The FDA, ECG and Your Future: Bringing the Pieces Together

Successful approaches to regulatory, technology and trial management within electrocardiology.

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Centralized Cardiac Services Symposium Summary:
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Introduction

On February 8, 2006, Centralized Cardiac Services of MDS Pharma Services sponsored a symposium regarding the International Conference on Harmonisation (ICH) E14 guidelines. These guidelines specify the new requirements for clinical risk assessment of QT interval prolongation and proarrhythmia for New Drug Applications (NDAs).

Currently, ECG evaluations of QT prolongation serve as a surrogate marker for the risk of arrhythmias including Torsades de Pointes (TdP; "twisting of the points"), the ventricular tachyarrhythmia that typically causes symptoms and death in patients with the rare, congenital Long QT Syndromes (LQTS). However, the recognition that TdP and sudden death can be drug-induced has led to the development of these new evaluative guidelines.

This symposium entitled, "The FDA, ECG and Your Future: Bringing the Pieces Together," featured presentations on the use of ECG measurements of QT prolongation as a surrogate marker for arrhythmias, ECG methodology, clinical study design, outcome interpretation, and the implications of positive and negative findings. Many of the presenters tabulated the difficulties and pitfalls of clinical ECG assessments.

Torsades de Pointes

Torsades de Pointes is a polymorphous VT: the morphology of the QRS complex varies from beat to beat with a ventricular rate ranging from 150 to 250 beats per minute. By definition, TdP occurs in the setting of prolonged repolarization as shown by a prolonged QT

interval on the surface ECG. The arrhythmia may be self-limited or may progress to ventricular fibrillation.

In the 1990s, the delayed recognition of the proarrhythmic nature of several drugs, notably drugs such as cisapride and terfenadine, instigated current regulatory concerns. "The differential diagnosis of Torsades is problematic," explained Borje Darpo, M.D., Ph.D., Vice President and Chief Medical Officer of Daiichi Medical Research, in his presentation, *Putting ICH E14 Regulations into Place*. "Its incidence is 100-fold lower than any other ventricular arrhythmia in susceptible populations. Cases are rarely identified during the clinical development of drugs; adverse drug reaction databases lack sufficient characterization, and the prevalence of drug-induced TdP may range from less than 0.8 to four per 100,000 patients per year."

"For cisapride, the risk of TdP was clearly recognized after 30,000,000 prescriptions and after 100,000,000 prescriptions for terfenadine," explained Philip Sager, M.D., Executive Director of Cardiac Research at AstraZeneca LP, and Clinical Professor of Medicine, New Jersey School of Medicine and Dentistry, in his presentation, *QT Assessment in Late Stage Development*. [1]

"Retrospectively, it's obvious that QT prolongation was under appreciated when based on inappropriately pooled data," said Dr. Darpo, speaking of clinical evaluations of drugs with proarrhythmia propensity. Murray Ducharme, Pharm.D., Vice President, Pharmacokinetics and Pharmacodynamics at MDS Pharma Services, presented the following data from his

[1] Dr. Sager's viewpoints are solely his own and do not reflect those of AstraZeneca LP or the ICH E14 Expert Working Group.

presentation, *The New Shape of QTc Clinical Pharmacology Studies*, that summarized the approval and removal of several drugs from the U.S. market:

Drugs with Proarrhythmic Propensity[2]

Drugs withdrawn in U.S.A. because of TdP: Terfenadine Astemizole Grepafloxacin Cisapride Complicated approval Moxifloxacin Ziprasidone Relabeling Thioridazine Droperidol Several Nonapproval or Approved with QT cautions

Risk Factors for TdP

A prolonged QT interval is a risk factor for TdP. Citing a published study, Dr. Ducharme said that prolongation of corrected QT intervals (QTc) of less than 5 milliseconds carries no increased risk of TdP onset. Based on regulatory experience[3], the risk increases with prolongation such that the risk of TdP onset could be considered "definite" with QTc intervals greater than 26 milliseconds. The FDA and Health Canada regard a mean increase of 20 ms as worrisome. However, Dr. Darpo stated that it remains unclear what a population mean QT prolongation of five to 20 ms means for the patients (most likely dependent on targeted indication and patient population).

[2] Heist EK, Ruskin JN. Heart Rhythm 2005; 11 (2 Suppl): S1-S
[3] Shah RR. Fund & ClinPharmacol 2002; 16:147-156

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"However, increasing the QT interval by itself will not cause Torsades de Pointes," said Dr. Ducharme in clarification. "All drugs known to cause Torsades de Pointes increase the QT interval, through blocking of cardiac potassium channels, specifically the delayed rectifier IK_R. However, the converse is not necessarily true. For example, amiodarone increases the QT interval and blocks the potassium channel, but rarely induces TdP, probably because it also blocks other cardiac ion channels, such as sodium and calcium channels."

However, a host of cofactors can contribute to TdP onset. Foremost, a congenital manifestation of LQTS occurs in patients with a hERG gene mutation; hundreds of gene mutations have been found. hERG encodes for the alpha subunit of IK_R. Approximately one in 10,000 carries the LQTS gene, which is associated with a higher occurrence of sudden death than in the normal population.

"Other general risk factors for TdP include a QTc greater than or equal to 500 ms, heart failure, female gender, high doses of proarrhythmic drugs (e.g., haloperidol), and electrolyte abnormalities," said Dr. Ducharme. "A similar set of cofactors seems associated and may exacerbate drug-induced QT prolongation: bradycardia, hypokalemia, IK_R blockade, hERG mutations, supratherapeutic dosages, female gender, structural heart disease, renal and/or hepatic dysfunction, rapid IV administration, and age."

