup>

Finally, while corrected QT is routinely employed to assess arrhythmogenic risk, most drugs that cause TdP increase both the absolute QT and the QTc intervals.<sup>9</sup>

Because of this undesirable pharmacological effect and potentially fatal outcome, QT prolongation or/and TdP have recently become an important cause of:

- drug non-approval (e.g. sertindole, lidoflazine)
- uncertain or delayed drug approval (ziprasidone, telithromycin)
- labeling limitations (thioridazine, droperidol, bepridil)
- drug withdrawal (cisapride, astemizole, terfenadine, grepafloxacin)

No class of pharmaceutical agents is exempt from this problem, which spans drug classes as diverse as antibiotics, antipsychotics and antihistamines. Recent experience teaches us that the QT effect of parent drug or metabolites, or the QT effect during metabolic inhibition through drug interaction is very important to understand, and such understanding is needed as early in development as practical. At this time, consensus in the scientific community seems to be endorsement of an intensive evaluation of QT effect, even for small changes, during some stage of preapproval drug development.

In the past, preclinical modeling of in vitro (e.g. hERG) and in vivo data was employed to establish safety margins for clinical use and to give some assurance of human safety. Monitoring of ECGs in Phase I/II studies was often performed for general safety assurance purposes and as part of a battery of other safety assessments. It was not standard practice to focus on the single cardiac electrophysiologic parameter, QT interval, when studying non-antiarrhythmic drugs and their metabolites, particularly in reference to positive controls or other compounds. Phase III clinical programs, though generally large and complex, likewise included ECG assessment usually for signal detection and general patient safety rather than absolute definition of QT effect. But the paradigm for new molecular entities has shifted. QT assessment has moved to the forefront of safety assessment in drug development.

## **5. Review of Guidances and Concepts on the Assessment of the QT Prolongation Potential of Non-Antiarrhythmic Drugs**

There are several issues regarding the assessment and interpretation of QT effects of drugs:

1. QTc prolongation has limitations as a surrogate for cardiac arrhythmias.
2. Measurement imprecision and natural variability can lead to mean QTc interval changes of 4 to 5 msec in the absence of drug treatment.<sup>4</sup>

3. It may be difficult to differentiate between a change in QT/QTc interval due to treatment and that related to spontaneous normal variation.<sup>5</sup>
4. The precise relationship between the magnitude of QT interval prolongation and the risk for serious ventricular arrhythmias remains controversial.
5. Standard rate correction formulae may not accurately correct for the effect of HR changes on QT in the case of drugs that alter HR.

Some of these points are addressed in regulatory guidance documents (or proposals) that were issued to guide drug development during the vardenafil development, and after submission of the vardenafil NDA (see Table 5-1).

**Table 5-1: Regulatory Guidance Documents**

Date/Agency	Title	Status/Reference
17 Dec 1997 /The European Agency for the Evaluation of Medicinal Products	The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products	Guidance <sup>6</sup>
15 Mar 2001/Health Canada/SantéCanada	Assessment of the QT prolongation potential of non-antiarrhythmic drugs	Draft Guidance <sup>7</sup> <a href="http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/guidmain.html">http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/guidmain.html</a>
7 Feb 2002/ICH	Safety pharmacology studies for assessing the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals	Guidance <sup>8</sup>
15 Nov 2002, FDA	The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.	Preliminary Concept Paper for Discussion Purposes Only <sup>9</sup>

In addition, several scientific conferences and meetings related to the clinical and regulatory implications of QT prolongation and proarrhythmia by non-antiarrhythmic drugs have taken place and their proceedings published. They include a report on a Policy Conference of the European Society of Cardiology<sup>10</sup> and an original article by Rashmi R. Shah from the Medicines Control Agency in the United Kingdom.<sup>11</sup> Finally, several conferences on the clinical evaluation of QT

interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs were organized by the Drug Information Association over the last two years and were attended by regulatory officials and representatives from academic institutions and the pharmaceutical industry.

A copy of the FDA concept paper is contained in Appendix 1 of this briefing document. These guidances and FDA concept paper suggest that because prolongation of the QT/QTc interval is the ECG finding associated with an increased susceptibility to cardiac ventricular 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 intervals, as well as systematic collection of clinical adverse event data that might indicate a cardiac arrhythmogenic potential. Nevertheless, the interpretation of relatively small changes in QT duration and the appropriate approach to correction of QT data in cases where drugs cause alteration of HR still remain controversial.

## **6. Presentation of the Effects of Vardenafil on Cardiac Repolarization**

### **6.1 Preclinical studies**

In accordance with the current scientific and regulatory discussion (cf. ICH S7b Draft guideline)<sup>8</sup>, vardenafil has been subject to pre-clinical investigations of its potential to prolong ventricular repolarization. Both, *in vitro* and *in vivo* electrophysiology studies have been performed.

#### **6.1.1 In vitro studies**

In electrophysiological studies using patch clamp techniques, the direct influence on the repolarizing  $I_{Kr}$  current was studied in a human cell line (HEK293) stably transfected with the hERG gene. The vardenafil and sildenafil data from this study are shown below. The ability to block the hERG current was shown for vardenafil, which is consistent with other PDE5 inhibitors, e.g., sildenafil<sup>26</sup> and tadalafil, although the concentrations of vardenafil necessary for hERG current block were

extremely high when compared to the peak ( $C_{max}$ ) free plasma concentration in man. In an extracellular potassium concentration of 4 mM with a depolarization to +20 mV for 1000 msec, the  $IC_{50}$  was determined to be  $30 \pm 9 \mu\text{M}$  and the threshold concentration for blockade of the hERG current was established as  $3 \mu\text{M}$  for both sildenafil and vardenafil (Table 6-1). Therefore, the peak ( $C_{max}$ ) free plasma concentration in man after a 20 mg vardenafil dose is approximately 15,000 times lower than the  $IC_{50}$  for hERG block and approximately 1,500 times lower than the threshold concentration for hERG, the margins are wider than those for sildenafil (Figure 2).

**Table 6-1: Effect of Vardenafil and Sildenafil on hERG Current**

Drug	IC <sub>50</sub> (mean $\pm$ SEM, n=7) under the conditions of:		
	10 mM K <sup>+</sup> <sup>a)</sup> depolarized to -20 mV	10 mM K <sup>+</sup> <sup>a)</sup> Depolarized to +40 mV	4 mM K <sup>+</sup> <sup>b)</sup> Depolarized to +20 mV
Sildenafil	111 $\pm$ 33 $\mu\text{M}$	56 $\pm$ 12 $\mu\text{M}$	47 $\pm$ 7 $\mu\text{M}$
Vardenafil	84 $\pm$ 28 $\mu\text{M}$	32 $\pm$ 7 $\mu\text{M}$	30 $\pm$ 9 $\mu\text{M}$

<sup>a</sup> 140 mM NaCl, 10 mM KCl, 2 mM CaCl<sub>2</sub>, 2 mM MgCl<sub>2</sub>, and 10 mM HEPES, pH 7.4, 21 $\pm$ 2°C

<sup>b</sup> 140 mM NaCl, 4 mM KCl, 2 mM CaCl<sub>2</sub>, 2 mM MgCl<sub>2</sub>, and 10 mM HEPES, pH 7.4, 21 $\pm$ 2°C

### 6.1.2 In vivo studies

Studies to investigate delayed ventricular repolarization or associated arrhythmias were performed in beagle dogs. The beagle dog is an appropriate and generally accepted laboratory species for the investigation and prediction of a possible cardiac risk for humans. In addition, the similarity of the metabolic pattern of vardenafil in humans and dogs made it the model of choice to assess the potential for QTc prolongation of vardenafil and its main human metabolites *in vivo*.

Hemodynamics and cardiac electrophysiology were investigated thoroughly in safety pharmacology studies with multiple time points and continuous telemetric ECG readings in both anaesthetized and conscious dogs. Doses ranging from 0.3 mg/kg to 10 mg/kg vardenafil were employed, spanning the vardenafil exposure ( $C_{max}$ ) range from slightly above the human exposure (at the maximum

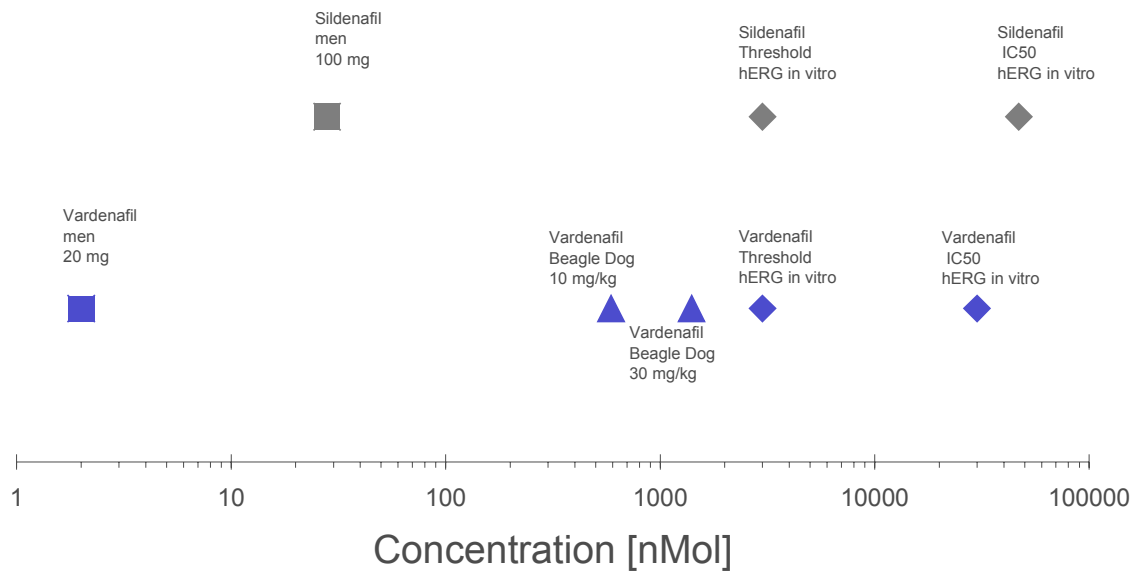
recommended therapeutic dose of 20 mg) to more than two orders of magnitude higher. ECG analysis did not reveal a QTc prolongation or any cardiac arrhythmia up to and including the highest doses tested. In fact a slightly decreased QTc (Bazett's correction) interval was determined at 10 mg/kg (a dose of 10 mg/kg in the dog yielded 317 times the free  $C_{\max}$  in man at the maximum recommended therapeutic dose). Even higher doses (up to 30 mg/kg/day) were administered in the toxicological studies in beagle dogs. In these studies vardenafil was administered for up to one year. Under the conditions of the toxicological experiments and as a consequence of the vasodilating properties of vardenafil, a significant decrease in blood pressure and subsequent tachycardia were observed. These effects were dose-limiting and a dose of 30 mg/kg/day was the maximum tolerated dose (MTD) for dogs. Even under such stringent conditions no QT prolongation or cardiac arrhythmia was observed. It can thus be concluded that the experiments in dogs, which were performed at doses far in excess of the highest therapeutic dose in man, showed no evidence of a cardiac risk for vardenafil.

### **6.1.3 Summary of pre-clinical investigations on delayed ventricular repolarization**

The potential for QTc prolongation of vardenafil and its main human metabolites has been comprehensively assessed in *in vivo* pre-clinical studies in both anaesthetized beagles (close monitoring with multiple time points) and conscious dogs (telemetric ECG readings). These investigations gave no indication for a potential of vardenafil and/or its metabolites to cause delayed ventricular repolarization at multiples of exposure of free  $C_{\max}$  up to 613 (vardenafil) and 193 (M-1) and 91 (M-4), respectively, for its main human metabolites. The absence of a QTc prolongation in the experimental mammalian organism even at doses well above the clinically relevant range is corroborated by the results of *in vitro* investigations on hERG channel blockade. A threshold concentration was determined at 3  $\mu\text{M}$  ( $\text{IC}_{50}$ : 30  $\mu\text{M}$ ), higher than the free  $C_{\max}$  of 1.4  $\mu\text{M}$  vardenafil at the MTD dose (30 mg/kg/d) employed in toxicological studies in the dog (see also Figure 2).

