

Evaluation of ventricular arrhythmias in early clinical pharmacology trials and potential consequences for later development

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This white paper, prepared by members of the Cardiac Safety Research Consortium, discusses several important issues regarding the evaluation of ventricular arrhythmias in early clinical pharmacology trials and their potential consequences for later clinical drug development. Ventricular arrhythmias are infrequent but potentially important medical events whose occurrence in early clinical pharmacology trials can dramatically increase safety concerns. Given the increasing concern with all potential safety signals and the resultant more extensive electrocardiographic monitoring of subjects participating in early phase trials, an important question must be addressed: Are relatively more frequent observations of ventricular arrhythmias related simply to more extensive monitoring, or are they genuinely related to the drug under development? The discussions in this paper provide current thinking and suggestions for addressing this question. (Am Heart J 2010;159:716-29.)

Ventricular arrhythmias are infrequent but potentially important medical events that can occur in healthy subjects during phase I clinical trials. Of particular interest in this white paper are those occurring in early clinical pharmacology trials (eg, first-in-human and multiple ascending dose studies), where any temporal association between the drug under development and an adverse event raises safety concerns. However, many points discussed are also relevant to phase I studies throughout the clinical development program, for example, pharmacokinetic (PK)/pharmacodynamic (PD) and drug-drug interaction studies.

Increasing regulatory scrutiny of drug cardiac safety has led to increased use of frequent or continuous electrocardiographic monitoring of subjects participating in early phase trials. Increased monitoring alone may lead to more frequent observations of asymptomatic ventricular arrhythmias. This occurrence can raise questions concerning whether or not it is appropriate to terminate the development program at this point. Although there are certainly cases when termination may be appropriate, this decision should not be made automatically. Rather, the decision to continue development or not should be made in the context of (1) assessment of the rate of ventricular arrhythmias in the test population relative to drug exposure, (2) assessment of the rate of ventricular arrhythmias in the test population relative to placebo-treated subjects, and (3) benefit-risk analysis of any potential drug-related arrhythmias. Factors considered in benefit-risk analysis include the risk of serious morbidity and mortality from the underlying disease state, the availability of other drugs in a class that may not have toxicity, the impact of the therapy on the disease, and the probability of life-threatening arrhythmias. Because the detection of such arrhythmias often triggers more intensified cardiac monitoring in subsequent studies, which can be associated with increases in development costs and prolonged drug development timelines, it is of considerable importance to assess whether an increased occurrence is likely due to the

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prolonged duration of monitoring in (or other conditions specific to) the phase I setting or more likely due to exposure to the drug.

An immediate problem in assessing the relative frequency of episodes of ventricular ectopy observed during phase I trials is the lack of comprehensive medical data addressing the occurrence of these episodes in apparently healthy general populations. It is very difficult to determine the expected “background frequency” of such episodes in the absence of a drug effect and, therefore, to evaluate whether a drug is specifically associated with an increased frequency of ventricular ectopy observations. The small number of control patients typically used in early phase studies may not be sufficient to detect a significant difference in the incidence of arrhythmic events between placebo- and drug-treated individuals. Consequently, there is currently no consistent approach regarding the ethics or clinical necessity of how to optimally evaluate or treat episodes of ventricular ectopy observed in a healthy subject in a phase I study, or how to decide between continued development of the drug or termination of the development program. Therefore, evidence-based considerations that lead to a consistent approach to the necessity and intensity of cardiac monitoring in early phase studies, medical evaluation of a subject displaying ventricular ectopy, study termination criteria for individual events of ventricular ectopy, additional evaluations for the drug, and appropriate termination of a development program after the occurrence of such an event are likely to be beneficial.

The most fruitful way to advance such suggestions is through the collaboration of regulatory, academic, and industry discussants, as outlined in the Food and Drug Administration Critical Path Initiative. Based on the Critical Path Initiative principles, the Cardiac Safety Research Consortium (CSRC) was created to facilitate such collaborations to develop consensus approaches addressing cardiac safety issues relating to development of new medical products.¹ A CSRC subgroup was established to foster stakeholder discussion about ventricular arrhythmia risk assessment and appropriate medical follow-up and drug development when observed in healthy subjects in early phase studies. This white paper is a result of the subgroup's discussions.

The paper provides suggestions for sponsors conducting early clinical pharmacology trials and is not intended to serve as a regulatory guidance. As will be seen, the current literature discussing the “normal occurrence” of such arrhythmias is relatively scant, which makes definitive determination of events as “drug induced” very difficult. This observation influences the content of this paper in 2 ways. First, it is not appropriate to make precise prescriptive recommendations. Sponsors are encouraged to take a flexible approach that best suits the particular situation of the drug in development.