QT Prolongation as Surrogate Marker

Since clinicians are unable to directly evaluate the risk of Torsades de Pointes, prolongation of the QT interval serves as a surrogate clinical marker for TdP and sudden death.

"The link between drug provocation of QT prolongation and the risk of Torsades de Pointes is not ideal," said Dr. Ducharme, expressing the viewpoint of the consensus. "A lot of drugs can cause increase in QT prolongation, but do not necessarily cause Torsades de Pointes; other events have to occur. Nevertheless, QT prolongation is a useful clinical surrogate marker."

Evaluation of QT Prolongation and Proarrhythmia

Currently, nonclinical risk assessments for QT prolongation and proarrhythmia are specified by ICH S7B. Such S7B assessments generally include *in vitro* identification of IK_R inhibitors through electrophysiological measures in heterologous expression systems and *in vivo* tests in animal models, prior to the first dose in humans.

ICH E14 specifies clinical tests for the assessment of QT prolongation in the form of a "thorough QT study" (TQTS) that evaluates the drug's effect on the QT/QTc in healthy volunteers. Negative findings in the TQTS allow for routine electrocardiology (ECG) safety evaluations in Phase II and III. Positive findings in the TQTS require expanded ECG safety evaluations in the targeted patient population. As initially conceived, E14 was a prescriptive document: detailing each step of study design, ECG monitoring, and ECG collection. "Currently, E14 is clearly less prescriptive." adds Dr. Darpo. "The sponsor needs to validate and defend the methodology."

Regional Differences in Interpretations of Outcomes

The requirements for ICH S7B assessments and the interpretations of the findings are likely to be interpreted somewhat differently in Europe and Japan compared to the United States.

"European regulators generally require these S7B assays, hERG test and *in vivo* assessment of QT prolongation before the first dose in man," explained Dr. Darpo, "whereas this may not be the case in the United States. The Americans don't place a lot of emphasis on nonclinical assays, believing the clinical data trump nonclinical. In Europe, negative nonclinical findings may obviate a thorough QT study, but in the United States, negative nonclinical assays will rarely obviate the QT study."

"With a negative thorough QT study, one need not thoroughly characterize the QT effect in the targeted patient population, and it is sufficient to adhere to standard practice for the therapeutic area. In these cases, there is no need to compile large databases with QT intervals from your Phase III trials," Dr. Darpo explains with the caveat, "in most cases, but clearly so in the United States. With a positive outcome, one must thoroughly characterize the QT effect in the targeted population."

QT Interval Dependent on ECG Method

"QT interval measurements are strongly dependent on ECG technology and methodology," stressed Paul Kligfield, M.D., Professor of Medicine at Cornell University and Weill Medical College; Director of the Cardiac Graphics Laboratory at The New York-Presbyterian Hospital, and Cardiology Advisory Board member for MDS Pharma Services, in his presentation, *On the Matter of Method: A Comparison of ECG Measurement Modalities.* ECG method, ECG algorithms, and ECG equipment affect the results almost as much as drugs do."

Unfortunately, many of the issues raised have no immediate solution. "Consistency" as a method of control was the refrain of many presenters.

Measurement From a Single Lead

Using the depicted signal from a single lead, Dr. Kligfield demonstrated how methodological variability for measuring the end of the T wave altered the measurement of QT from 410 milliseconds (baseline method) to 430 ms (tangent method) to 550 ms (inclusion of the U wave). In this discussion, Dr. Kligfield first unveiled a repetitive issue underlying ECG assessment: "There is no medical definition of the end of a T wave, rather we have proprietary engineering solutions imposed by different manufacturers."

Computer-assisted Measures

Representative Complex

The representative ECG complex is also known as the "median beat." In the creation of a representative complex, an automated algorithm creates a digital synthesis of the average or median complex by averaging 10 seconds of data from a single lead; removing some of the beat-to-beat variability. A single representative complex is generated for each of the 12 leads.

Global Complex

"Creating a global complex takes this process one step further," explained Dr. Kligfield. "All temporally coherent representative complexes of all 12 leads are superimposed on top of one another in perfect temporal alignment to form a global complex. The global complex provides insight into the earliest onset and latest offset of waveform in any lead." As such, global QT measurements are longer than apparent QT of lead II measurements of representative

complexes (for both baseline and tangent methods). Both the earlier onset of global QRS and the later termination of the T wave, relative to localized representative complexes, contribute to this longer global QT. In Dr. Kligfield's example, the average QT of a single lead was 377 milliseconds whereas that of the representative complex was 390 milliseconds and 370 milliseconds by baseline and tangential methods, respectively, while global QT interval was 410 milliseconds.

According to Dr. Kligfield, global complexes are the standard in Europe and becoming the standard worldwide. The automated measurements derived by most 12-lead digital electrocardiographs are global.

"Consistency there becomes a critical factor," said Dr. Kligfield; a statement that was to become a refrain.

Automatic ECG Algorithms

The individual ECG algorithm may also affect QT measurement. "I really encourage you to understand how algorithms work," stated Justin Mortara, Ph.D., Vice President of Mortara Instrument, Inc. "Not all ECG algorithms are equal in performance, and human input is required in the decision making. The results should be systematically reviewed with a well thought out methodology that isn't simply outlier analysis on QT values."