It can be concluded that the results from the *in vitro* investigations on the hERG channel and the results from the *in vivo* studies in dogs provide no signal for a clinical risk of delayed ventricular repolarization induced by mechanisms known to induce electrophysiological abnormalities.

**Figure 2: Free Concentration ( $C_{max}$  for In Vivo) of Vardenafil and Sildenafil**



## 6.2 ECGs in initial clinical pharmacology studies

The purpose of this section is to describe the effects of vardenafil on the QT interval in humans (males) and to provide our interpretation of these data. The focus of the document will necessarily be a trial (10929) specifically designed to describe the QT effects of 10 and 80 mg vardenafil.

In the data originally submitted in the NDA, Bayer provided QT data from a variety of Phase I and Phase II trials. In a series of six standard Phase I studies with 5 to 26 subjects receiving single doses of vardenafil 5 to 80 mg, ECGs were recorded at

baseline and 1 hour post-dosing. Small, inconsistent effects of vardenafil on the QTc interval were observed in these studies. Consequently, a definitive QT study was undertaken after agreeing the study design with FDA.

The clinical pharmacology program for vardenafil also included drug-interaction studies (including studies with alpha-blockers), but these studies did not specifically address the QT interval.

### **6.3 A definitive study of the QT effects of vardenafil**

#### **Design considerations**

The design of Study 10929 was the result of discussions with FDA. Study design aspects considered included: the statistical framework of the study, the need to characterize the effects of suprathreshold concentrations (based on a consideration of pharmacokinetically-based drug-drug interactions), the appropriateness of single (versus multiple) dose evaluation, the timing and number of ECGs to be obtained, the methodology for reading ECGs, the inclusion of a positive control in the study, and approaches to the issue of correction of the QT interval for HR. Clearly, decisions regarding the study design adopted were influenced by the characteristics and intended use of vardenafil. However, there are a number of aspects to the design that may have general applicability in drug development.

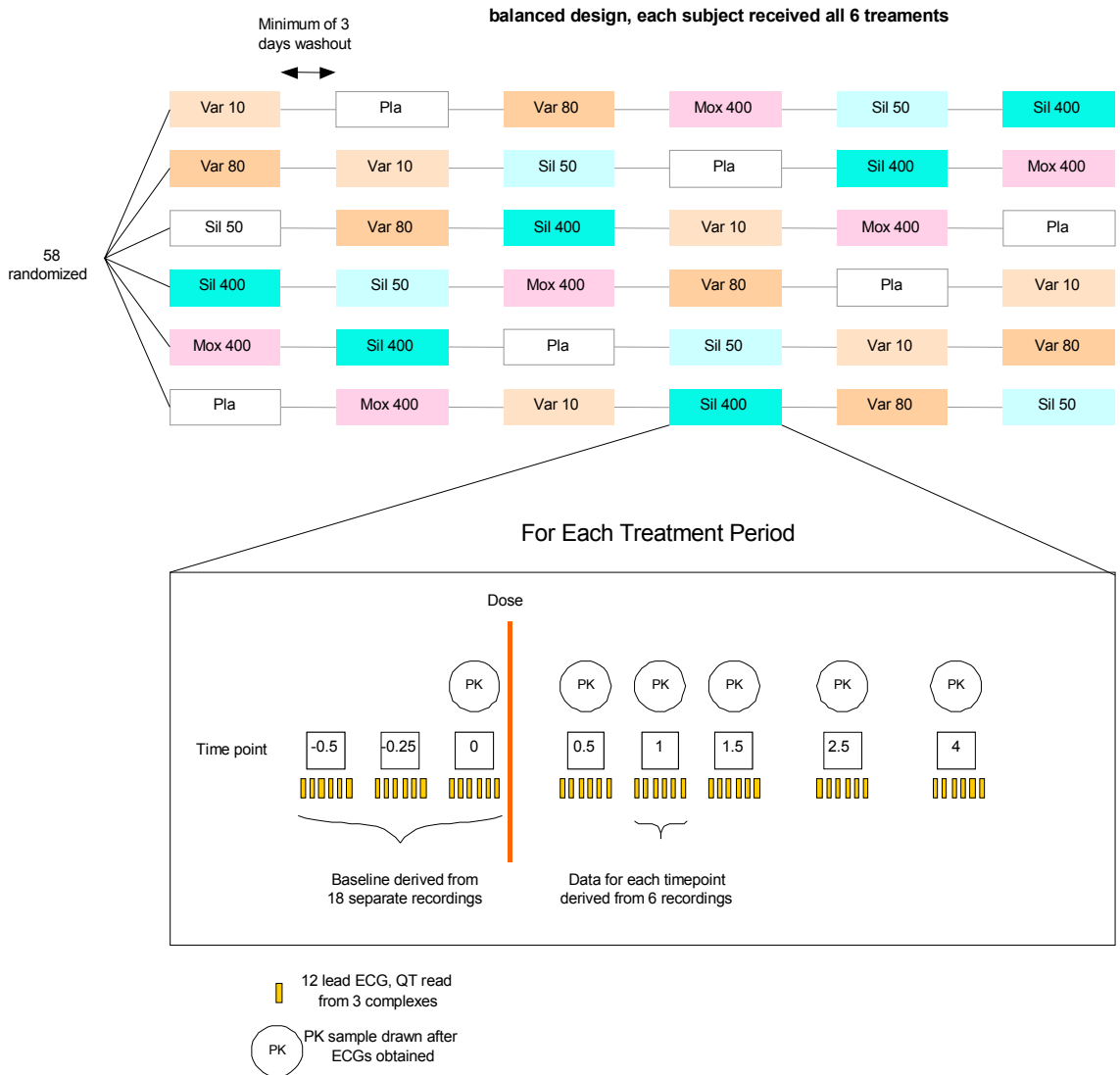
#### **Study 10929 design**

Study 10929 was designed with the primary objective of excluding a greater than 10 msec effect of a single 80 mg oral dose of vardenafil on QTc interval as compared to placebo, measured by the change from baseline at the 1 hour post-dose time point. Sample size calculations based on previous estimates of variance for QTc measurements indicated the need for 54 subjects. This sample size was based on obtaining six replicate ECG tracings for QT measurement at each time point. Eighteen ECG tracings were obtained prior to dosing (-0.5, -0.25 and 0 hours). The timepoints selected for evaluation (predose, 0.5, 1, 1.5, 2.5 and 4 hours) were based



on the known pharmacokinetics of vardenafil and ensured that ECGs would be obtained at (or close to) maximum concentration. The study was of a balanced six-period crossover design. In addition to placebo and 80 mg vardenafil, moxifloxacin (400 mg) was included as a positive control to demonstrate assay sensitivity. A 400 mg oral dose of this quinolone antimicrobial produces an increase in QTc at  $T_{\max}$  of between 5 and 10 msec.<sup>21-23</sup> The selection of 80 mg as the dose for evaluation (as the primary endpoint) was based on the demonstration of a pharmacokinetically based drug-drug interaction of vardenafil with CYP inhibitors (vardeafil concentrations are increased in this circumstance). In addition to this dose, 10 mg vardenafil (the proposed starting dose for therapy) was studied. Additionally the PDE5 inhibitor sildenafil, a marketed treatment for erectile dysfunction, was included in the study design. Two doses of sildenafil were studied; the starting dose of 50 mg and eight times this dose (400 mg). In view of the extensive real-life exposure data obtained during five years of marketing of sildenafil, it was proposed that data from these treatment arms would be useful in providing a context for a comprehensive interpretation of the QT data from vardenafil. The study design adopted is shown schematically in Figure 3.

**Figure 3: Schematic of Study Design**



Based on the pharmacokinetic behavior of vardenafil, accumulation of vardenafil or its metabolites is not anticipated in clinical use. This justified the study of the QT effects of single doses. Based on prior experience with vardenafil and knowledge of sildenafil's behavior, increases in HR were anticipated.

The limitations of the Bazett's correction factor, particularly in situations where HR increases are now well recognized.<sup>2,23</sup> As has been shown<sup>24-25</sup> there is considerable between-individual variability in the QT/RR relationship. This results in some

interpretative difficulty if a *single* correction formula is applied uniformly to all subjects.

Fridericia's correction was used for analysis of the primary objective since it is a more appropriate correction method than the Bazett's method when studying the QT effect of drugs that also produce an increase in HR. Additionally, the analysis plans included in the protocol anticipated the use of HR correction based on an individualized approach this is further described in Section 7.2.

### **Objectives**

The primary objective was to rule out a greater than 10 msec effect of a single 80 mg oral dose of vardenafil on QTc interval as compared to placebo, as measured by the change from baseline at the 1 hour post-dose time point.

Secondary objectives included the characterization of other QT and HR data both for the 80 mg dose of vardenafil and also for each of the other treatments investigated: vardenafil 10 mg, sildenafil 50 and 400 mg and moxifloxacin 400 mg, the latter as an indicator of assay sensitivity. Additionally, blood samples were obtained immediately after the recording of ECGs in order to evaluate the relationship between drug concentration and effect (PK/PD).

### **Study population**

Healthy adult male subjects between 45 and 60 years of age, and a body mass index of less than 35 kg/m<sup>2</sup> were eligible for the study.

### **Dosing**

Study medication was administered with 240 mL of tepid water under blinded conditions.

## **QT and HR**

Six 12-lead ECGs taken approximately 1 minute apart were obtained at specified times prior to dosing and over the 4 hour period following administration of study drug (Figure 3). Study conditions were designed to keep the subjects relaxed, particularly at the time of ECG recording; blood samples were always obtained after ECG recordings were performed at each time point. ECG measurements were performed by a contract research organization unaware of treatment assignment. A magnified paper record was analyzed using a digitizing pad (SigmaScan). By default, Lead II was used for analysis (unless the T-wave morphology made this unsuitable). T-waves were analyzed even if notched, biphasic or inverted. The default method for the identification of the end of the T-wave was by identification of the time of return to baseline (or isoelectric line). In circumstances where the T-wave morphology rendered this method inappropriate, a gradient intersection method was used. The maximum gradient of the descending portion of the T-wave was visualized; the intersection of this gradient with the isoelectric line defined the end of the T-wave. RR duration was determined from the peaks of two consecutive R waves (starting with the R wave prior to the T-wave of interest).

## **Endpoints**

The primary parameter was the corrected QT interval (QTc). Fridericia's correction formula ( $QTc_F = QT/RR^{1/3}$ ) was used to calculate QTc. Corrections based on individual subject data were performed as additional exploratory analyses.

Individually corrected QT (QTc<sub>i</sub>) was calculated using the formula  $QTc_i = QT + [b*(1-RR)]$ . The variable “b” was obtained from fitting each subject’s data (baseline and placebo) to the linear regression model  $QT = a + b * RR$ , where  $RR = 60/HR$ . Other secondary parameters included the raw QT interval and HR.

The primary endpoint was change from baseline at 1 hour post dose.

An analysis of effect at  $T_{\max}$  was also performed. For each subject, this endpoint was determined as the difference in change from baseline at the time of the maximum concentration ( $T_{\max}$ ) for each active regimen and the time-matched change from baseline for the placebo regimen.

An analysis of maximum change was also performed. This endpoint was determined as the difference in maximum change from baseline in QTc and the maximum change from baseline for the placebo regimen. (For raw QT and HR, the change was determined at the time of maximum change in QTc).

In all cases, post-dose values were the average of the 6 replicate measurements taken at the post-dose time, and baseline values were the average of all 18 pre-dose measurements.

### **Assays for pharmacokinetics**

Blood samples for pharmacokinetic analysis of vardenafil, sildenafil and moxifloxacin were collected from each subject prior to dosing and in the period up to 4 hours following single oral administration (0, 0.5, 1, 1.5, 2.5 and 4 hours). Plasma concentrations of vardenafil and moxifloxacin were quantified using HPLC with fluorescence detection. The lower limits of quantification (LLQ) for vardenafil and moxifloxacin were 0.20 ng/mL and 10.0 ng/mL. Plasma concentrations of sildenafil were quantified using LC/MS/MS (LLQ 1.00 ng/mL).