Second, information and knowledge generated by additional research are needed. Therefore, the future directions discussed include some ideas for potentially instructive research. Indeed, prompting such research may be the ultimate benefit of this paper.

Primary topics discussed

The paper first summarizes the currently available medical literature on ventricular ectopy in apparently healthy populations. It then discusses several important issues regarding the evaluation of ectopic ventricular episodes in early clinical pharmacology trials and potential consequences for later clinical development. These include the following:

- Nonclinical and relevant clinical evidence (eg, structural/pharmacologic class effects) that may merit consideration for intensive cardiac monitoring during early clinical development;
- Potential selection criteria for subjects participating in early clinical trials using intensive cardiac monitoring (eg, excluding individuals with any baseline arrhythmias, history of heart disease, or other factors that may influence arrhythmias in some studies vs inclusion of an enriched “at-risk” population of patients in other studies) and the use of screening technologies;
- Approaches to intensive cardiac monitoring, for example, frequent resting surface electrocardiograms (ECGs) and continuous ambulatory ECG recording with or without real-time cardiac telemetry;
- Approaches to clinical follow-up of subjects in whom ventricular arrhythmia is discovered during the study to ensure the subjects' safety, and to provide meaningful information to guide further drug development;
- Regulatory considerations related to ventricular ectopy in early clinical development;
- Potential stopping criteria for individual subjects, dosing cohorts, and a particular study;
- Next steps for drug development programs when ventricular ectopy is encountered.

The paper concludes with the presentation of 3 case studies as hypothetical examples of how the considerations discussed may impact a drug's clinical development program and discussion of future research directions for ventricular arrhythmia in healthy subjects or, in later studies, particular patient subgroups.

Background prevalence of ventricular arrhythmias in healthy populations

Review of the literature

The evaluation of prevalence of all forms of ventricular ectopy is affected by the sampling duration of ECG waveform data. The reported prevalence in apparently healthy populations (ie, the populations from which healthy subjects in phase I studies are drawn) is often assessed using standard resting surface ECGs. However, the prevalence in these assessments, which only capture 10 seconds of electrocardiographic information, is lower than that determined via continuous ECG waveform recordings by a factor that could exceed 100-fold.² Evenson et al³ reported that 2-minute resting surface ECG recordings poorly predict ventricular ectopy on subsequent 24-hour continuous ECG recording. In studies that used the cutoff of 200 to 300 premature ventricular contractions (PVCs) per 24 hours, only between 1% and 5% of apparently healthy subjects had PVCs more frequently.^{4,7} Therefore, in studies using continuous ECG monitoring over prolonged periods, more prolonged ECG assessment during screening may identify and, hence, exclude healthy subjects with preexisting cardiac arrhythmias.

The studies using resting surface ECGs have by far the largest sample sizes. The prevalence of PVCs observed on paper tracings ranged from 0.8% to 14%,⁸⁻¹⁴ with an increasing prevalence with age. Nonsustained ventricular tachycardia (NSVT) (≥ 3 consecutive beats of ventricular ectopy) was reported infrequently, 6 times among >135,000 subjects. Other studies have confirmed increased prevalence of NSVT with age and presence of hypertension.^{15,16} Including younger subjects and excluding subjects with preexisting cardiovascular disease (including hypertension) may be beneficial in early phase trials to reduce the likelihood of non-drug-related frequent or complex ventricular ectopy. Alternatively, if there is still a concern regarding potential proarrhythmia, an enriched population of "susceptible" individuals with cardiovascular disease can be studied to determine if the drug promotes the development of arrhythmias.

Although the association between the sampling duration of continuous ECG waveform recording and the prevalence of detection of ventricular ectopy is not consistent across all published studies, Kennedy et al¹⁷ showed that increasing the duration of recording from 24 to 36 hours increased the probability of detecting maximal and more complex grade PVCs by 25% and 50%, respectively. Kostis et al¹⁸ showed that progressively increasing the sampling duration increased the probability of detecting PVCs. The study that reported the highest prevalence of NSVT recorded ECG waveforms for 48 hours.¹⁹ Given these results, it is perhaps not surprising that more events of ventricular ectopy are being seen during the more intensive telemetry or

Holter monitoring now being conducted for cardiac safety evaluation in early phase trials.

Table I summarizes the results of studies available in the English-language medical literature that reported on the prevalence of different forms of ventricular ectopy in apparently healthy subjects. The determination of "healthy" status of the subjects in these studies was not uniformly assessed. In addition, some of the data below were observed in subjects who were healthy controls for either diseased or athletic populations.