Dr. Kligfield reported a difference of 26 milliseconds between the current Phillips algorithm and its previous generation, and a difference of 15 milliseconds between current and previous generations of General Electric algorithms. "Any ECG machine purchased before 2003 has the earlier algorithm, so most hospitals have a mixture of equipment enough to torpedo many

drug development projects for nonessential drugs." Dr. Kligfield adds that, although the current Phillips and GE machines have a strong correlation, the estimated standard deviation of the mean difference is 13 milliseconds (including 67 percent of the comparison of 218 tracings). "For any single patient, the values are quite divergent and there's no rhyme or reason to it."

Normal versus Abnormal Rhythms

Unfortunately, the measurement of QT is relatively simple when the ECG is normal, but accurate QT measurement becomes more difficult when the T wave is abnormal. "It's most difficult to measure when it is most important," laments Dr. Kligfield. "If we break the population into patients with normal, abnormal, or borderline ECGs, using automated measurements by the GE and Phillips current algorithms, we get an increase in the variability of the average QT interval."

Subject Status

Dr. Mortara reports an enigma in the thorough QT studies he has examined: "How is it possible for healthy volunteers lying at rest in a controlled stable environment to exhibit heart rates of 120 beats per minute? The subject should be at rest."

Pierre Maison-Blanche, M.D., Hôspital Lariboisière, Cardiology Unit, and Chairman of the Cardiology Advisory Board, MDS Pharma Services, strongly iterates this need in his presentation, *Heart Rate Stability Control*: "Prior to recording an ECG, you should put your subject in supine position for five minutes." Using an exercise model, Dr. Maison-Blanche demonstrated a QT shortening effect of a 15-millisecond magnitude related to heart rate, gender, and ECG lead placement. However, when the patients are supine, the effect is reduced to two to

three milliseconds. His suggestion is to replace the traditional 10-second ECG acquisition with longer acquisitions with intervals of 20 or 30 seconds and/or using Holter devices to continuously record up to 12 or 24 hours.

"As adaptation of the QT/QTc interval to changes in heart rate is not instantaneous, care should be taken to exclude ECG recordings collected during times of heart rate instability due to this QT/RR hysteresis effect," say the ICH E14 guidelines. "Sources of QT interval variation include heart rate, gender, circadian sympathetic and parasympathetic activity, drugs, LQTS, electrolyte disorders, disease states, and ECG methodology," said Dr. Maison-Blanche.

Study Design

According to the presenters, the ICH E14 TQTS, should be randomized and blinded and include positive and negative (placebo) control groups. The positive control group should be treated with a drug whose effect on the mean QT/QTc is about five milliseconds. If the agent under investigation belongs to a class known for QT/QTc prolongation, use of a positive control drug belonging to this class might be preferable. Patients should be exposed to the highest dose possible. Single or multiple doses of the investigative agent are allowed, but steady state is preferred. Active metabolites should be measured. Genotyping or phenotyping might be necessary for certain drugs.

"The thorough QT study is a landmark clinical development," claims Dr. Darpo, "as higher precautionary measures to protect the volunteers are required before the conduct of this study." Exclusion criteria should include marked baseline prolongation (QT/QTc interval >450 milliseconds), a history of risk factors for TdP and concomitant medications that prolong the

QT/QTc interval. In accordance, specific discontinuation criteria apply, such as QT interval exceeding 500 milliseconds or an increase from baseline exceeding 60 milliseconds. "After the drug has been characterized, then one can expand the population to whom the drug is given."

Underlying Concept

"The purpose of the thorough QT study is to evaluate the QT prolonging effects of a drug, not to determine its proarrhythmic propensity," explained Dr. Darpo. "It's to determine whether one should characterize the QT effect more carefully in targeted patient populations. The underlying concept is that a drug having proarrhythmic propensity within its targeted patient population, will demonstrate a QT prolonging effect in the volunteers, if one exposes these individuals to sufficiently high plasma concentrations. This concept remains yet to be proven."

Protocol Design

"The best designed protocol is only as good as the data collected," Kathryn Van Nest, Global Trial Manager, Johnson & Johnson Pharmaceutical Research and Development, reminded symposium attendees in her presentation, *Global Study Management Challenge*. "It's a balancing act between the perfect scientific experiment and a protocol your staff group can realistically execute. The best data in the world pockmarked by a plethora of protocol violations isn't going to please regulators." Ms. Van Nest reminded attendees of the need to identify and document responsibilities in a face-to-face group "sit down," prioritizing the "must have" data from the "distractions," and keeping lines of communication open between vendors. Monitoring and sampling equipment and communications capabilities must be suited to the staff, environment (Phase I unit versus hospital versus clinic), and the host country. When working in

other countries, "Involve your in-country partners in protocol design … their expertise is priceless," she said, "and budget money and time for customs and importation."

Parallel versus Cross-Over

"Sometimes one needs to use a parallel design study for drugs with a long elimination half-life, expected carry-over effects, or when multiple doses or treatment groups are to be compared," instructed Dr. Darpo, "but the default position should always be cross-over design because 'within' individual variability is clearly lower than 'between' variability, and the cross-over design also facilitates individual heart rate corrections, if used."

Consistency of ECG Methodology

"Ideally, it would be nice to have the ECGs all digitally collected in a centralized laboratory for Phase II and III studies," Dr. Sager said. "Nevertheless, it is important to standardize methods to the greatest degree possible between studies. A large multicentered trial contains a lot of variability, so education, training, and quality checks are vital in order to standardize ECG collections in a consistent methodological manner to facilitate pooled analyses." Dr. Sager also stressed the need for optimal skin prep and precise ECG sampling so that collections occur at the anticipated time of peak drug effect. "Also, it may not be possible to use automatic ECG measurements in patients who have significant T wave changes and underlying abnormal ECGs (as opposed to normal volunteers). Lastly, attention to equipment servicing and calibration are important," Sager said, "particularly in a multicentered trial."