### **Statistical Methods**

The primary comparison of interest was 80 mg vardenafil versus placebo. A greater than 10 msec effect was to be ruled out when the upper limit of the 90% confidence interval (CI) for the difference in change from baseline at 1 hour post-dose in QTc between single 80 mg oral dose of vardenafil and placebo was less than 10 msec.

Secondary effects of interest included the effect on QTc of 10 mg vardenafil, each active dose of sildenafil (50 and 400 mg) and moxifloxacin (400 mg). For these

active regimens and all secondary and exploratory endpoints, an estimation approach was taken and 90% CIs were constructed to provide a range of plausible values in addition to the estimate of the mean effect. All effects were evaluated in relation to the placebo response.

The primary endpoint, change from baseline in QTc at 1 hour was analyzed by analysis of covariance (ANCOVA) fitting terms for sequence, subject-within-sequence, period and regimen and fitting baseline QTc as a covariate. Point estimates and 90% confidence intervals were constructed for the difference, active - placebo, for each dose of vardenafil, sildenafil and moxifloxacin using the residual variance.

The secondary endpoint, QTc at  $T_{max}$ , was analyzed by analysis of covariance (ANCOVA) fitting terms for sequence, subject-within-sequence, period and regimen and fitting each regimen's baseline QTc as a within-subject covariate. Point estimates and 90% confidence intervals were constructed for the adjusted least-squares mean for each regimen (excluding placebo) in order to provide a range of plausible values for the secondary effects of interest.

Maximum QTc were analyzed in a similar manner to the primary endpoint. Secondary endpoints for raw QT and HR were analyzed in a similar manner as those for QTc.

### **Study 10929 results**

A total of 60 healthy male subjects were enrolled in the study. One subject was withdrawn prior to dosing. Two subjects were withdrawn after dosing, one after receiving vardenafil 80 mg and sildenafil 50 mg, another after receiving vardenafil 10 mg, sildenafil 400 mg, moxifloxacin and placebo. Thus 57 subjects completed the study, 58 subject-sessions were completed for each regimen, and 59 subjects were exposed to study medication. The mean age of all subjects was 53 years (range 45 to 60) with a mean (SD) weight of 87 (14) kg and a mean height of

1.79 (0.07) m. Twelve percent of the population studied were black, 81% white and 7% Hispanic.

As shown in Table 6-2 and Table 6-3, vardenafil 80 mg produced a 10 msec increase in QTcF (relative to placebo) one hour after dosing. The upper bound of the confidence interval was 11 msec.

**Table 6-2: QTcF (msec) at 1 Hour**

Treatment	Adjusted arithmetic mean (SEM)	Treatment effect (placebo subtracted)	90% CI
10 mg vardenafil	8 (0.7)	8	(6, 9)
80 mg vardenafil <sup>a</sup>	10 (0.7)	10	(8, 11)
50 mg sildenafil	7 (0.7)	6	(5, 8)
400 mg sildenafil	9 (0.7)	9	(8, 11)
400 mg moxifloxacin	8 (0.7)	8	(6, 9)
Placebo	0 (0.7)	-	-

a primary endpoint of study

Note: above results are rounded to the nearest integer.

Table 6-2 illustrates a number of features of the response to vardenafil and sildenafil that we consider critical to the interpretation of the effect. The relationship between vardenafil dose and response is shallow; an eight-fold increase in dose causes an increase of around 2 msec in mean QTcF. In addition to the QTcF data already described, Table 6-3 provides the treatment effect data for QTraw and HR.

**Table 6-3: QTcF, QTraw and HR at 1 Hour (placebo subtracted change from baseline)**

Treatment	Treatment effect (90% CI)		
	QTcF (msec)	QTraw (msec)	HR (bpm)
10 mg vardenafil	8 (6, 9)	-2 (-4, 0)	5 (4, 6)
80 mg vardenafil	10 (8, 11) <sup>a</sup>	-2 (-4, 0)	6 (5, 7)
50 mg sildenafil	6 (5, 8)	-2 (-4, 0)	4 (3, 5)
400 mg sildenafil	9 (8, 11)	-1 (-3, 1)	5 (4, 6)
400 mg moxifloxacin	8 (6, 9)	3 (1, 5)	2 (1, 3)

Placebo mean(SEM) values of QTcF QTraw and HR from ANCOVA were; 0 (0.7), 6 (1.0), and -3 (0.5) respectively

<sup>a</sup> primary endpoint of study

Note: above results are rounded to the nearest integer.

In relation to the placebo response, QTraw was decreased following vardenafil or sildenafil while it showed an increase in response to moxifloxacin. The placebo subtracted HR increased in response to all treatments, although this effect was small in the case of moxifloxacin. The pattern of response observed for vardenafil was also seen for sildenafil at its therapeutic dose of 50 mg and the 8-fold multiple of this dose.

**Additional analyses (QT effect at T<sub>max</sub> and maximal QT effect)**

In order to exploit the crossover design of the study, it was desirable to have a single value under placebo conditions with which to evaluate treatment effects. The 1 hour time point was prospectively selected for the primary analysis (this timepoint was anticipated to be T<sub>max</sub> for vardenafil).

Table 6-4 provides the distribution of T<sub>max</sub> observed in the study. For each timepoint, the number of subjects in which T<sub>max</sub> occurred is given in this table. It is noted that T<sub>max</sub> was most frequently observed at 1 hour for vardenafil 10 and 80 mg, and for sildenafil 50 mg. For sildenafil 400 mg, T<sub>max</sub> was rather uniformly distributed across the timepoints.

**Table 6-4: Distribution of T<sub>max</sub> (n<sup>a</sup>)**

Timepoint	Var 10	Var 80	Sil 50	Sil 400	Mox 400
0.5	6	12	14	10	15
1	30	28	24	12	14
1.5	15	6	12	10	10
2.5	5	6	4	14	12
4	1	5	3	11	6
Total	57	57	57	57	57

a n represents the number of subjects in which T<sub>max</sub> was observed

Recognizing the possibility that, for a given subject, maximal effects on the QT duration might not occur at the population T<sub>max</sub>, two additional analyses were also performed. The first of these used the QT data at the time of the subject's maximum concentration (whether or not this was at 1 hour) see Table 6-5.



**Table 6-5: QTcF, QTraw and HR at T<sub>max</sub> (placebo subtracted change from baseline)**

Treatment	Treatment effect (90% CI)		
	QTcF (msec)	QTraw (msec)	HR (bpm)
10 mg vardenafil	7 (5, 9)	-3, (-5, 0)	4 (3, 5)
80 mg vardenafil	9 (8, 11)	-1 (-3, 2)	5 (4, 6)
50 mg sildenafil	6 (5, 8)	-3 (-5, 1)	4 (3, 5)
400 mg sildenafil	6 (4, 7)	1 (-1, 4)	2 (1, 3)
400 mg moxifloxacin	8 (7, 10)	4 (2, 7)	2 (1, 3)

Note: above results are rounded to the nearest integer.

Table 6-6 provides the results of the analysis of maximum effect on QTcF and the effects on QTraw and HR at the corresponding timepoint.

**Table 6-6: QTcF, QTraw and HR at Time of Maximum QTcF (placebo subtracted change from baseline)**

Treatment	Treatment effect (90% CI)		
	QTcF (msec)	QTraw (msec)	HR (bpm)
10 mg vardenafil	6 (5, 7)	-2 (-4, 0)	4 (3, 5)
80 mg vardenafil	9 (7, 10)	-1 (-3, 1)	5 (3, 6)
50 mg sildenafil	5 (4, 6)	-2 (-4, 1)	3 (2, 4)
400 mg sildenafil	8 (7, 9)	0 (-2, 3)	3 (2, 5)
400 mg moxifloxacin	9 (7, 10)	7 (4, 9)	1 (0, 2)

Placebo mean(SEM) values of QTcF QTraw and HR from ANCOVA were; 4 (0.6), 7 (1.2) and -1 (0.6), respectively.

Note: above results are rounded to the nearest integer.

Broadly similar results were seen in both these analyses.

### Individualized QT correction

Finally, an analysis was performed that attempts to address problems arising from fixed approaches to HR correction. In this analysis the placebo and baseline QT/RR data were fitted according to the equation  $QT = a + b(RR)$ , with QT<sub>ci</sub> being equal to  $QT + b*(1-RR)$ . The assumption of this correction is that the slope of the RR/QT relationship is the same for all regimens. Under this assumption, the difference

between an active regimen and placebo in QTci is analogous to the difference between intercepts of the two RR/QT linear relationship as depicted in Figure 4.

**Figure 4: Schematic Showing Derivation of QTci**

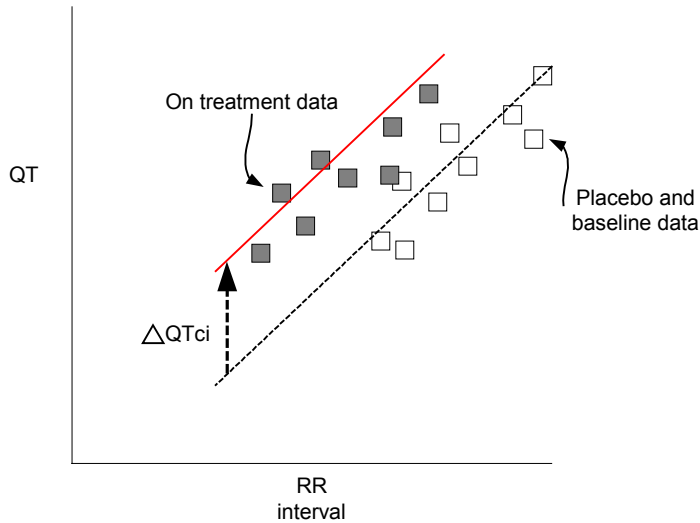


Table 6-7 provides the results of the analysis using individualized correction of the QT interval. For both vardenafil and sildenafil use of this correction method (in contrast to the Fridericia's method) resulted in small reduction in the estimate of the treatment effect, nevertheless the pattern of response was comparable to that previously shown (see Table 6-2, Table 6-5 and Table 6-6). There was a numerically smaller effect on the estimate of the response to moxifloxacin.

**Table 6-7: QTci at 1 hr, at T<sub>max</sub> and at Time of Maximum QTci (Placebo Subtracted Change from Baseline)**

Treatment	Treatment effect (90% CI)		
	at 1hr (msec)	at Tmax (msec)	at Max. QTci (msec)
10 mg vardenafil	4 (3, 6)	3 (2, 5)	4 (2, 5)
80 mg vardenafil	6 (4, 7)	6 (5, 8)	6 (5, 8)
50 mg sildenafil	4 (2, 5)	3 (2, 5)	3 (2, 5)
400 mg sildenafil	5 (4, 7)	5 (3, 6)	6 (5, 8)
400 mg moxifloxacin	7 (5, 8)	7 (6, 9)	8 (7, 9)

Placebo mean (SEM) values of QTci at 1hr and max. QTci from ANCOVA were; 2 (0.7) and 6 (0.7), respectively. (For changes at T<sub>max</sub>, placebo effect was subtracted prior to analysis and varied from regimen to regimen)

Note: above results are rounded to the nearest integer.

### Categorical analysis

The analyses provided in this section of the document reflect changes in QT/QTc of 30 msec and the occurrence of values greater than 450 msec. By convention, it is usual to consider changes of 60 msec and values of 480 and 500 msec in these analyses. However, there were no changes of 60 msec or greater and no occurrences of QTcF greater than 450 msec.

Table 6-8 shows the number and proportion (as a percentage) of ECGs where the change from baseline in QT, QTcF or QTci was greater than 30 msec. The percentages provided in parentheses reflect the large number of ECGs evaluated (n=1740 for each regimen). Following correction for rate (using either the Fridericia's equation or an individualized correction) the proportion of changes greater than 30 msec was comparable in the sildenafil and vardenafil groups and these rates were in general greater than those observed under placebo conditions. Consistent with mean change data already provided, when compared with either vardenafil or sildenafil, it is apparent that moxifloxacin shows a greater effect on QTraw and QTci.