Various factors, including diurnal rhythm and psychologic stress, may influence the occurrence of ventricular arrhythmias during a study. Evidence for the influence of diurnal rhythm on ventricular ectopy was not consistent among studies, although one study reported a statistically significant increased prevalence during waking or daytime hours.⁴¹ Psychologic stress, which may be present in some subjects in the typical phase I inpatient environment,⁴⁶ has been associated with increased ventricular ectopy,^{47,48} an association made more salient by the plausible mechanisms through which psychologic stress can affect ventricular repolarization.⁴⁹

Phase I studies in healthy subjects have a tendency to recruit younger, male subjects with lower body mass index. Biffi et al⁵⁰ studied the effect of physical deconditioning of 70 trained athletes presenting with frequent and/or complex ventricular arrhythmias ($\geq 2,000$ PVCs and/or ≥ 1 burst of NSVT per 24 hours) with (28%) or without (72%) underlying structural cardiovascular abnormalities. Twenty-four-hour ambulatory ECGs before and after a deconditioning period of 19 (± 6) weeks revealed a decrease in both the incidence and number of subjects presenting with PVCs and NSVTs. Therefore, the general physical condition of healthy subjects enrolled in a clinical study may have an influence on their arrhythmia profile.

Limitations of the current literature

There are considerable limitations in extrapolating prevalence rates from the studies just reviewed to the likely incidence of ventricular ectopy events during phase I studies. The typical phase I environment (including confinement in a clinical pharmacology unit) is likely considerably different from the settings in which the majority of studies in Table I were conducted (outpatient setting).⁴⁶ Second, the rigor with which subjects were excluded on the basis of underlying structural (such as mitral valve prolapse) or ischemic heart disease or hypertension (conditions that increase the prevalence of ventricular ectopy⁵¹⁻⁵⁵) in the majority of studies in Table I varied considerably, in particular with varying access to functional (stress) testing, echocardiographic imaging, and blood pressure monitoring. These exclusions may differ from those for subjects participating in phase I studies. Third, inter- and

Table I. Literature review

Reference	Sample size	Age range (y)	Sampling duration time (h)	Prevalence of ventricular ectopy (%)	Prevalence of multiform ventricular ectopy (%)	Prevalence of NSVT (%)
[20]	65	25-39	2.5	0	0	0
[21]	27	NK	8-12	44	NK	NK
[22]	35	NK	10	14	NK	NK
[23]	53	20-70	24	8	2	0
[24]	86	16-65	48	73	15	2
[25]	23	35-65	48*	35	9	0
[26]	74	20-80	24	76	38	1
[27]	50	23-27	24	50	12	2
[28]	30	Mean age 47	24	33	7	3
[17]	23	NK	48	35	0	0
[29]	189	20-70	24	41	7	NK
[30]	13	60-84	24	100	8	0
[31]	131	10-13	48	26	25	0
[32]	33	24-34	24	9	NK	0
[33]	100	20-70	24	21	3	0
[34]	50 [†]	22-28	24	54	10	2
[18]	101	16-68	24	39	NK	0
[35]	300	40-59	24	76	33	2
[36]	98	60-85	24	80	35	4
[37]	20 [‡]	19-28	24	70	20	0
[38]	70 [‡]	Mean age 23	16	39	3	3
[4]	260	40-79	24	69	23 [¶]	2
[39]	80 [‡]	<40	24	50	NK	1
[5]	170	18-70	24	41	15	2
[40]	100	14-16	48	41	10	3
[7]	101 ^b	20-59	24	34	9	1
[6]	111	20-79	24	61	NK	1
[41]	147	15-65	24	46	12	1
[42] Dijane's data	50	22-57	24	22	8	2
[42] Leitner's data	100	40-69	24	63	22	3
[19]	40 [‡]	Mean age 56	48	83	10	5 [§]
[43]	60 [‡]	Mean age 25	24	40	0	0
[44]	152	18-59	24	≈19	<1	2
[45]	624	NK	24	60	NK	1

NK, Not known.

* Including 24 hours during and after stress ECG testing.

† All women.

‡ Samples included athletes.

§ Incidence was 10% in sedentary controls.

|| Studies done in clinical pharmacology units.

¶ Only 5% of subjects had PVCs of >2 different morphologies.

intrasubject diurnal and day-to-day arrhythmia variability can have a considerable impact. Whereas intersubject variability was the higher source of variation, intrasubject variability contributed considerably to differences between hours and days of ECG waveform sampling.⁵⁶⁻⁶⁰ Biological variability is more pronounced over long periods of observation (6-12 months) than short periods (2-14 days).⁶¹ Finally, different monitoring technologies were used in older studies compared with contemporary phase I studies.