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Dose

"The relationship between drug concentration and the increase in the QT interval, as well as understanding how drug interactions can influence drug concentrations are very important," stated Dr. Ducharme. "Supratherapeutic concentrations due to drug interactions were the culprit with terfenadine, astemizole, and cisapride." According to E14: "In general, the duration of dosing or dosing regimen should be sufficient to characterize the effects of the drug and its active metabolites at relevant concentrations." In addition, Dr. Darpo commented: "Use the maximum tolerated dose, or justified lower doses, accounting for variability in targeted patient population. The dose must cover the worst case scenario."

An alternative approach to achieving high plasma concentrations, suggested by Dr. Darpo, is the use of a metabolic inhibitor, thus resulting in the same exposure to the parent compound, "but you need to know the effect of the major metabolites on the cardiac potassium channels," he adds. "A gut wall metabolism inhibitor was the co-culprit with terfenadine, whose concomitant administration with ketoconazole increased the QT interval prolongation from six seconds to 74 seconds in one study," stated Dr. Ducharme.

Duration of dosing

ICH E14 does not specify single or multiple doses and opinions differ slightly on what is appropriate. "Major sponsors have used single doses for their TQTS," states Dr. Darpo, "and high single doses may be easier to tolerate for the volunteers than multiples of a somewhat lower dose or multiples of the same dose." Dr. Ducharme, however, says that steady state is preferable: "We've not conducted a study at single dose," citing a study wherein moxifloxacin

was the control – requiring five days dosage to reach steady state while the investigative agent required seven days. “You require at least 12 ECG samples after the dose at steady state.”

Population Issues

Demographics

According to Dr. Darpo, the E14 guidelines specify healthy volunteers for the thorough QT study, but there are no requirements, per se, for age, gender or ethnicity. It is clearly the case, though, that females are at higher risk for TdP. In line with this, Dr. Sager stated that when there is a positive thorough QT signal, additional ECG data must be carefully collected during Phase III, and that this data should be retrospectively analyzed to assess the effects in special groups, including females and individuals more than 65 years of age. Dr. Sager stressed that in late stage development, the clinical trials must include individuals belonging to higher risk groups: “patients with cardiac disease should be represented.”

Population Size

The requirements for the size of the TQTS relate to the powering of the study, which is affected by the effect size of the investigational drug, the variability of the QT measurement, and the study design. “If you have zero drug effect, you are allowed a wider confidence interval and require fewer subjects,” explained Dr. Darpo. “However, when your drug has a small effect on the QT interval, many more individuals are needed to demonstrate that the effect does not exceed 10 milliseconds. The problem is that we many times do not know and cannot estimate in advance the ‘true’ effect size of our drug. So most sponsors power the study with a notion, the

assumption that the effect would be zero, but in many cases it's probably wiser to power the study and calculate the sample size based on a small effect of your drug."

For example, you could decrease the variability to below the 10 milliseconds level with proper study design and methodology, which means that only 50 or 60 individuals would be required. Sloppy design and ECG collection methods create a higher variability, perhaps driving the sample size up to 150-160, Dr. Darpo says.

Referring to studies such as the aforementioned study positively controlled by moxifloxacin, Dr. Ducharme stated that one needs to finish with 35 volunteers per arm, so he usually starts with about 40 subjects per treatment arm. Dr. Sager stated that when examining QT interval changes in larger populations, the focus shifts to the outliers.

Positive Controls

"A well-designed study uses a positive control to establish assay sensitivity," explained Dr. Darpo. A positive control is a validation of the study's ability to detect a small QT effect. If correctly chosen and used, it enables comparisons of methods across studies, and enables positioning of a drug's QT effect. According to E14, the positive control should be "… well characterized and consistently produce an effect corresponding to the largest change in the QT/QTc interval that is currently viewed as clinically not important (a mean change of around five milliseconds or less). …" This positive effect is compared with placebo. The confidence interval for this placebo-corrected effect must be above zero milliseconds. "When applicable, the control drug should ideally be from the same class with the same indication as the drug under investigation," he adds. "A positive control is a protection against flawed design, but not a

guarantee," warned Dr. Darpo. "For example, you could design a TQTS with a positive control and still miss the Cmax of your investigational drug."

In some regulatory domains, there are ethical issues regarding the use of drugs as positive controls. The use of a positive control also complicates the study design if there is a requirement to blind the control drug, and by adding another treatment arm. A control must have undergone repeated studies in order to be recognized as consistent and "well characterized." Currently, moxifloxacin, which produces a QT prolongation >five milliseconds, is widely used, well-characterized, and seems to have "regulatory buy-in. The absence of a positive control should be justified and alternative methods used to establish assay sensitivity provided," Dr. Darpo said.

Case Example – Moxifloxacin in Thorough QT Study (Darpo)

Design:

- 5-way cross-over
- Single dose
- Placebo, 1X, 3X, 9X investigational drug, moxifloxacin 400 mg
- 60 subjects (30 male, 30 female)
- 1 manual and 1 machine (automated) QT method

Outcome: Moxifloxacin caused 11 to 15 milliseconds QT increase; manual method performed with a digitizer compared with raw values as generated by the machine algorithm; clinical conclusion same by both methods[4]

[4] Darpo B et al. *J Clin Pharmacol* 2006;46:598-612.