**Table 6-8: Occurrences of Changes From Baseline >30 msec in QT and QTcF**

Frequency (Percent)	Regimen					
	Var 10 mg	Var 80 mg	Sil 50 mg	Sil 400 mg	Moxi 400 mg	Pla
QT	2 (0.11)	28 (1.61)	26 (1.49)	22 (1.26)	53 (3.05)	14 (0.80)
QTcF	10 (0.57)	16 (0.92)	10 (0.57)	8 (0.46)	16 (0.92)	2 (0.11)
QTci	2 (0.11)	4 (0.23)	1 (0.06)	4 (0.23)	18 (1.03)	1 (0.06)

In Table 6-9 the number and proportion of *subjects* who experienced a 30 msec or greater change in QT/QTc was analyzed by regimen.

**Table 6-9: Number of Subject-Sessions with Changes from Baseline >30 msec in QTcF**

Frequency (Percent)	Regimen					
	Var 10 mg	Var 80 mg	Sil 50 mg	Sil 400 mg	Moxi 400 mg	Pla
QT	2 (3.45)	7 (12.07)	6 (10.34)	7 (12.07)	16 (27.59)	5 (8.62)
QTcF	7 (12.07)	9 (15.52)	5 (8.62)	5 (8.62)	9 (15.52)	2 (3.45)
QTci	2 (3.45)	4 (6.90)	1 (1.72)	2 (3.45)	10 (17.24)	1 (1.72)

As shown in Table 6-10, rates of QT >450 were in general comparable (or less than) those observed during placebo conditions. There were no QTcF data in excess of 450 msec.

**Table 6-10: Occurrences of QT or QTci >450 msec**

Frequency (Percent)	Regimen					
	Var 10 mg	Var 80 mg	Sil 50 mg	Sil 400 mg	Moxi 400 mg	Pla
QT	3 (0.17)	47 (2.70)	40 (2.30)	12 (0.69)	55 (3.16)	41 (2.36)
QTci	0	2 (0.12)	19 (1.09)	0	2 (1.03)	N/A <sup>a</sup>

a not calculated

Taken together, these categorical analyses reflect the mean change previously presented. The thresholds for these analyses are small (30 msec change from baseline and 450 msec absolute values). These analyses do not suggest exaggerated responses in a subset of the population studied.

#### **Pharmacokinetics of vardenafil, sildenafil and moxifloxacin in Study 10929**

Mean  $C_{max}$  and median  $T_{max}$  data obtained following single oral administration of vardenafil, sildenafil and moxifloxacin to healthy male subjects are summarized in Table 6-11. Exposure (AUC) was not calculated due to the limited PK sampling schedule employed in the study.

**Table 6-11:  $C_{max}$  and  $T_{max}$  for vardenafil, sildenafil and moxifloxacin (Study 10929)**

	Vardenafil 10mg	Vardenafil 80 mg	Sildenafil 50 mg	Sildenafil 400 mg	Moxifloxacin 400 mg
$C_{max}$ (ng/ml) mean (SD)	8.83 (3.87)	106 (59)	178 (68.4)	1519 (563)	2931 (684)
$T_{max}$ (h) median (range)	1.17 (0.53-4.17)	1.17 (0.52-4.28)	1.17 (0.53-4.17)	1.167 (0.53-4.20)	1.22 (0.52-4.17)

Based on the mean data,  $C_{max}$  values for vardenafil increased with dose in a greater than dose proportional manner (approximately 12-fold increase in mean  $C_{max}$  for an 8-fold increase in dose). The  $C_{max}$  values observed following single oral 10 and 80 mg vardenafil administration were consistent with those observed previously in Phase I clinical trials.

## Pharmacokinetics/Pharmacodynamics

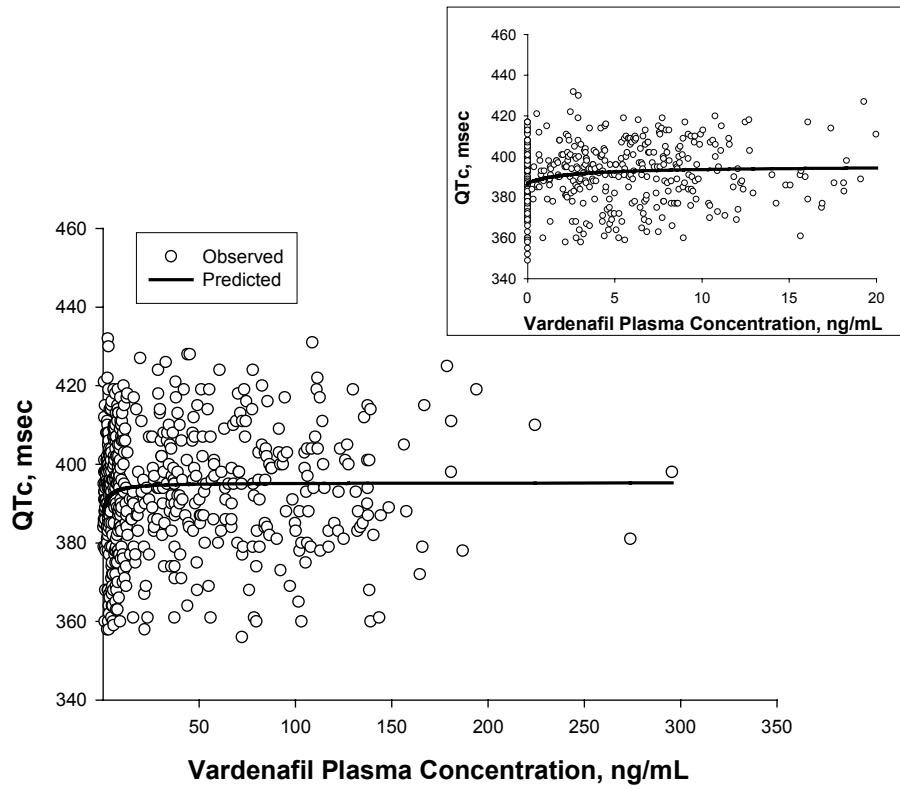
Graphical examination of the relationship between vardenafil, sildenafil and moxifloxacin concentration and QTcF interval indicated that QTcF increased with increase in plasma concentration for each of these agents. Although hysteresis was observed in a number of subjects, there was no consistent pattern indicative of a large variability in the response. In a large number of subjects, the maximal increase in QTcF prolongation was observed at the time to reach maximum plasma concentration. Consequently direct effect models were employed in the PK/PD analysis. Using population PK/PD modeling, the best description of the relationship between QTcF interval and plasma concentration for vardenafil and sildenafil was provided by an  $E_{max}$  model, while a slope-intercept model best described the moxifloxacin data. The equation used to describe this model is given below:

$$E = E_0 + \frac{E_{max} * C_{p\text{vardenafil}}}{EC_{50v} + C_{p\text{vardenafil}}} + \frac{E_{max} * C_{p\text{sildenafil}}}{EC_{50s} + C_{p\text{sildenafil}}} + S_M * C_{p\text{moxifloxacin}}$$

where,  $E_0$  is the QTcF response in the absence of the active medication,  $E_{max}$  is maximal prolongation of QTcF which was assumed to be similar for vardenafil and sildenafil,  $EC_{50v}$  and  $EC_{50s}$  are the concentrations of vardenafil and sildenafil at which half of the maximal prolongation was achieved and  $S_M$  represents the slope of the linear relationship between QTcF prolongation and plasma moxifloxacin concentration.

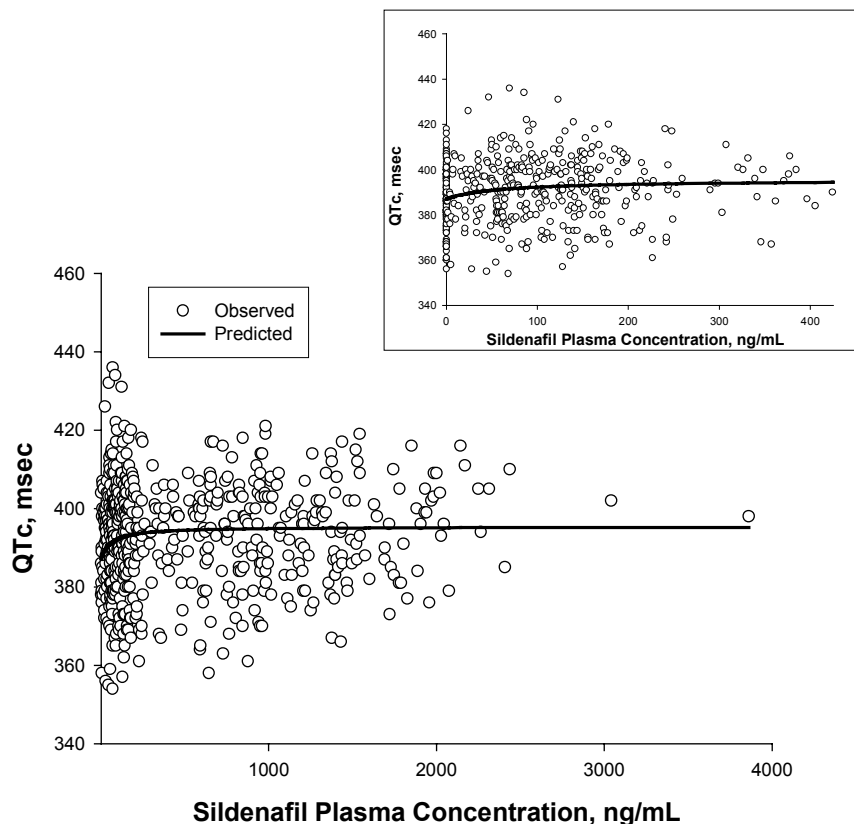
A plot of the population predicted QTcF and the observed QTcF values versus vardenafil, and sildenafil plasma concentrations (Figure 5 and Figure 6) indicated a reasonable fit of the model to the data. The fit of the data at concentrations reflective of the low doses (i.e., 10 mg vardenafil and 50 mg sildenafil) is illustrated in the inset of Figure 5 and Figure 6, for vardenafil and sildenafil, respectively.

**Figure 5: Observed and Predicted QTc versus Vardenafil Plasma Concentration Following 10 & 80 mg Oral Vardenafil Administration**



Inset provides an expanded view of the concentration-effect relationship over the range 0-20 ng/mL.

**Figure 6: Observed and Predicted QTc versus Sildenafil Plasma Concentration Following 50 & 400 mg Oral Sildenafil Administration**



Inset provides an expanded view of the concentration-effect relationship over the range 0-425 ng/mL.

These figures corroborate the conclusions obtained from examination of the dose-response relationship for vardenafil. The QTcF effect of 10 mg vardenafil is minimally increased with an 8-fold augmentation of dose; this corresponds to the flat portion of the concentration/effect relationship (as concentrations of vardenafil increase beyond values of around 10 ng/mL). A similar pattern was observed for sildenafil (Figure 6).

The PK/PD analysis for moxifloxacin is subject to the limitation that only one dose of this agent was studied (the plot is not provided). However, as shown in the



equation for the model (above), QTc is linearly related to concentration for moxifloxacin.

### **Summary of Findings in Study 10929**

Using Fridericia's correction and data obtained at 1 hour following dosing, 80 mg of vardenafil (4 times the upper range of the therapeutic dose) causes a mean prolongation of 10 msec in the corrected QT interval duration. Based on the narrow confidence interval there is very little uncertainty about this estimate. This study showed comparable data for the widely used agent, sildenafil. Based on a comparison of the QTc data from 10 and 80 mg vardenafil (and 50 and 400 mg sildenafil), the dose (and concentration) response relationship is shallow and remains so even at supratherapeutic concentrations. Both vardenafil and sildenafil caused small increases in HR and a small reduction in raw QT duration; by contrast, the effect of moxifloxacin is to increase both Q<sub>Traw</sub> and QTc with minimal effects on HR. In the categorical analysis, there were no instances of outlier values of extreme magnitude (change in QT/QTc<sub>≥</sub>60 msec, QTc<sub>F</sub>>450 msec).