The background prevalence of ventricular ectopy in healthy subjects is highly variable and, in a given study, is a function of the specific population used and the duration of monitoring. The differences in the duration

of monitoring and observed subject characteristics (eg, age, sex, underlying exclusionary criteria) may account for the differences in the prevalence of arrhythmias seen in healthy subjects participating in clinical trials compared with the cited prevalence of arrhythmias in the literature. In addition, given the small size of typical early phase studies (as well as the frequent use of nonbalanced drug-treated vs placebo-treated cohorts), there are often too few placebo-treated individuals to make a meaningful quantitative comparison of the relative rates of observed arrhythmias. Therefore, it is not possible to conclude that arrhythmias that occur with increased frequency in clinical trials with extensive ECG monitoring are necessarily drug related.

Utility of nonclinical signals in guiding clinical cardiac monitoring

Although the limitations of nonclinical data in accurately predicting human responses to a drug are well acknowledged, such data can still prove useful. If a safety signal is seen in nonclinical studies, this may lead to a decision to conduct a greater degree of cardiac monitoring during phase I trials. However, it should be emphasized that the absence of a safety signal in nonclinical studies does not preclude the need for monitoring during the clinical development program. Nonclinical investigations should pursue safety pharmacology studies in addition to standard multiple-dose toxicology studies. The design and validation of nonclinical models of proarrhythmia have been subjects of significant focus.⁶² The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidances S7A⁶³ and S7B⁶⁴ recommend an *in vitro* *hERG* or I_{Kr} ion channel assay and an *in vivo* cardiovascular safety pharmacology study in nonrodent species. Additional informative safety pharmacology tests include repolarization assays and proarrhythmia models. Repolarization assays measure action potential parameters in isolated cardiac preparations such as Purkinje fibers,⁶⁵ papillary muscles,⁶⁶ arterially perfused left ventricular wedges,⁶⁷ and Langendorff hearts.⁶⁸ Proarrhythmia models include both *ex vivo* test systems, such as isolated Langendorff-perfused hearts,⁶⁹ as well as *in vivo* models, such as the chronic atrioventricular block dog.⁷⁰

The selection of suitable studies for a given drug should be flexible and optimized based upon information gained during drug discovery. Additional considerations include the relationship between the therapeutic index and the predicted efficacious concentration in humans. For instance, a low *hERG* IC_{50} ($\leq 1 \mu\text{mol/L}$ or overlap with clinically relevant exposures), abnormal cardiac intervals or arrhythmias observed in an animal cardiovascular study, or a ventricular wedge preparation assay that suggests a risk of ventricular arrhythmia may indicate a possibility of clinically significant cardiac arrhythmias and need for real-time ECG monitoring in clinical studies.

Such findings may facilitate the decision to discontinue development of the compound or to optimize cardiovascular monitoring in early clinical studies, taking into consideration the potential benefits of the compound and knowledge about other drugs in the class. If a cardiovascular safety signal is observed during nonclinical development (or the nonclinical cardiovascular signals are considerably discordant) and a decision is made to progress to clinical investigation, additional safety pharmacology studies incorporating intensive cardiac monitoring could be considered to complement intensive cardiac monitoring in clinical studies.

Understanding the time course and exposure-response relationship of cardiovascular changes in the animal species (either as an end point or as a prodromal signal for more serious downstream events) benefits the clinical investigation in a number of ways, including the following:

- Use of appropriate cardiovascular monitoring techniques and determination of their duration in a phase I study. Monitoring options are outlined in “Cardiac monitoring options,” and their use in intensive monitoring in clinical trials is discussed in “Intensive cardiac monitoring during clinical trials.”
- Use of study stopping criteria based upon observation of a prodromal signal. For example, quantifying changes in heart rate, blood pressure, QT interval duration corrected for heart rate (QTc), PR interval, QRS duration, or R-R interval compared with placebo-matched data allows stopping criteria to be enacted with reduced risk of stopping for placebo effects.
- Enabling the clinician to more quantitatively assess the occurrence, nature, and timing of any cardiovascular events that are observed during clinical development but were not seen during nonclinical development.

Thus, the first question that needs to be asked is this: What degree of cardiac monitoring is needed in early clinical trials? Although a detailed answer/analysis is beyond the scope of this paper, we certainly do not suggest that more than “routine” monitoring is needed for all new chemical entities. Rather, nonclinical data, any available clinical data, and known pharmacologic and class effects should determine whether intensive cardiac monitoring should be used.

Consideration should also be given to limitations in early clinical development due to the small sample sizes used in early phase studies. Although matching numbers of placebo controls should be considered, an overall causality assessment is still difficult because of the low incidence rate of ventricular arrhythmias in a healthy population. A few cases can significantly affect the incidence rate in a given study and may not always be matched in the group receiving the drug and the group receiving placebo. Even if the drug group and the placebo group are matched in size, the study may still be underpowered to demonstrate a statistically significant difference between the groups with respect to arrhythmia occurrence. Isolated events may not pose a significant safety signal, and caution should be exercised in interpreting the impact of asymptomatic benign arrhythmias. A careful evaluation of such events, together with key monitoring of those subjects, is of paramount importance.