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Examples Pharmacological Positive Controls (Darpo)

Terfenadine[5], 60 mg BID	
28HVs	QTcB+ 6 ms
28 CV patients	QTcB+ 12 ms
+ketoconazole	QTcB+ 82 ms
Cisapride[6], SD 10 mg	
10HVs	QTc+ 18 ms
+clarithromycin	QTc+ 25 ms
Sparfloxacin[7], SD 200 and 400 mg	
15HVs	QTc+ 14 and 15 ms
Ketoconazole[8], SD 800 mg	
80HVs	Qtc+ 12 $\pm$ 4.2 ms

Case Example – Moxifloxacin in Thorough QT/QTc Study (Ducharme)

Treatment given for 7 days to steady state
Placebo given for 7 days
Moxifloxacin 400 qd given for 5 days

Inclusion: QTc < 430ms men, <450 women

ECGs baseline, day 5 and 7

Sampling (PK & ECGs): 0, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24

105 subjects total; 35 on the Rx; 35 placebo; 35 moxifloxacin

(sd 7.3ms, 80% power, alpha 0.05, diff. 5ms)

[5] Honig PK et al. *Jama* 1993;269:1513-8.
[6] Kivisto KT et al. *Clin Pharmacol Ther* 1999;66:448-53 and van Haarst AD et al. *Clin Pharmacol Ther* 1998;64:542-6.
[7] Demolis JL et al. *Br J Clin Pharmacol* 1996:41:499-503.
[8] Darpo 16.

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Timing of Thorough Study

According to Dr. Darpo, the best timing of the thorough QT study remains a debate within the pharmaceutical industry. The E14 document does not specify where to place the therapeutic study within the drug development time line. "The thorough QT study is rarely the first study performed in humans," he stated. "Sufficient knowledge of the pharmacokinetic profile is required, including the anticipated Cmax, and concentration ranges in patients with impaired metabolic capacity. Otherwise, if the therapeutic exposure is not sufficiently known, doses up to maximum tolerated may have to be used."

QT assessment in later stages of development has implications on labeling and risk management strategies. In Phase III trials, when the early thorough QT study is positive, Dr. Sager opined that although automated measurements and manual readings may be considered, manual methods are superior in the presence of changes in T-U wave morphology. "Ideally, one should utilize methods that reduce variability, i.e., consistent methods, centralized ECG analysis, and digital ECGs, although this may be challenging in large, international programs."

Late development strategies also may entail ECG collection and analysis in patient sub-groups that are of particular interest, such as patients who develop electrolyte abnormalities (e.g., hypokalemia), or have congestive heart failure or impaired drug metabolizing capacity or clearance (e.g., renal or hepatic impairment, drug interactions). Female patients and patients younger than 16 or older than 65 years might also be analyzed separately, Dr. Sager suggested. Late stage evaluations also tend to focus on the outliers, "QT increases greater than 30 and 60 milliseconds, and absolute QTc greater than 500 milliseconds are common cut points," he said.

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Adverse Event Monitoring

An increased rate of certain adverse events (AEs) in patients taking an investigational agent can signal potential proarrhythmic effects, and the frequency of AEs should be compared in the treated and control patients, particularly when there is evidence of an effect on the QT/QTc interval. These AEs include TdP (consider genotyping for Long QT Syndromes), sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, and seizures.

Discussion with Regulators

Dr. Darpo strongly advised symposium participants to "build the case for your study design and seek agreement with regulators beforehand." Of particular importance, he said, was to discuss the planned highest dose with regulators. "The less you know about exposure in the patient population, the higher the dose you need to use, often up to maximum tolerated doses.

"Eventually you will need to demonstrate that you have covered and exceeded the maximum plasma levels observed in patients with impaired clearance, also taking the pharmacokinetic variability among these patients into account." Other issues of discussion might be the use of a particular positive control, the degree of follow-up characterization required in Phase II and III studies after a positive outcome in a TQTS, and the risk-benefit analysis of further development of a drug with a marked QT effect vis-à-vis the clinical importance – medical impact – of the drug under investigation.

Outcome Interpretation and Consequences

Dr. Ducharme cautioned against the temptation to selectively interpret the findings of the TQTS. For example, the comparison of the maximum change in QTc interval with that of the maximum change due to placebo, because they are obtained at different time points. The most conservative approach, and the one preferred by regulators, is to look at the same time point for the largest difference between the drug under investigation and placebo.

Negative Outcomes

By E14 definition, a negative finding in the TQTS means that the one-sided 95 percent confidence interval of the placebo-corrected effect of the investigational drug does not exceed 10 milliseconds. The positive control should demonstrate a placebo-corrected QT effect exceeding five milliseconds, with the lower 95 percent confidence interval above 0 milliseconds.

Per ICH 14: "A negative 'thorough QT/QTc study,' even in the presence of nonclinical data of concern, will 'almost always' allow the collection of on-therapy ECGs in accordance with the current practices in each therapeutic area to constitute sufficient evaluation during subsequent stages of drug development." Accordingly, outlier analysis can be handled through AE reporting, added Dr. Darpo.

However, as previously stated, a negative finding is not a warranty against proarrhythmic effect. "The theoretical concern is that you don't see an effect because you didn't test long enough," cautioned Dr. Ducharme. Dr. Darpo also had sobering words: "Retrospectively considering the known proarrhythmic drugs, QT prolongation was demonstrated in healthy

volunteers using the appropriate measures, but we don't know for certain whether some drugs might fail to demonstrate such effect, yet still manifest proarrhythmic effects in certain settings."