## **7. Discussion**

According to regulatory guidance still under development, an adequate pre-marketing investigation of any non-antiarrhythmic drug should include rigorous characterization of its effects on the QT/QTc intervals. Three major issues discussed below need to be taken into consideration when designing and interpreting such investigations.

### **7.1 Clinical trial designs for the assessment of QT prolongation**

Because of the spontaneous physiological variations of the QT interval in relation to various factors (circadian rhythm, physical activity, food intake, etc), a well designed definitive QT study is required to gather valid data allowing sturdy conclusions. We believe that we have completed what ought to be considered a prototype for a well designed QT study involving non-antiarrhythmic drugs when a

single dose cross-over design is appropriate. Our study had the following key features:

- A cross over design with subjects serving as their own controls. This design reduced variability and provided statistical power in a reasonable number of subjects.
- The inclusion of a well-characterized positive control (moxifloxacin) that confirmed the sensitivity of the methodology used to detect QT alterations.
- The inclusion of a control belonging to the same therapeutic class permitting comparison between related chemical entities.
- The inclusion of doses to cover therapeutic and supra-therapeutic concentrations of the drug. This approach helps to define the steepness of the relationship between the dose/concentration of the drug and QT/QTc prolongation.
- Replicate ECG recordings (n = 6 at each time point) under resting conditions and at similar times of the day to reduce variability of the QT measurements.
- Centralized-blinded manual readings of QT intervals using a digitizing pad for accuracy.
- Twelve-lead ECG assessments taken at various times to encompass maximum plasma concentrations of the regimens under study.
- In our study ECGs were performed at timepoints from -30 to +240 minutes.
- Use of the Fridericia's correction formula because of an expected HR increase with PDE5 inhibitors, allowing accurate and unbiased assessment of QT values.
- Sufficient numbers of ECGs were collected to allow the application of individualized QT correction methods to correct for HR.

The quality of the data harvested during this well-controlled study was confirmed by the very narrow standard deviation of the QT interval.

## 7.2 Approaches to the correction of the QT interval for drugs that affect heart rate

Because the QT interval is inversely related to HR, it is necessary to correct for changes in HR in order to evaluate intrinsic effects on the QT interval following drug treatment. More than 30 correction formulae have been proposed, of which Bazett's and Fridericia's corrections are the most widely used. Both correction formulae were developed early in the 20<sup>th</sup> century using sparse datasets. A "perfect" correction formula producing a corrected QT that is completely independent of HR should yield a horizontal linear regression line with a zero slope. More recently it has been shown that there is considerable between-subject variability in the QT/RR relationship.<sup>24</sup> This implies that for some subjects, the uniform application of any given correction procedure will result in an unreliable estimate of the corrected QT.<sup>12</sup> This is obviously of great importance when small changes in corrected QT are being investigated in a drug that causes changes in HR. One approach, which is justified by the relatively robust agreement in the QT/RR relationship *within* an individual (examined on different occasions)<sup>24</sup> is provided by the individualized QTc (QTc<sub>i</sub>).

In our definitive QT study, we examined:

1. Absolute QT interval variations
2. Corrected QT interval variations using Fridericia's formula
3. Corrected QT interval variations based on linear regression modeling of QT and RR for each subject (QTc<sub>i</sub>)

For each subject, the pre-dose values from all sessions (18 pre-dose measurements/session) and all post-dose placebo values (30 post-dose measurements) were used to fit a linear regression model:  $QT = a + b * RR$ , where

$RR = 60/HR$ . Using the estimated slope “b” from the above regression model,  $QTc_i$  for each replicate was obtained using the formula:  $QTc_i = QT + [b*(1-RR)]$ . A total of 138 points were included in the regression modeling for each subject.

From published literature, there is agreement that Bazett’s formula produces the least accurate correction when there is a HR increase on therapy. Fridericia’s formula generates a more accurate correction in this circumstance. The use of an individualized correction requires at least 50 to 100 ECGs off therapy (which may not be compatible with the design of an already complex study) versus fewer than 20 ECGs for a full extent of exposure analysis employing the Fridericia’s fixed formula. The extra complexity of using individual correction approaches requires more data in different study designs and with different types of pharmacologic agents to establish its best role in clinical research. In our study, the Fridericia’s correction method appeared to be an appropriate method and the  $QTc$  results obtained via this method or by the individualized correction approach were similar.

### **7.3 Risks of cardiac arrhythmia associated with different degrees of QT prolongation**

The relationship between QT interval prolongation and TdP is complex and multifactorial. Furthermore, any quantitative relationship is certainly not well characterized. Acquired QT prolongation can be observed in the presence of multiple conditions and circumstances besides drugs. They include female gender, increasing age, meals, sleep, obesity, alcoholism, electrolyte disturbances, hypoglycemia, myocardial infarction and ischemia, cardiomyopathy, hypertension, hypothyroidism, stroke and cerebral hemorrhage. Not all the drugs that prolong the QT interval carry the same torsadogenic risk. For instance, a drug like amiodarone prolongs the QT interval, but its torsadogenic potential appears limited. Perhaps this is because of its differential effect on homogeneity of cardiac repolarization changes compared to drugs like sotalol which has similar effects on QT duration, yet a far greater risk of TdP.

From a clinical and safety viewpoint, one would like to know if there is a direct and quantitative relationship between the degree of QT interval prolongation and the risk of TdP. For obvious ethical reasons and because of the rarity of TdP events, there has been no randomized clinical trial assessing the relationship between QT prolongation and TdP. Population-based studies have attempted to document the relationship between QT/QTc interval and TdP. It appears that there is no precise QT interval threshold for TdP, but most of the reported cases of TdP were observed in subjects whose QTc exceeded 500 msec. In the Framingham study (30 years of follow up in 5,125 subjects aged 30 to 62 years), there was no association between QTc and mortality.<sup>13</sup> In the Amsterdam study (3,091 subjects aged 40 to 65 years, followed up for 28 years), there was no relationship between QTc prolongation and cardiac mortality in subjects without cardiac disease.<sup>14</sup> However, other studies concluded that in the general population a prolonged QT is associated with increased risk for cardiac death, in particular in patients with altered myocardial function.<sup>15-18</sup>

Regarding drug-induced QT/QTc prolongation with various cardiac and non-cardiac drugs, it has been suggested that a QTc interval >500 msec on drug carries a high risk of TdP. Available data also suggest that in individual subjects, an increase of 60 msec in the duration of QTc interval is highly predictive that this change is due to drug and not spontaneous variability and therefore implies an increase in the potential risk of TdP. For instance, terfenadine (an antihistamine drug that is metabolized by CYP 3A4), was found to block the  $I_{Kr}$  current as well as the Phase 2 fast sodium current and the L-type calcium channel. At the usual recommended terfenadine dose of 60 mg bid, a peak QTc prolongation of 18 msec was measured in the absence of metabolic inhibition. The risk for TdP became a problem only when its metabolism was inhibited by concomitant medications. The peak QTc prolongation was 39 msec in the presence of erythromycin, 41 msec in the presence of itraconazole, and 82 msec in the presence of ketoconazole.<sup>2</sup> Similarly, the average QTc prolongation was 25 msec for cisapride in the presence of the CYP 3A4 inhibitor clarithromycin.<sup>2</sup> These and other examples of compounds with

effects on the QT interval of known magnitude, and sufficient post-marketing data, led to the following suggestions in the FDA Concept Paper:

- 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 TdP.
- 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 QT/QTc interval 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 more than 20 msec have a substantially increased likelihood of being proarrhythmic, and may have clinical arrhythmic events captured during drug development.
- Other data relevant to the assessment of the risk of cardiac arrhythmia from drugs associated with QT prolongation are the nature and frequency of clinical events that can be considered as possible signals or surrogates for TdP.

In the review of the clinical data submitted in the vardenafil NDA, Bayer has examined the clinical experience of the 5727 males (4436 ED patients in Phase II and Phase III and 1291 subjects in Phase I) who were exposed to vardenafil for adverse events which may be considered surrogates for ventricular arrhythmia. Based on the FDA preliminary concept paper<sup>9</sup>, the following clinical events were evaluated as potential signals for proarrhythmic events:

1. Ventricular arrhythmia
2. Ventricular ectopy or premature ventricular complexes (PVC)

3. Ventricular tachycardia
4. Torsades de pointes
5. Ventricular fibrillation and flutter
6. Death
7. Syncope
8. Dizziness
9. Palpitations
10. Seizures (convulsions)

Due to their vasodilatory actions, PDE5 inhibitors like vardenafil may have significant effects on hemodynamic parameters such as blood pressure and HR. The clinical events of syncope and dizziness may therefore occur as a consequence of hemodynamic effects with or without any contribution of potential proarrhythmic effects of the drug. Seizures (or convulsions) may be a possible consequence of cerebral ischemia resulting from arrhythmia.

The above mentioned clinical events (treatment-emergent) were reported in the vardenafil clinical program either as a clinical adverse event or as an ECG finding. The review of the data revealed no signal for the occurrence of occult ventricular arrhythmia in association with vardenafil. The treatment emergent clinical adverse events and ECG findings on vardenafil in relation to placebo are shown in Table 7-1 and Table 7-2.

**Table 7-1: Incidence of Clinical Adverse Events (Treatment-Emergent) Which May be a Potential Signal for Proarrhythmic Events in Placebo-Controlled Studies**

Clinical events	Placebo (n=1199) n (%)	Vardenafil (n=2203) n (%)
Death	1 (<0.1%)	0 (0%)
Syncope	1 (<0.1%)	2 (<0.1%)
Dizziness	11 (0.9%)	48 (2.2%)
Palpitations	3 (0.3%)	11 (0.5%)
Seizures (convulsions)	0 (0%)	1 (<0.1%)

**Table 7-2: Incidence of coded ECG Findings (Treatment-Emergent) Which May be a Potential Signal for Proarrhythmic Events in Placebo-Controlled Studies**

Clinical events	Placebo n (%)	Vardenafil n (%)
Ventricular arrhythmia	0 (0%)	0 (0%)
Ventricular ectopy or premature ventricular complexes	30/1114 (2.7%)	67/2093 (3.2%)
Ventricular tachycardia	0 (0%)	0 (0%)
Torsades de pointes	0 (0%)	0 (0%)
Ventricular fibrillation and flutter	0 (0%)	0 (0%)

In summary, the adverse events that have occurred during clinical trials with vardenafil do not suggest the occurrence of an arrhythmia resulting from a delay in ventricular repolarization. The circumstances of deaths occurring in patients taking vardenafil in all clinical trials, including ongoing studies, did not suggest a relation to cardiac arrhythmia occurring in a temporal association with vardenafil dosing.

## 8. Conclusions

In the preclinical studies with vardenafil, there was no signal for QT prolongation and pro-arrhythmic activity.

In the vardenafil Phase I-Phase III clinical development program, there was no evidence of drug-induced TdP and related cardiovascular events.

The well-designed QT study conducted in accordance with current regulatory guidance concepts allows more definitive conclusions regarding the QT effect of vardenafil.



1. Exposure to therapeutic and supra-therapeutic concentrations of vardenafil decreased absolute QT interval by 2 msec (compared to placebo), while HR increased by 5 to 6 bpm.
2. The magnitude of corrected QT prolongation observed with both PDE5 inhibitors vardenafil and sildenafil varies slightly with the method of correction used but remains in a range that is considered to be of little or no risk for pro-arrhythmia and TdP for therapeutic doses and of little risk for supratherapeutic doses.
3. The relationship between corrected QT values and vardenafil doses/concentrations that encompass strong metabolic inhibition is very shallow.
4. Several characteristics listed below should reduce the risk of QTc prolongation while using vardenafil. They include:
  - a) an increase in HR due to the inherent pharmacological properties of vardenafil and the conditions under which the drug is used (sexual intercourse)
  - b) an intermittent use
  - c) a male population
5. The effect of vardenafil on the QT/QTc interval (peak mean QTc effect of 5-10 msec and no effect on absolute QT) is similar to that of sildenafil which has been prescribed to millions of patients worldwide and has not been shown to increase cardiovascular events when compared to age-matched general population.<sup>19-20</sup>

In conclusion, we believe that the definitive QT study presented in this briefing document has demonstrated that a large range of vardenafil doses/concentrations may produce a small QTc prolongation that is not associated with absolute QT

prolongation. This prolongation is similar to that observed with another widely prescribed PDE5 inhibitor sildenafil and is unlikely to be clinically relevant.