Cardiac monitoring options

Cardiac monitoring options used in early phase clinical studies for the detection of arrhythmias (or increased risk for arrhythmias) include the following:

- Telemetry (real-time monitoring in 2-12 cardiac leads);
- Traditional 12-lead ECGs (with discrete 10-second sampling durations);
- Holter monitoring (delayed evaluation of 3-12 cardiac leads);
- Various combinations of the above listed methodologies.

Each of these options has advantages and disadvantages. Therefore, care should be taken when choosing a specific approach in a clinical trial.

Although telemetry may only allow inspection of data from a few leads and is not historically used for long-term review of data, modern telemetry units are capable of storing multiple rhythm strips for 24 hours or more of data for retrospective analysis and can review up to 12 leads. Importantly, this option facilitates subject safety by providing ongoing, real-time assessment of clinically significant events, for example, substantial changes in heart rate or rhythm, which allows rapid clinical intervention when appropriate. Unfortunately, this option may not be widely available for certain studies such as early phase I oncology drug trials in patients with advanced cancer. Oncology units are typically not designed for telemetry monitoring, and patients with advanced cancer may not be appropriate for drug trials on traditional cardiac telemetry units. When telemetry is available, consideration should be made to incorporate the actual rhythm strips into the study database for future safety analysis if feasible.

The use of 12-lead ECG monitoring can provide a broader range of data but often only at intermittent intervals, with 10 seconds being a typical sampling time. Holter monitoring is typically performed to assess the occurrence of asymptomatic rate, rhythm, or interval changes or to evaluate symptomatic events. Both Holter monitoring and intermittent 12-lead ECGs do not typically allow for immediate arrhythmia recognition and treatment. Current generations of Holter monitoring equipment are capable of recording high-fidelity 12-lead Holters (500-1,000 Hz) and thus are frequently used for thorough QT/QTc studies. These recordings, however, are examined by experts as and when appropriate at a later time and may not be appropriate for real-time detection of cardiac rhythm changes.

Subject selection criteria for clinical trials using intensive cardiac monitoring

More extended/intensive cardiac monitoring may lead to an increased detection of background (ie, non-drug-

related) ventricular arrhythmia, thereby making it more difficult to differentiate between drug- and non-drug-related arrhythmias. One strategy to reduce the occurrence of ventricular arrhythmia due to baseline rates or subject variability is to carefully define eligibility criteria for apparently healthy subjects entering such phase I trials with intensive cardiac monitoring. The study sample should be selected by use of appropriate inclusion and exclusion criteria. In addition, an appropriate or matching number of placebo subjects should be considered for this type of study. As previously noted, ventricular ectopy or arrhythmia increases with increasing age. Therefore, an upper age limit (eg, 50 years of age) can be considered for some studies. A medical history suspicious for arrhythmias (eg, palpitations, syncope) or consistent with cardiac disease (eg, hypertension, angina, myocardial infarction) or a personal or family history of long QT syndrome (LQTS) should also be considered for exclusion. In addition, if the subject has had previous cardiac evaluation (eg, echocardiogram, exercise stress testing), those findings should be considered when determining the subject's eligibility. Minimally, an assessment of electrolytes and a 12-lead ECG should be obtained at screening. Subjects with significant ECG abnormalities (ie, prolonged QTc, ventricular ectopy/arrhythmia, prior infarction, ventricular hypertrophy) or significant electrolyte abnormalities (especially potassium and magnesium) should be excluded. Subjects with ECG abnormalities, such as supraventricular arrhythmia with aberrant conduction, which could mimic ventricular arrhythmias and/or render it more difficult to monitor should also be excluded. Potentially rare events such as PVCs or NSVT can be missed with 12-lead ECGs but are more likely to be captured with Holter monitoring because of the extended duration of recording. Therefore, Holter monitoring may enhance arrhythmia detection before study entry when real-time ECG monitoring will be used in a study.

If a drug has significant liability for arrhythmias on the basis of nonclinical data or the target subject population, various strategies are appropriate for subject selection. Screening techniques such as conducting a 2-dimensional echocardiogram, continuous ambulatory ECG monitoring for 24 hours or longer (preferably closer to the planned monitoring duration after dosing), and/or exercise stress testing in this setting could be considered to exclude subjects with subclinical structural heart disease and/or evidence of cardiac ischemia and those at risk of asymptomatic changes in rhythm (ie, frequent ventricular ectopy, NSVT, or sustained ventricular tachycardia [VT]).