Positive Outcomes

A positive TQTS will almost always call for an expanded ECG safety evaluation during later stages of drug development through, e.g., "a thorough QT study in the targeted patient population and further characterization in susceptible patients, with ECGs at baseline and peak exposure in a substantial number of patients (several hundred) in pivotal trials," according to Dr. Darpo.

Why is it Positive?

"The definition of a positive result from the thorough QT study will most likely generate a number of false positives (e.g., drugs that affect autonomic tone)," suggested Dr. Darpo. "We really don't know much about the proarrhythmic effects of drugs that generate five to 20 milliseconds effect."

"Is there anything that could explain this measured QT prolongation other than the drug-effect on ventricular repolarization? That's the first thing to ask," stated Dr. Sager, "but there is a battery of questions. Is the finding consistent with preclinical studies? Was there a significant autonomic effect that altered heart rate? Due to the imprecise nature of correcting for heart rate changes with our QTc formula, small changes in heart rate can result in an increase of QTc interval, without a direct effect on cardiac repolarization. We do not have ways currently to statistically discriminate this effect with high accuracy. Is the observed QT effect an artifact of ECG methodology? Was there standardized consistency for ECG reading? Were the same

technicians and/or machines present at baseline versus drug effect ECGs? Was training sufficient to ensure data capture technique and practices (e.g., skin preparation, lead placement, patient position). Increased measurement variability due to multiple readers is to be expected in large, multisite, Phase III programs. Was there an increase in variability due to other methodological issues?"

Implications of a Positive Effect

"A positive thorough QT study places an increased burden to show a higher level of benefit than may have been planned during the drug's initial development," explained Dr. Sager. "There is an increased degree of perceived risk, and corresponding costs and delays in filing and obtaining regulatory approvals are possible." As stipulated in E14, "Substantial prolongation of the QT/QTc interval, with or without documented arrhythmias, could be the basis for nonapproval 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." Positive QT prolongation findings are likely to cause delays in filing and/or approval; increase costs during development, and carry potential label implications with consequent competitive implications.

Significant Development Burden

"The onus is on the sponsor to determine whether the drug really does affect cardiac repolarization, and the configuration of Phase III evaluations has to be individualized. Discussion with regulators is critical, " Dr. Sager said.

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"If the TQTS is positive, the expanded safety ECG evaluation in Phase II and III must contain ECG assessment adequate to fully describe the effect of the drug on the QT/QTc interval in the target patient population with particular attention to dose- and concentration-related effects. It can have a significant impact on clinical development," Dr. Sager added. Dr. Ducharme added that genotyping and phenotyping might be necessary if the drug is metabolized with a polymorphic distribution in the population. "Not doing anything could potentially result in having a delay of the application until a TQTS is performed," cautioned Dr. Sager.

Several relatively subjective concerns may surround continued development: the size of the effect seen in the TQTS; the constellation of the outliers; the class of the investigational drug; the nature of the indicated disease or disorder; and the degree of clinical benefit – does it fulfill an unmet medical need? A higher order of risk might be acceptable with an effective oncology drug, for example.

Post-marketing Risk Assessment

The histories of cisapride and terfenadine illustrate the difficulty of post-marketing identification of proarrhythmic risk. "The FDA is working hard at the current time and reworking some of the adverse event reporting procedures and analyses," reported Dr. Sager. "There are three basic resources for safety analyses: (1) spontaneous reports, (2) epidemiological studies, and (3) insurance databases. However, interpreting the risk is often challenging due to the reporting bias of spontaneous voluntary reports, insufficient or poor quality data in many cases, and lack of proper controls. An event with a lot of publicity can increase reporting rates – or spontaneous reports."

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The epidemiological approach, such as the large Medicaid database, offers the possibility of prospective studies. For example, the evaluation of a Tennessee Medicaid cohort confirmed the risk of sudden death due to cardiac causes consequent to concomitant erythromycin and CYP3A inhibitor use. Insurance databases also offer the opportunity for retrospective epidemiologic work.

Post-marketing Risk Management

Given an approved drug that induces QT prolongation, the sponsor is challenged to create and implement a post-marketing risk management strategy that successfully minimizes the risk. "Although the label may carry a warning, labeling is complex," explained Dr. Sager, "and as demonstrated by the situation with terfenadine, educational campaigns for healthcare practitioners and consumers, and prescribing precautions (high-risk subsets, drug interactions, overdosage, etc.) are often limited in effect."

Direct prescription requirements also can be implemented, which are effective but difficult to implement. Dr. Sager described the prescription requirements for dofetilide (the U.S. label): "Dofetilide can only be prescribed by physicians who have completed an educational program to be certified. It can only be used in hospitals where the hospital and the pharmacist have also undergone training and certification, and if doctors write prescriptions for dofetilide and they're not on the database where they've been certified, the pharmacy cannot fill those prescriptions. Unfortunately, this approach has resulted in part for dofetilide being very rarely used in the United States. The risk was managed, but the drug is not actually being utilized. Not the desired outcome."

Examples of Proarrhythmic Drugs

Terfenadine

Terfenadine alone prolongs the QT interval, but this prolongation is substantially greater when administered concomitantly with a metabolic inhibition. The proarrhythmic potential of terfenadine was not clearly identified until after 100 million prescriptions.