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## **10. Appendices**

### **10.1 Appendix 1**

**THE CLINICAL EVALUATION OF QT/QT<sub>c</sub> INTERVAL PROLONGATION AND  
PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS**

**PRELIMINARY CONCEPT PAPER**

*For Discussion Purposes Only*

*November 15, 2002*

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45 **PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS**  
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51 **1.0 INTRODUCTION**  
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53 **1.1 Background**  
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55 Certain drugs have the ability to delay cardiac repolarization, an effect that is manifested on the  
56 surface electrocardiogram (ECG) as prolongation of the QT interval. The QT interval represents  
57 the duration of ventricular depolarization and subsequent repolarization, beginning at the initiation  
58 of the Q wave of the QRS complex and ending where the T wave returns to isoelectric baseline.  
59 QT interval prolongation creates an electrophysiological environment that favours the  
60 development of cardiac arrhythmias, most clearly torsade de pointes, but possibly other ventricular  
61 arrhythmias as well. Torsade de pointes (TdP) is a polymorphic ventricular tachyarrhythmia that  
62 appears on the ECG as continuous twisting of the vector of the QRS complex around the  
63 isoelectric baseline. A feature of TdP is pronounced prolongation of the QT interval in the sinus  
64 beats preceding the arrhythmia. TdP can degenerate into life-threatening cardiac rhythms, such as  
65 ventricular fibrillation, which can result in sudden death.  
66

67 Delayed cardiac repolarization is an undesired side-effect when caused by non-antiarrhythmic  
68 drugs such as pimozide, thioridazine, bepridil, lidoflazine, terfenadine, astemizole, and cisapride.  
69 Even when the effect is part of the therapeutic mechanism of an anti-arrhythmic drug, excessive  
70 QT interval prolongation can lead to new arrhythmias with potentially fatal consequences.  
71

72 Because of its inverse relationship to heart rate, the QT interval is routinely transformed  
73 (normalized) by means of various formulae into a heart rate independent “corrected” value known  
74 as the QT<sub>c</sub> interval. The QT<sub>c</sub> interval is thus intended to represent the QT interval at a  
75 standardized heart rate (essentially the QT interval at a heart rate of 60 bpm). It is not clear,  
76 however, whether arrhythmia development is more closely related to an increase in the absolute  
77 QT interval or an increase in the relative (“corrected”) QT interval (QT<sub>c</sub>). Most drugs that have  
78 caused TdP clearly increase both the absolute QT and the QT<sub>c</sub>.  
79

80 The combination of a drug’s effect to prolong QT/QT<sub>c</sub> interval and documented cases of TdP  
81 (fatal and non-fatal) associated with the drug’s use has resulted in a substantial number of  
82 regulatory actions, including withdrawal from the market (terfenadine, cisapride, astemizole,  
83 grepafloxacin), relegation to second-line status (bepridil, thioridazine), and denial of marketing  
84 authorization (lidoflazine). Because prolongation of the QT/QT<sub>c</sub> interval is the  
85 electrocardiographic finding associated with the increased susceptibility to these arrhythmias, an  
86 adequate pre-marketing investigation of the safety of a new pharmaceutical agent should include

87 rigorous characterization of its effects on the QT/QTc interval, as well as systematic collection of  
88 clinical adverse event data that might represent cardiac arrhythmias.

89  
90 This document provides recommendations to drug developers concerning the design, conduct, and  
91 interpretation of clinical studies intended to assess the effects of new agents on the QT/QTc  
92 interval. The study, measurement, and interpretation of QT/QTc interval effects are the subject of  
93 intense evaluation and discussion.

## 94 95 **1.2 Scope**

96  
97 The recommendations contained in this document are generally applicable to new  
98 pharmaceuticals having systemic bioavailability. The focus is on agents being developed for uses  
99 other than the control of arrhythmias, as anti-arrhythmic drugs may prolong the QT/QTc interval  
100 as a part of their mechanism of clinical efficacy. The investigational approach used for a particular  
101 drug should be individualized, depending on the pharmacodynamic, pharmacokinetic, and safety  
102 characteristics of the product, as well as on its proposed clinical application.

103  
104 While this document is concerned primarily with the development of novel agents, the  
105 recommendations may also be applicable to approved drugs when a new dose or route of  
106 administration is being developed that may result in higher  $C_{max}$  or AUC values. Additional ECG  
107 data may also be appropriate if a new indication or patient population is being pursued. The  
108 availability of a comprehensive evaluation of QT/QTc interval effects in the supplemental  
109 submission will be particularly important if the drug or members of its therapeutic class have been  
110 associated with QT/QTc interval prolongation, torsade de pointes, or sudden cardiac death over  
111 the course of clinical trials or during post-marketing surveillance.

## 112 113 114 **2.0 CLINICAL TRIALS**

### 115 116 **2.1 General**

117  
118 All drugs should receive a systematic electrocardiographic evaluation during the early stages of  
119 clinical development, whether or not positive findings were noted in non-clinical  
120 electrophysiology studies. A suspicion of delayed cardiac repolarization on the basis of non-  
121 clinical studies should, however, lead to a more rigorous ECG assessment program with larger  
122 sample sizes, higher systemic concentrations, and more frequent ECG measurements. Because  
123 initial clinical trials are generally limited to a relatively small number of healthy volunteers,  
124 negative findings in these studies cannot necessarily be extrapolated to the intended patient  
125 population, in which additional, population-specific, risk factors may be present.

126  
127 As with other routine safety variables such as vital signs or laboratory tests, the ECG should be  
128 monitored in phase 2 and phase 3 clinical trials, even in the absence of a positive signal of  
129 repolarization impairment in non-clinical or earlier clinical studies. If the earlier clinical trials  
130 provide evidence of QT/QTc interval prolongation, a more intensive phase 3 evaluation will be  
131 needed.

132

## 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.

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### *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*

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

238  
239 Figure 1 provides a schematic representation of the roles played by non-clinical assessments and  
240 phase 1 clinical trials in determining the extent of the ECG safety evaluation in subsequent phases  
241 of the drug development process. The major differences between routine and intensive phase 2/3  
242 evaluation are shown in Table 1. As a general matter, any evidence of QT interval prolongation in  
243 human studies will lead to an intensive phase 3 evaluation. A positive non-clinical finding can be  
244 “rebutted” by failure to observe an effect in phase 1 and 2 studies. The findings in phase 3  
245 (magnitude of effect, steepness of dose-response relationship, etc.), will determine the need for  
246 further studies and will affect the ultimate risk/benefit conclusion.

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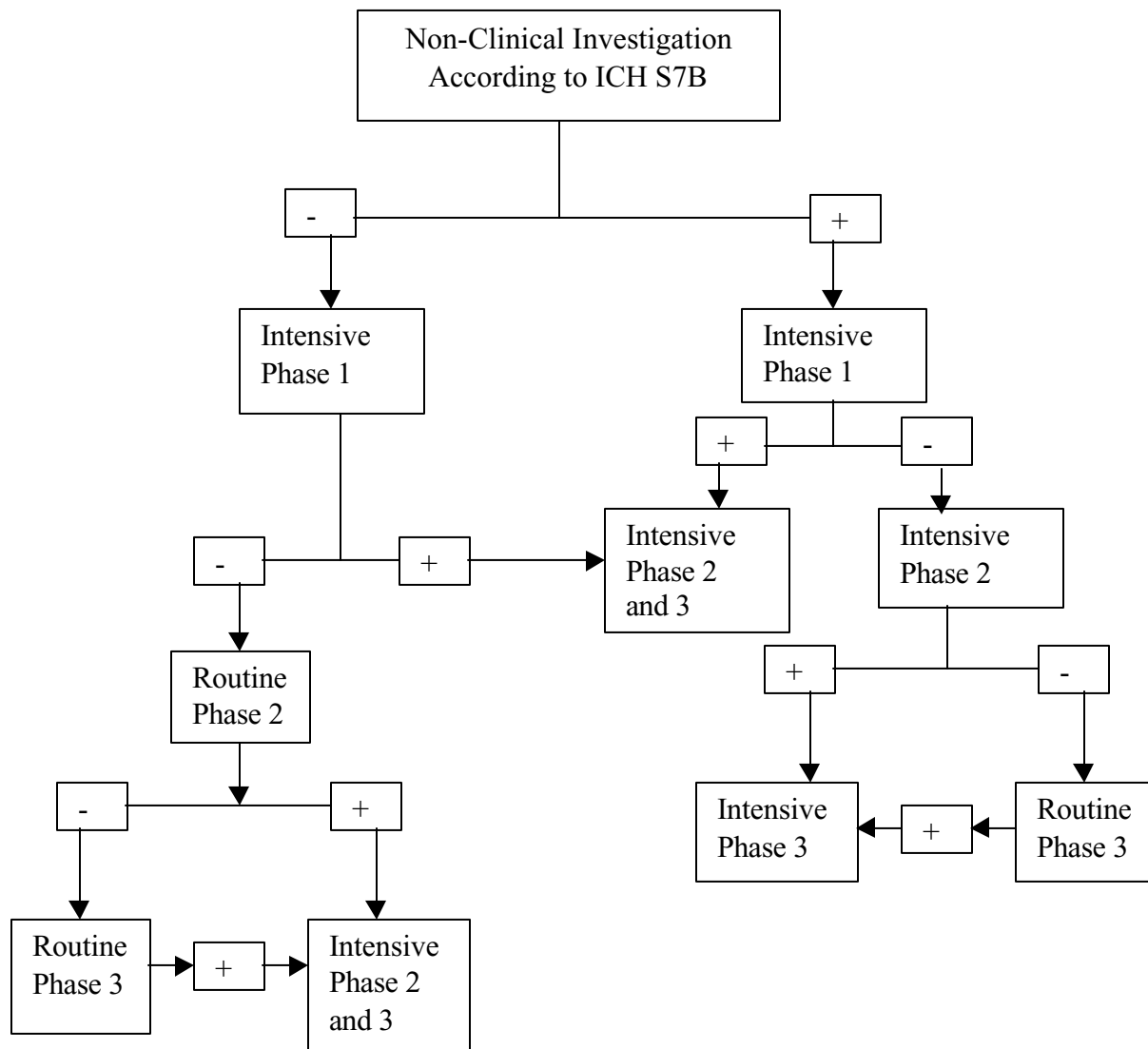
Table 1

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

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Figure 1



+ = Positive signal of QT/QTc interval prolongation liability

- = No signal of QT/QTc interval prolongation liability

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

264  
265 Evidence of repolarization impairment potential in the non-clinical studies would call for an  
266 intensive phase 2 clinical investigation of ECG safety, even in the absence of a QT/QTc interval  
267 prolongation effect in phase 1 trials. If the results of both the phase 1 and 2 clinical trials do not  
268 provide evidence of QT/QTc interval prolongation, these would supersede the positive non-  
269 clinical findings and qualify the drug for a routine ECG safety assessment in the phase 3 clinical  
270 trials. If the phase 2 clinical trials have findings consistent with repolarization impairment, then  
271 an intensive ECG safety evaluation would be required in the phase 3 clinical trials.

### 272 273 *2.2.3 Demographic Considerations*

274  
275 The following patient groups are of particular interest in relation to an agent's effects on the  
276 QT/QTc interval:

- 277
- 278 • Patients with electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia)
- 279 • Patients with congestive heart failure
- 280 • Phenotypic poor metabolizers, for drugs cleared by CYP 450 enzymes that are subject to
- 281 genetic polymorphisms
- 282 • Females
- 283 • Patients aged <16 and over 65 years
- 284 • Patients with renal or hepatic impairment, depending on the routes of excretion of the drug
- 285

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

290  
291 All applications should include QT/QTc interval subset analyses for the above population groups,  
292 derived from phase 2/3 clinical trials. If sufficient numbers of patients are available, a subset  
293 analysis may sufficiently address a drug-population interaction while, in other cases, the analyses  
294 may suggest the need for studies specifically designed to explore the influence of the covariate of  
295 interest.