Once subjects have been appropriately screened, the nature of the study may determine additional precautions. If telemetry or other continuous ECG monitoring is to be used during the study, 24-hour Holter evaluations can be performed during screening to identify and exclude

subjects with an increased baseline frequency of ventricular ectopy or evidence of ventricular arrhythmia. Preferably, the Holter evaluation should be performed under conditions that simulate the phase I environment and be of a duration that is similar to that planned following study drug administration. If frequent ECG recordings are to be obtained at the expected time of maximum concentration (T_{max}) during the study, then similarly intensive ECG sampling should be done at the same time of day during screening. Studies including subjects with some baseline ectopy may consider longer periods of placebo exposure to amplify evidence that observed ectopy is not drug related.

Although subject recruitment may take longer by restricting enrollment, the overall development timeline could avoid significant delays if there are fewer false-positive signals for proarrhythmia that require extensive cardiac monitoring in later development. However, the more restrictive the entry criteria for a study population, the less likely it may be to detect a true arrhythmia signal. Therefore, as development continues, consideration for more susceptible (eg, geriatric subjects) or at-risk populations should not be excluded from the clinical studies (if the preceding nonclinical and clinical data support it) to determine the true cardiac risk of the drug.

Intensive cardiac monitoring during clinical trials

If intensive cardiac monitoring is deemed necessary, the nature of this monitoring must be determined. This monitoring may involve simultaneous use of more than one of the items discussed in "Cardiac monitoring options." Options include more frequent resting surface 12-lead ECG recording, telemetry (real-time monitoring in 2-12 cardiac leads), and Holter monitoring (delayed evaluation of 3-12 cardiac leads). Newer devices may combine all 3 of these technologies into a single recording/transmission device. Continuous cardiac monitoring with or without real-time telemetry (inpatient or outpatient) provides additional valuable information to resting surface ECGs, such as trends in heart rate and rhythm and more accurate characterization of various ECG parameters. If continuous cardiac monitoring is used, high-fidelity, multilead recording with appropriate storage of data (rather than reliance on printing representative data) should be ensured. In addition, if an abnormal rhythm is detected, additional clinical evaluations as well as specialist review of the finding should be completed.

For example, episodes of supraventricular tachycardia (SVT) with aberration and artifact can closely mimic episodes of VT, but have very different implications for both patient safety and drug development. It is thus imperative to retain high-fidelity multilead recordings of any suspected episodes of wide complex tachycardia, including the periods immediately preceding and

following the arrhythmia. Subsequent specialist review of these episodes, preferably by a clinical cardiac electrophysiologist, is critical to determine whether they are in fact true episodes of VT. If the episode was noted on telemetry with <12-lead recording, a confirmatory standard 12-lead ECG should be recorded immediately to look for evidence of ischemia and to assess the QRS/QT interval. In addition, as much clinical information as possible should be obtained, including the following:

- Details of drug dosing;
- Other medications;
- Subject activity at the time of the episode;
- Adverse events at the time of the episode;
- A PK sample near the time of the event;
- A thorough physical examination and/or vital signs evaluation;
- Questioning the patient if they have had similar episodes in the past that may suggest a preexisting arrhythmic condition.

Examining the drug-event relationship for potential causality

Points to consider when performing a causality assessment for an episode of ventricular arrhythmia in a clinical trial include the following:

- Frequency relative to background prevalence or compared with the incidence in placebo subjects.
- Pharmacology:
 - Relationship to structural/pharmacologic class associated with electrocardiographic effects and/or proarrhythmia;
 - Electrophysiologic effects in nonclinical studies (eg, cardiac ion channel assays, in vivo cardiovascular safety pharmacology studies, repolarization assays, proarrhythmia models, toxicology studies);
 - Exposure-response (dose- and/or concentration-response) relationship for QTc, QRS, PR, or heart rate in human subjects or laboratory animals;
 - Central tendency analyses showing treatment-emergent change(s) in one or more ECG parameters in human subjects or laboratory animals;
 - Occurrence of treatment-emergent ECG intervals or changes from baseline that exceed reference ranges;
 - Secondary PD or toxic effects that might increase risk of proarrhythmia (eg, diuretic, nephrotoxic, or hormonal effects leading to decreases in electrolytes; effects on myocardial contractility).
- Characteristics of the ventricular ectopy event:

- Number and complexity (eg, single PVCs vs triplets) of ectopic beats;
- Morphology of the ventricular arrhythmia (eg, rapid polymorphic vs sustained slow monomorphic VT);
- Concomitant prolongation of the QTc and/or QRS intervals;
- Frequency of the event in an individual and across the study;
- Temporal relationship to adverse events or laboratory abnormalities.