Terfenadine[9]

Mean QT change over 12 hours: 6 ms

Mean change at Tmax: 12 ms

Mean change with metabolic inhibition: > 82 ms

- 14 Studies have reported on QTc
  - 2 studies no effect
  - 4 studies < 5 ms
  - 7 studies: 8-18 ms
  - 1 study 24 ms

[9] Drug Safety 2001; 24:323-351

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Alfuzosin

Alfuzosin is an alpha-1 blocker for benign prostatic hyperplasia. Its NDA was filed on December 11, 2000, and was judged "approvable" on October 5, 2001. Although alfuzosin was approved in Europe, Canada and Australia (first approval in 1987), the FDA stated that the application lacked "adequate information, including clinical pharmacology data, to determine whether the product is safe for use because alfuzosin may increase the QTc interval." Despite a hERG test that was basically negative, a lack of QT effects in the clinical trials, and an absence of TdP in the large post-marketing database (including 3.7 million patients in the EU), the FDA mandated QTc interval measurement using a validated methodology. Ultimately, the prolongation of the QT interval was less than five ms, and a fairly benign comment was placed on the label.

Vardenafil

Vardenafil had no effects on hERG and no QT effects in animal models. The clinical trials contained small inconsistent effects as did the TQTS. Although vardenafil was discussed at the same meeting as alfuzosin, the cardiorenal advisory committee had more concern about this drug, and several members abstained from voting. A stronger label was imposed on vardenafil: QT prolongation to be considered, and avoid use of drug in patients who have QT prolongation or taking drugs that prolong the QT interval.

Vardenafil

Absence of significant hERG effect

No QT effect in dog models

Small, inconsistent QTc effects observed in initial clinical trials

Thorough QT Study:

- o Vardenafil 8-10 ms
- o Moxifloxacin 9 ms

US PI: "This observation [QT prolongation] should be considered in clinical decisions when prescribing LEVITRA. Patients with congenital QT prolongation and those taking Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications should avoid using LEVITRA."

Ziprasidone

Both Dr. Darpo and Dr. Sager described the ziprasidone 054 study as a way of positioning a drug versus its competitors. "It was an absolutely impressive study," Dr. Darpo commented. "Ziprasidone versus five other neuroleptics – risperidone, olanzapine, thioridazine, haloperidol and quetiapine – administered to schizophrenic patients with and without metabolic inhibition in open label, parallel design; a central ECG laboratory; manual technique; and QTc captured at median Tmax for each drug." Ziprasidone induced a QTc in the range of 15 milliseconds whereas thioridazine induced QTc prolongation in the range of 30 milliseconds,

while haloperidol had a smaller effect. However both thioridazine and haloperidol are associated with TdP.

Consequently, U.S. prescribing information for ziprasidone states: "Ziprasidone [has a] greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs. … raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs…" and contraindicates ziprasidone in patients with a known history of QT prolongation, with recent acute myocardial infarction, or with uncompensated heart failure.

Ranolazine

Ranolazine treats angina in patients who were not responsive to other pharmacologic agents. Ranolazine increases QT in a dose-related manner related directly to plasma concentrations. The mean increase in QT prolongation at 1000 mg BID is six milliseconds. In five percent of the population, the prolongation of QTc is 15 ms.

"Ranolazine underwent an extensive preclinical program," explained Dr. Sager. "No preclinical evidence of TdP risk was found: no early after-depolarizations (EADs), no transmural dispersion, no TdP in dog model of heart block, and a negative finding in the TRIAD model. Moreover, ranolazine was found to block the late inward sodium current, which may be associated with preventative effects on TdP occurrence. Additionally, ranolazine was found to suppress EADs associated with quinidine, E4031, or sotalol."

"The drug was recently approved," stated Dr. Sager, "but the glass is half empty or half full, depending on your viewpoint." The ranolazine US PI reads: "[Since] Ranolazine prolongs the QT interval, it should be reserved for patients who have not achieved an adequate response

with other antianginal drugs. [Ranolazine] should not be used with drugs that prolong the QTc interval or drugs that inhibit CYP3A or in patients with hepatic dysfunction."

ECG Warehouse

The presentation of Justin Mortara, Ph.D., Vice President, Mortara Instrument, Inc., was *Warehousing of Digital ECGs: How Sponsors Interface with FDA ECG Warehouse*. "The FDA needed an ECG repository for annotated ECG submissions and tools to facilitate review of the data," he explained.

Initially the FDA convened with sponsors, academia, central labs and ECG manufacturers to create a digital standard (HL7 Standard) where none existed. "Digital, of course, had the ability to improve the overall quality of ECG acquisition and analysis," Dr. Mortara explained, "moving away from the instability of ECG data recorded on thermal paper, with precision limited by mechanical writers enabled the submission of annotated ECG waveform data, the superimposition of waveforms, and the ability to view all leads simultaneously as well as providing greater uniformity in data collection. Digital ECGs enable the FDA the ability to review not only ECG findings, but the actual ECG annotations."

Reluctant to create its own facility, the FDA engaged Mortara Instrument, Inc. in a Cooperative Research and Development Agreement (CRADA), creating a public/private partnership in which development of the ECG warehouse by Mortara Instrument, Inc. was free of charge. Mortara Instrument, Inc. is free to commercialize the technology to third parties.

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Shortly after publication of the HL7 annotated ECG standard, sponsors began submitting data to the FDA on CDs and DVDs by the thousands. "We started out with 15 studies or so, and now we're up to 27 studies with greater than a quarter million ECGs. There was no way in a reasonable time frame to review 10-, 15-, or 20,000 ECGs, so we had to develop some quantitative metrics to help tease out the ECGs of interest; based on annotation statistics, QT analysis quality or signal acquisition quality," Dr. Mortara explained.

Using the ECG Warehouse

Sponsors access the ECG Warehouse via the Internet by visiting "www.ecgwarehouse.com" and clicking for instructions under "Request Upload for FDA Access."