### 296 297 *2.2.4 Drug-Drug Interactions*

298  
299 If the blood levels of a drug that prolongs the QT/QTc interval can be increased by a drug-drug or  
300 drug-food interactions involving metabolizing enzymes (e.g., CYP3A4, CYP2D6) or transporters  
301 (e.g., P-glycoprotein), systematic clinical pharmacology studies of these interactions should be



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

310  
311 Population pharmacokinetic-pharmacodynamic analyses may have a useful role in the  
312 identification of unsuspected drug-drug interactions leading to cases of marked QT/QTc interval  
313 prolongation in the pivotal clinical trials.

#### 314 2.2.5 Eligibility and Discontinuation Criteria

315  
316  
317 If QT/QTc interval prolongation is anticipated on the basis of non-clinical studies or preliminary  
318 clinical trial data, the following exclusion criteria should be used for early clinical trials, especially  
319 those enrolling healthy volunteers:

- 320
- 321 • A marked baseline prolongation of QT/QTc interval (see below).
- 322 • A history of additional risk factors for torsade de pointes (*e.g.*, heart failure, hypokalemia).
- 323 • The use of concomitant medications that prolong the QT/QTc interval.

324  
325 A commonly-used definition of baseline prolongation of the QT/QTc interval is repeated  
326 demonstration of a QT/QTc interval of >450 msec on a baseline ECG. If supported by the QT/QTc  
327 interval safety data from the early studies, later clinical trials should expand the eligibility criteria  
328 to include a fuller spectrum of patients who are likely to receive the drug once approved.  
329 Depending on the population, this could include patients with prolonged QT/QTc intervals at  
330 baseline or additional risk factors for arrhythmia.

331  
332 If a clinical trial subject experiences a significant, treatment-emergent increase in the QT/QTc  
333 interval, procedures for more intensive cardiac monitoring of that individual should be  
334 implemented immediately; these should be considered before the trial and specified in the clinical  
335 trial protocol. In the event of overdose with a QT/QTc interval-prolonging drug, ECG  
336 monitoring is recommended until plasma concentrations of the drug have declined to the  
337 therapeutic range and the QT/QTc interval has returned to normal. Discontinuation of a subject  
338 from a clinical trial should be considered if there is a prolongation of the QT/QTc interval during  
339 treatment with the study drug. While an increase in QT/QTc to >500 msec or an increase of >60  
340 msec over baseline are commonly used as thresholds for potential discontinuation, the exact  
341 criteria chosen for a given trial will depend on the risk-tolerance level considered appropriate for  
342 the indication and patient group in question.

343

## **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.

390  
391 All ECG readings should be performed by a few designated cardiologists operating from a  
392 centralized (core) ECG laboratory who are blinded to time, treatment and patient identity. The  
393 generation of multiple databases should be discouraged. Inter-reader variability can be minimized  
394 by having one or two cardiologists serve as readers for the entire database. The degree of inter-  
395 and intra-reader reliability should be established by having the cardiologist(s) reread a subset of  
396 the data under blinded conditions. The participation of cardiology specialists is also valuable for  
397 diagnostic evaluation of the ECG recordings. Criteria to assess ECG diagnoses and identify  
398 adverse events should be pre-defined by the sponsor. If it proves impractical to have a small  
399 number of readers, at a minimum any ECGs that pose reading problems or are above some  
400 threshold (e.g., 440 msec) should be over-read by a single or small number of readers.

401  
402 The quality of the ECG database may depend on the use of modern equipment with the capacity  
403 for digital signal processing. Such equipment should be recently serviced and calibrated.  
404 Machine calibration records and performance data should be maintained on file. In the case of  
405 multicentre trials, training sessions are encouraged to ensure consistency of operator technique  
406 (e.g. skin preparation, lead placement, patient position) and data acquisition practices.

### 407 408 *2.3.2 Holter Monitoring*

409  
410 Holter monitoring is an ambulatory ECG recording obtained from one (usually) or multiple (up to  
411 12) leads. Although Holter monitoring is not sufficiently well standardized to serve as the primary  
412 assessment ECG for QT/QTc interval effects, it has clear potential value. It may, for example,  
413 allow detection of extreme QT/QTc interval events that occur infrequently during the day. If a  
414 lead with a well-defined T wave can be found, Holter monitoring allows measurement of the  
415 QT/QTc interval over an extended period (up to 72 h) so that the effects of diurnal fluctuation and  
416 variations of heart rate during exercise and rest can be explored. QT/RR data from Holter  
417 monitoring can be used in the calculation of individualized QT corrections. However, as QT/QTc  
418 intervals measured by Holter methodology do not correspond quantitatively to those for standard  
419 ECGs, data obtained from the two methodologies are not suitable for direct comparison or  
420 pooling.

### 421 422 *2.3.3 Submission of Interval Data and Overall Assessments*

423  
424 In general, intervals and overall interpretations of all ECGs recorded throughout the drug  
425 development program should be submitted as part of the full study reports. For guidance on the  
426 submission of ECG interval data and overall assessments, see “Regulatory Submissions in  
427 Electronic Format; General Considerations.”

### 428 429 *2.3.4 Submission of Annotated Waveform Data*

430  
431 For the purpose of validating assessments of ECG intervals and overall interpretations, it is  
432 necessary to review the placement of fiducial marks on the ECG waveform. A standard format  
433 for the submission of annotated ECG waveforms is being developed in cooperation with the HL7  
434 standards organization. When such a standard is available, annotated ECG waveform data may be  
435 submitted to supplement ECG interval and overall assessment datasets for any study, according to

436 applicable guidance. However, it will be critical to have annotated ECG waveform data for those  
437 studies intended to definitively address the effects of a drug on ventricular repolarization.  
438

439

### 440 3.0 ANALYSIS OF ECG DATA FROM CLINICAL TRIALS

441

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

445

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

459

#### 460 3.1 QT Interval Correction Formulae

461

462 As the QT interval has an inverse relationship to heart rate, the measured QT intervals are  
463 generally corrected for heart rate in order to determine whether they are prolonged relative to  
464 baseline. Various correction formulae have been suggested, of which Bazett's and Fridericia's  
465 corrections are the most widely used.

466

467 Bazett's correction (exponential square root)

468

$$469 \text{QTc} = \frac{\text{QT}}{\text{RR}^{1/2}}$$

470

471 Fridericia's correction (exponential cube root)

472

$$473 \text{QTc} = \frac{\text{QT}}{\text{RR}^{1/3}}$$

474

475 Bazett's formula has been more frequently used in the medical literature than Fridericia's formula,  
476 so that most reported criteria for normal and abnormal values are derived from Bazett's formula<sup>1</sup>:

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<sup>1</sup> 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

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481  
482 Bazett’s correction, however, overcorrects at elevated heart rates and undercorrects at rates below  
483 60 bpm. Fridericia’s formula may therefore be more accurate in subjects with extreme heart rate  
484 values.

485  
486 Correction formulae based on linear regression techniques have also been proposed. In such a  
487 method, one would fit a linear model of  $QT = a + b \times RR$  to the placebo/unexposed (baseline)  
488 study population. Using this estimated slope “b,” one could standardize the data for both drug and  
489 control treatment groups to a normalized heart rate of 60 bpm using the following equation:  
490 observed QT(in msec) + [slope ( 1-RR)] = standardized QT. The Framingham formula, [QTc=  
491 QT + 0.154(1-RR)] is one example of a correction formula derived by linear regression.

492  
493 Linear or non-linear regression modeling has also been used to analyze pooled data from large  
494 databases to derive population-based heart rate corrections.

495  
496 Finally, heart rate corrections using individual patient data have been proposed, applying  
497 regression analysis techniques to obtain individual pre-therapy QT/RR interval data over a range  
498 of heart rates, then looking for a change in regression line with treatment<sup>2</sup>. This approach is most  
499 suitable for phase 1 and early phase 2 studies of crossover design, where it is possible to obtain  
500 many QT interval measurements for each study subject. As adaptation of the QT/QTc interval to  
501 changes in heart rate is not instantaneous, care should be taken to exclude ECG recordings  
502 collected during times of heart rate instability (e.g., during exercise protocols) due to this QT/RR  
503 hysteresis effect.

504  
505 As the optimal correction approach is a subject of controversy, uncorrected QT interval data, along  
506 with QT interval data corrected using Bazett’s and Fridericia’s corrections, should be submitted in  
507 all applications, as should corrected QT intervals using less standard corrections. Concurrent  
508 active control groups are strongly encouraged to support the use of novel correction approaches  
509 (e.g., individual patient correction, Holter-based correction) in order to demonstrate the ability of  
510 the correction method to allow detection of relevant effects on the QT/QTc interval. The sponsor  
511 should attempt to explain any discrepancy between the results obtained by application of different  
512 correction formulae.

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<sup>2</sup> 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

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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.

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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.

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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:

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

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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

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

606

### 607 3.2.3 QT/QTc Interval Dispersion

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

618

## 619 3.3 Morphological Analyses of ECG Waveforms

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

625

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

633

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

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<sup>3</sup> 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.



639 **3.4 Statistical Considerations**

640  
641 QT/QTc interval data should be presented in terms of means, standard deviations, ranges, and  
642 confidence intervals. Clinical trials that investigate the QT/QTc interval prolongation potential of  
643 a drug should have sufficient power (*i.e.*,  $\geq 80\%$ ) to detect modest mean differences between  
644 treatment groups (*e.g.*, 4-5 msec). The power calculation should take into account the expected  
645 precision of the QT/QTc interval measurement. The actual precision should be experimentally  
646 verified in each study. The most direct way to accomplish this is through the inclusion of a  
647 concomitant positive control in the trial design.

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650 **4.0 ADVERSE EXPERIENCES**

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

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

658  
659 **4.1 Clinical Trial Adverse Experience Reports**

660  
661 Although drug-induced prolongation of the QT/QTc interval is usually asymptomatic, an  
662 increased rate of certain adverse events in patients taking an investigational agent can signal  
663 potential proarrhythmic effects. The rates of the following clinical events should be compared in  
664 the treated and control patients as a part of a product's submission for marketing, particularly  
665 when there is evidence that a drug affects the QT/QTc interval.

- 666
- 667 • Torsade de pointes.
  - 668 • Ventricular tachycardia.
  - 669 • Ventricular arrhythmia.
  - 670 • Ventricular ectopy.
  - 671 • Ventricular fibrillation and flutter.
  - 672 • Cardiac arrest.
  - 673 • Sudden death.
  - 674 • Syncope.
  - 675 • Dizziness.
  - 676 • Palpitations.
  - 677 • Seizures (a possible consequence of cerebral ischemia resulting from arrhythmia).

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679  
680 The occurrence of torsade de pointes is captured infrequently in most clinical databases, even  
681 those for drugs known to have significant proarrhythmic effects (*e.g.*, dofetilide). Given this, the  
682 failure to observe an episode of torsade de pointes in a drug application database is not sufficient  
683 grounds for dismissing the possible arrhythmogenic risks of a drug when these are suspected on  
684 the basis of ECG and other clinical data. The other adverse events listed, while less specific for an

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

690  
691 Detailed patient narratives should be provided for all serious cardiac adverse events, as would be  
692 the case for any serious event or events leading to discontinuation. In assessing the possible  
693 causal relationship of drug-induced QT/QTc interval prolongation to the event, attention should be  
694 directed to considerations such as temporal relationship and ECG results collected at the time of  
695 the event. As the QT/QTc interval is subject to considerable fluctuation, a possible role for  
696 QT/QT interval prolongation cannot be dismissed on the basis of normal on-therapy ECG  
697 measurements performed prior to near the time of the adverse event. For adverse events that  
698 appear to be dose-related, potential relationships to patient age, gender, pre-existing cardiac  
699 disease, electrolyte disturbances, concomitant medications, and the other risk factors listed in  
700 section 5.2 should be explored. In addition to an appropriate adverse reaction report, patients with  
701 marked QT/QTc prolongation or an episode of torsade de pointes may provide useful information  
702 on risk management. When identified, they should therefore be examined closely for other risk  
703 factors, including genetic predisposition (see section 4.3). When conducted in a well-monitored  
704 environment starting at low doses, exploring the dose and concentration-responses of the drug in  
705 these individuals could also prove useful.