Detection of a signal in a nonclinical study, especially at exposure levels analogous to the human dose, should lead to consideration of a drug effect. In addition, the timing of the event relative to the PK profile (exposure/response relationship) should be put into the context of the PK profile of the parent drug and metabolites (if known) in the individual subject and study population. In general, the closer in time the event occurs to T_{max} (and hence C_{max}), the greater the biological plausibility of the event being drug related (unless one suspects cardiac accumulation or other reasons for delayed effects). Therefore, if ventricular ectopy is consistently observed at higher drug exposures, a drug relationship may be more likely.

There are many morphologic variations of potentially serious arrhythmias. An expert ECG reader such as a cardiologist or cardiac electrophysiologist should be consulted to review the ECG or telemetry/Holter recordings to determine if the observed wide complex tachycardia is actually an episode of VT, an episode of SVT with aberration, or simply artifact. In general, the more leads that have been recorded and can be reviewed, the better, with 12-lead ECGs preferable to 2- or 3-lead Holter or telemetry recordings, which are in turn preferable to single-lead telemetry strips. The expert ECG reader should make a best attempt to determine if there is sufficient evidence to label the episode as VT or not.

Occurrences of ventricular ectopy that are potentially not clinically significant

Ventricular arrhythmias detected during routine clinical study monitoring should not be considered “benign” until there has been an appropriate evaluation to rule out structural heart disease or primary electrical disease of the heart. If the evaluation rules out these conditions, the significance of an arrhythmia may then be incorporated into the context of what is expected as “background baseline” in the general healthy population and may be considered “benign” for the individual subject. If arrhythmias occur at a low incidence in the study or in a ratio similar to that of placebo-treated patients and if a plausible mechanism for drug-induced arrhythmias is lacking, they may represent a “benign” type of arrhythmia

unrelated to the drug. The designation of “benign” arrhythmia is generally a diagnosis of exclusion.

Ventricular arrhythmias that may represent “background” arrhythmias include the following:

- Premature ventricular depolarizations, *nonsustained* (defined as ≥ 3 consecutive ventricular ectopic beats), or monomorphic VT with a morphology suggestive of a right ventricular outflow tract (RVOT) origin.
- Nonsustained monomorphic VT or PVCs predominantly with a morphology suggestive of a left posterior fascicular origin. The resulting arrhythmia is often referred to as a *fascicular tachycardia*.
- Monomorphic PVCs that are present at baseline and at a similar frequency while on therapy.
- Slow monomorphic ventricular rhythms with heart rate <100 beat/min.

If, on the other hand, the arrhythmia occurs at a relatively high incidence relative to what would be expected from the population under study, it may indicate a proarrhythmic drug effect. In addition, it is critical to rule out SVT with aberration or preexcitation (ie, Wolff-Parkinson-White syndrome) that in certain instances can mimic, and thus be misinterpreted as, either benign or malignant forms of ventricular arrhythmias.

Serious and potentially serious ventricular arrhythmias

The following is a (nonexhaustive) list of ventricular arrhythmias that should be considered clinically serious:

- Ventricular arrhythmias associated with QTc interval prolongation or short QTc interval.
- Torsades de pointes.
- Ventricular arrhythmias associated with increased QRS duration in beats preceding ventricular ectopy.
- Ventricular arrhythmias in a subject with a family history of sudden death or primary arrhythmia syndrome.
- Ventricular arrhythmias occurring in a subject with baseline ST/J point elevation suggestive of Brugada syndrome.
- Ventricular arrhythmias in the setting of structural heart disease.
- Polymorphic VT.
- VT sustained for >30 seconds, or associated with hemodynamic compromise or other symptoms of end-organ compromise (eg, dizziness, shortness of breath).
- Ventricular fibrillation.

In general, all subjects who have an unexpected finding of one or more episodes of VT should undergo a further evaluation by either their regular medical caregiver or a cardiologist. The purpose of evaluation (and potentially treatment) initiated by the finding of

nonsustained ventricular arrhythmias is not for the prevention of recurrences of nonsustained arrhythmias, as nonsustained ventricular arrhythmias are almost invariably asymptomatic and pose no intrinsic danger. The concern that mandates further workup is that these may be the first evidence of previously undiagnosed structural cardiac disease and may be the harbinger of life-threatening sustained VT or ventricular fibrillation. The evaluation can be considered to serve 2 purposes: evaluation of the individual subject's underlying cardiac status and potentially the cardiac health of family members, and the evaluation of relatedness to the drug.