"Sponsor submission of data to ECG Warehouse for FDA review is free of charge," explained Dr. Mortara. "Mortara technicians are available for support. The site is secure. Data are transmitted utilizing XML and a technology called WebDAV that enables the sponsor to physically transmit the data securely from its locale or the vendor's place through the Internet to the warehouse for importation directly into the ECG warehouse." After submission of data to the ECG Warehouse, reviewers can probe the data to help assess study quality.

After submission, FDA reviewers probe the data to help assess the overall quality of the study. Quantitative metrics are used to help identify ECGs of interest for reviewers. Metrics include: ECG Annotation Statistics, QT Analysis Quality, and Signal Acquisition Quality.

These tools are also available for sponsor use on a commercial basis. Histograms are used to provide a study-level view of metrics; enabling comparisons with other studies. Histogram entries are linked back to waveform records.

Future for the ECG Warehouse

"We're projected to exceed 500,000 ECGs within the first full year of operation," Dr. Mortara said, "which will quickly constitute the richest set of ECG data in the world, and provide the opportunity to redefine some very important concepts – perhaps first and foremost what is the normal QT in a healthy individual … nobody can agree about that right now – and for further research into alternate biomarkers. The ECGs of healthy volunteers are interesting at one level, but ECGs of clinical populations are extraordinarily interesting, and hopefully the warehouse will begin to see some of that data." Dr. Mortara said that ideas are being formulated for how to make data in the ECG Warehouse available for research purposes, and sponsor utilization of ECG Warehouse tools underway and expanding, and exploration on how to perform blinded, anonymous studies.

Future

"Looking to the future, hopefully, we'll know more about the link between proarrhythmic assays, the thorough QT assessment and the proarrhythmic propensity in the clinic within four or five years," said Dr. Darpo. "Our concern, regarding the patient, is not QT prolongation as such, which is harmless, but TdP. It is evident that we will know substantially more about the predictive value of nonclinical assays, not the least proarrhythmia models, for QT prolongation.

Perhaps we'll see significant improvements in pharmaco-epidemiology research (e.g., improved end-points, data on conconmitant meds and concurrent diseases) as well."

"It is possible that instead of this very large, multicentered Phase III program, we'll perform QT studies in selected high risk subsets of patients within a controlled setting for some agents, if this can be negotiated with regulators. If so, overall data collection, variability control and data quality will improve," claimed Dr. Sager.

"Another suggestion could be to initiate a collaborative effort and run drugs with a small, but proven proarrhythmic propensity (such as cisapride, astemizole, terfenadine) and drugs clearly devoid of this adverse effect, through TQTS. This could serve several purposes: Improve our understanding of the frequency of false positives in these studies, a better estimate of the effect size observed for positive drugs and also provide a unique data base enabling further research on risk markers, such as T wave morphological changes. Otherwise, we will eventually know a lot about the link between nonclinical assays and QT prolongation, but we would still not know what this means clinically in terms of proarrhythmic risk" said Dr. Darpo.

Dr. Ducharme believes that other analytical techniques might be applied to QT/QTc evaluation: "Concentration modeling (PK/PD) – modeling the slope of the interactions over concentrations – might be used potentially as a way to salvage a positive TQTS and minimize the ramifications; either in addition to or potentially in lieu of the TQTS. Population approaches should be used more often. It's a sophisticated technique that should better elucidate the relationship between the exposure of a drug, its concentrations, and the effect. After population analysis, individual plots could provide a basis for very reasonable predictions of QTc interval

and provide an understanding of the relationship between the QT prolongation and the drug exposure. Individual analyses could also link clinical covariates in those patients or volunteers, perhaps clarifying the risk factors contributing to prolongation, or demonstrating differences for gender, concomitant drugs, genotyping results, etc."

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Speaker	***Presentation***
Borje Darpo, M.D., Ph.D. Vice President, Chief Medical Officer Daiichi Medical Research, UK and USA	*Putting ICH E14 Regulations into Place: Phase I Studies Through Phase III Trials*
Murray Ducharme, Pharm.D., F.C.C.P., F.C.P. Vice President, Pharmacokinetics and Pharmacodynamics MDS Pharma Services Professeur Associé, Faculté de Pharmacie, Université de Montréal	*The New Shape of QTc Clinical Pharmacology Studies: Practical Design and Interpretation in the Current Regulatory Environment*
Kathryn Van Nest Global Trial Manager Johnson & Johnson Pharmaceutical Research and Development	*Global Study Management Challenges: Finding the Right Fit for Successful ECG Collection in Global Trials*
Justin Mortara, Ph.D. Vice President Mortara Instrument, Inc.	*Warehousing of Digital ECGs: How Sponsors Interface with FDA ECG Warehouse*
Philip Sager, M.D., F.A.C.C., F.A.H.A. Executive Director, Cardiac Research AstraZeneca LP, Clinical Professor of Medicine New Jersey School of Medicine and Dentistry	*QT Assessment in Late Stage Development: Further Characterization of QT Liability and Proarrhythmic Propensity of "Positive" Drugs During Late Stage Development*

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Paul Kligfield, M.D., F.A.C.C. Professor of Medicine Cornell University, Weill Medical College Director, Cardiac Graphics Laboratory The New York-Presbyterian Hospital Cardiology Advisory Board, MDS Pharma Services	*On the Matter of Method: A Comparison of ECG Measurement Modalities*
Pierre Maison-Blanche, M.D. Hôspital Lariboisière, Cardiology Unit Chairman Cardiology Advisory Board, MDS Pharma Services	*Heart Rate Stability Control: Solving the Thorough QT Studies Puzzle or Creating New Problems?*