706  
707 In evaluating the safety database of a new drug, consideration should be given to the extent to  
708 which the inclusion and exclusion criteria for patient eligibility may have influenced the study  
709 population with respect to the risk of QT/QTc interval prolongation and associated adverse events  
710 (*e.g.* exclusion of patients with cardiac co-morbidities or renal/hepatic impairment, prohibition of  
711 diuretics as concomitant medications). Ideally, the major clinical studies should include an  
712 adequate representation of female and elderly patients, as well as patients with co-morbidities and  
713 concomitant medications typical of the expected user population.

714  
715 If a subject experiences symptoms or ECG findings suggestive of an arrhythmia during a clinical  
716 trial, immediate discontinuation of the suspect drug and evaluation by a cardiac specialist are  
717 recommended, both for purposes of treating the patient and for discussions related to continuation/  
718 re-institution of the therapy.

## 719 **4.2 Premature Discontinuations or Dosage Reductions**

720  
721 Particular attention should be directed to subjects or patients who discontinue clinical trials due to  
722 QT/QTc interval prolongation. Information should be provided on the basis for premature  
723 termination of the patient (*e.g.*, a QT/QTc interval value in excess of a protocol-defined upper  
724 limit, occurrence of QT/QTc interval prolongation in association with symptoms of arrhythmia),  
725 as well as the dose and duration of treatment, plasma levels if available, demographic  
726 characteristics, and the presence or absence of the other risk factors listed in section 5.2.

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

730

### 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

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

770  
771 Special considerations apply to anti-arrhythmic drugs that utilize delayed repolarization as part of  
772 their mechanisms, but in this case, it will be critical to provide outcome data to quantify risk.  
773 Whether such a drug could be approved would depend on the nature of its benefit, the size of its  
774 effect on the QT/QTc interval, and the potential for managing or reducing risk by dose limitation,  
775 monitoring, or other approaches.

776  
777 For non-antiarrhythmic drugs, the outcome of the risk benefit assessment will be influenced by the  
778 size of the QT/QTc interval prolongation effect, whether the effect occurs in most patients or only  
779 in certain defined outliers, the overall benefit of the drug, and the utility and feasibility of risk  
780 management options. The inclusion of precautionary material in the prescribing information will  
781 not necessarily represent an adequate risk management strategy, if implementation of the  
782 recommendations in a clinical use setting is judged to be unlikely.

783  
784 If QT/QTc interval prolongation is a feature shared by other drugs of the therapeutic class in  
785 question, evaluation of the new drug will involve a comparison of the magnitude and incidence of  
786 any QT/QTc interval prolongation effects relative to those of other members of its class in  
787 concurrent active control groups. An excess risk for the new drug relative to approved therapies  
788 would, other things being equal, have a negative impact on its risk-benefit assessment.

789  
790 For drugs that prolong the QT/QTc interval, the mean degree of prolongation has been roughly  
791 correlated with the observed risk of clinical proarrhythmic events. Whether there are drugs that  
792 cause extreme prolongation (*e.g.*, >500 msec) in a small fraction of patients with only modest  
793 mean effects is not clear, but this would seem to be a troublesome property.

794  
795 It is difficult to determine whether there is an effect on the mean QT/QTc interval that is so small  
796 as to be inconsequential, although drugs whose maximum effect is less than 5 msec at high doses  
797 and during co-administration of saturating doses of metabolic inhibitors, have not so far been  
798 associated with torsade de pointes. Whether this signifies that no increased risk exists for these  
799 compounds or simply that the increased risk has been too small to detect is not clear. To date,  
800 drugs that prolong the mean QT/QTc interval by 5-10 msec under conditions of maximum effect  
801 have also not been clearly associated with risk. Drugs causing a mean 10-20 msec increase under  
802 conditions of maximum effect are of concern, but have been approved if they appear to have  
803 important therapeutic roles. Drugs that prolong the mean QT/QTc interval by >20 msec have a  
804 substantially increased likelihood of being proarrhythmic, and may have clinical arrhythmic events  
805 captured during drug development. While it has been suggested that some drugs might prolong  
806 the QT/QTc interval up to a “plateau” value, above which there is no dose-dependent increase, this  
807 has not been demonstrated adequately to date. As noted, it is critical to identify the “worst case  
808 scenario,” *i.e.*, the QT/QTc interval measured in the target patient population at the time of peak  
809 effect and under conditions of the highest blood levels that can be attained during therapy as a  
810 result, *e.g.*, of a drug-drug interaction.

811

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

819  
820 QT/QTc interval prolonging drugs having primary metabolic pathways involving enzymes that are  
821 subject to genetic polymorphisms (*e.g.*, CYP2D6, CYP2C19) or inhibition by many drugs  
822 (CYP3A4) would be regarded with particular concern due to the possibility of markedly elevated  
823 plasma levels in those patients who are poor metabolizers or who receive an interacting  
824 xenobiotic, unless it has been established that these higher levels do not lead to greater effect on  
825 the QT/QTc interval. A susceptibility to drug-drug interactions due to effects on transporter  
826 proteins would also have a negative impact on the risk-benefit assessment.

## 827 828 **5.2 Labeling Issues for Drugs that Prolong the QT/QTc Interval**

829  
830 If approval is granted to a drug that affects cardiac repolarization to an extent that is considered a  
831 clinical concern, sponsors should consider the following prescribing information:

- 832
- 833 • A warning/precautionary statement about the effects of the drug on cardiac repolarization,  
834 appropriate to the risk observed in the development program.
  - 835 • A clear description of the trials used to obtain QT/QTc interval information, including the  
836 numbers and demographics of the patients who received ECG evaluations in clinical trials.  
837 Any entry criteria that limited the patient exposure (*e.g.*, excluding the use of antiarrhythmic  
838 drugs).
  - 839 • A description of the effects of the drug on the QT/QTc interval in the relevant patient  
840 populations in terms of both the mean change in the QT/QTc interval and the percentage of  
841 patients with on-therapy QT/QTc readings in excess of a defined upper limit (*e.g.*,  $\geq 480$  msec).  
842 Information on the dose-, concentration-, and time-dependency of the QT/QTc interval  
843 prolongation effect.
  - 844 • Where possible, dosage recommendations encouraging the use of the lowest effective dose of  
845 the drug and specifying maximum recommended single and total daily doses that should not  
846 be exceeded. Restrictions on the size and frequency of incremental dose adjustments.  
847 Identification of a time after which the drug should be discontinued if there has not been a  
848 satisfactory response. For an intravenously administered QT/QTc interval-prolonging drug,  
849 limitations on the injection and/or infusion rates if known.
  - 850 • A list of the diseases or disorders known to increase the possibility of arrhythmic events.  
851 Emphasis should be placed on the need to exercise particular care in patients having these  
852 conditions. In some cases, contraindications may be appropriate. Risk factors for drug-  
853 induced arrhythmias secondary to QT/QTc interval prolongation include, but are not limited  
854 to, the following:

855

- 856 • Congenital long QT interval syndrome (*e.g.* Romano-Ward syndrome, Jervell and
- 857 Lange-Nielson syndrome, and Andersen syndrome).
- 858 • Family history of sudden cardiac death at <50 years.
- 859 • Ischemic heart disease or infarction.
- 860 • Congestive heart failure.
- 861 • Left ventricular hypertrophy.
- 862 • Positive history of arrhythmias (especially ventricular arrhythmias, atrial
- 863 fibrillation, or recent conversion from atrial fibrillation).
- 864 • Cardiomyopathy.
- 865 • Bradycardia.
- 866 • Myocarditis.
- 867 • Cardiac tumours.
- 868 • Valvular heart disease.
- 869 • Bundle branch block.
- 870 • Sinus node dysfunction.
- 871 • Severe hepatic or renal dysfunction, if the drug is excreted renally or hepatically.
- 872 • Electrolyte imbalance (*e.g.*, hypokalaemia, hypomagnesaemia, hypocalcaemia,
- 873 acidosis, intracellular Ca<sup>2+</sup> loading) or conditions (*e.g.*, chronic vomiting, anorexia
- 874 nervosa, bulimia nervosa) and drugs (*e.g.*, diuretics) predisposing the patient to
- 875 electrolyte imbalances .
- 876 • Concomitant treatment with other drugs or foods that inhibit the metabolism of the
- 877 QT/QTc interval prolonging drug.
- 878 • Subarachnoid haemorrhage.
- 879 • Hypothermia.
- 880 • Nutritional deficits (*e.g.* eating disorders, liquid protein diets).
- 881 • Alcoholism.
- 882 • Autonomic neuropathy.
- 883
- 884 • Discouragement (or contraindication of ) the concomitant use of two or more QT/QTc interval
- 885 prolonging drugs. Where available from the clinical trials, information about the concomitant
- 886 use of such medications. The list of drugs that affect cardiac repolarization and prolong the
- 887 QT/QTc interval (it would be lengthy and change as new information becomes available).
- 888 Examples of such agents include, but are not limited to, the following:
- 889
- 890 • Class IA antiarrhythmics (*e.g.*, quinidine, procainamide, disopyramide).
- 891 • Class III antiarrhythmics (*e.g.*, amiodarone, dofetilide, sotalol, ibutilide).
- 892 • Tricyclic antidepressants (*e.g.*, amitriptyline, imipramine, doxepin, nortriptyline,
- 893 desipramine).
- 894 • Bepridil.
- 895 • Certain phenothiazine antipsychotics (*e.g.*, thioridazine, mesoridazine,
- 896 chlorpromazine).
- 897 • Pimozide.
- 898 • Maprotiline.
- 899 • Macrolide antibiotics (*e.g.*, erythromycin, clarithromycin).
- 900 • Certain fluoroquinolone antibiotics (*e.g.*, moxifloxacin, gatifloxacin).

- 901           • Pentamidine.
- 902           • Antimalarials (*e.g.*, halofantrine, quinine, chloroquine, mefloquine).
- 903           • Probucof.
- 904           • Droperidof.
- 905           • Dolasetron.
- 906           • Tamoxifen.
- 907           • Tacrolimus (intravenous).
- 908           • levo-alpha-acetylmethadol (LAAM).
- 909           • Arsenic trioxide.
- 910
- 911   • Recommendations for screening ECGs, depending on the information available from the  
912   clinical trials. In general, a drug that prolongs the QT/QTc interval should not be initiated in  
913   patients with abnormally long baseline QT/QTc intervals. Monitoring of the QT/QTc interval  
914   during treatment may also be advisable, particularly during the initial stages of treatment, after  
915   a dosage increase, or for drugs administered intravenously. Discontinuation of the drug should  
916   be considered if an arrhythmic event occurs or if the QT/QTc interval becomes markedly  
917   prolonged.
- 918   • Warning that serum potassium, calcium, and magnesium levels should be measured prior to  
919   initiation of treatment with a QT/QTc interval prolonging drug. Treatment should not be  
920   initiated in any patient with uncorrected electrolyte abnormalities. Serum electrolyte levels  
921   should be monitored during treatment, with prompt correction and/or discontinuation of the  
922   QT/QTc interval-prolonging drug in the event of an electrolyte abnormality.
- 923   • Recommendations to physicians who prescribe a drug that prolongs the QT/QTc interval to  
924   counsel their patients concerning the nature and implications of the ECG changes, underlying  
925   diseases and disorders that may represent risk factors, demonstrated and predicted drug-drug  
926   interactions, symptoms of possible arrhythmia, and other information relevant to the use of the  
927   drug.
- 928   • Information for the consumer that explains in lay language the effect of the drug on the  
929   electrical activity of the heart and the relationship between this ECG effect and the theoretical  
930   or demonstrated risk of arrhythmias and sudden death. Any risk management strategies  
931   recommended for a given drug. An alert to patients about the symptoms of possible  
932   arrhythmia such as dizziness, palpitations, and fainting and instructions to seek immediate  
933   medical attention if these occur.

### 934           **5.3 Post-Marketing Risk Management for Drugs that Prolong the QT/QTc Interval**

935

936

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