General clinical evaluations for subject safety, separated here into acute and follow-up evaluations, include the following:

Conditions to consider acutely:

- Electrolyte disturbance;
- Other drugs or conditions potentially causing cardiotoxicity;
- Acute coronary ischemia (VT associated with acute ischemia is typically polymorphic in appearance).

Cardiac conditions to consider in follow-up:

- Preexistent left ventricular dysfunction due to chronic coronary artery disease with or without prior infarction, nonischemic cardiomyopathy, valvular or hypertensive heart disease;
- Electrical diseases, including "normal heart" VT from the RVOT or left ventricle, arrhythmogenic right ventricular dysplasia, Brugada syndrome, short QT syndrome, catecholaminergic polymorphic VT;
- LQTS: the evaluation might include genetic screening for known LQTS genotypes of the subject and family members.

The clinical evaluation should generally include evaluation of standard electrolytes, including potassium and magnesium. Any suggestion of coronary ischemia should be investigated (eg, troponins, other cardiac serum biomarkers). A 12-lead ECG and thorough history and physical examination should be obtained as close to the index event as possible. The minimal noninvasive workup will generally include a 12-lead ECG to look for evidence of previously undiagnosed electrical or structural heart disease, a 2-dimensional echocardiogram to look for evidence of previously undiagnosed structural heart disease, and an exercise or pharmacologic stress test to evaluate possible ischemia. If there is a consideration of LQTS, arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy, Brugada syndrome, or other genetic structural or electrical disease, other noninvasive testing modalities may be used.

Once the initial noninvasive clinical evaluation is complete, further decisions may be made as to whether subsequent treatment or invasive evaluation with cardiac catheterization or electrophysiology study is appropriate for the subject. Follow-up Holter monitoring off drug may be performed, as recurrences off medication may suggest that the arrhythmia is a preexistent phenomenon. In addition, it may be helpful to find out if the subject has ever had previous Holter recordings; review of such recordings, if available, may reveal that the subject has had previous episodes of VT. Importantly, however, if no similar arrhythmias occur on Holter recordings off drug, that does not prove that the arrhythmia was drug related. Rather, this may be a reflection of the underlying variability of arrhythmia occurrence. Further evaluations could be conducted by the clinical trial physicians or by a private physician not involved in the study, depending on which the subject prefers and is in his or her best interests. In either case, it would be advantageous from the sponsor's perspective to have access to data that would allow the sponsor to evaluate possible association between recorded arrhythmias and the drug.

It is important to conclusively determine if the subject has underlying structural or electrical cardiac disease because these underlying cardiac conditions may be responsible for episodes of VT. However, for a specific subject, it is important to recognize that it will never be possible to completely ascertain whether an episode of VT was entirely due to preexistent cardiac disease or whether it was triggered by the drug in the setting of preexistent cardiac disease. Compounds that have a minimal risk of ventricular proarrhythmia in normal hearts may behave very differently in subjects with structural or electrical heart disease, with a clear example being the increased risk of proarrhythmia for sodium channel blockers in patients with structural heart disease.⁷¹

Appropriate clinical follow-up when an event of interest occurs

Ventricular arrhythmias that occur during the course of a clinical study need to be characterized as nonserious or serious (ie, associated with an adverse prognosis). In general, ventricular arrhythmias that occur in the setting of significant structural heart disease, such as reduced left ventricular ejection fraction regardless of etiology, significant valvular disease, severe hypertrophy, ischemia, other diseases such as pulmonary hypertension, genetic conditions, or even those associated with electrolyte abnormalities, may carry a negative prognosis with respect to morbidity and mortality. In some individuals, ventricular arrhythmias may be the first manifestation of a subclinical cardiomyopathy such as arrhythmogenic right ventricular dysplasia or hypertrophic cardiomyopathy; primary electrical disease of the heart such as

congenital long or short QT syndrome, the Brugada syndrome, or catecholaminergic polymorphic VT; or other genetically determined arrhythmia syndromes. In contrast, ventricular arrhythmias that occur in the setting of a structurally normal heart and normal baseline 12-lead ECG are often not clinically significant. Therefore, to determine if the observed arrhythmia has prognostic implications, a cardiovascular evaluation by a qualified physician (preferably a cardiologist) is usually warranted.

Steps to consider when ventricular arrhythmias are encountered

As noted in the beginning of this paper, the current state of knowledge in this area makes definitive statements regarding “stopping rules” in such situations limited. This paper has therefore presented some steps to consider when these arrhythmias are encountered. Although discontinuation in some circumstances may be appropriate, it is equally the case that some specific situations may warrant continuation. In addition, “stopping” the participation of an individual subject (actively withdrawing the subject from the study) is a different situation than stopping a study; and the former may require less stringent criteria than the latter. Again, the authors encourage flexibility on the part of sponsors to tailor steps and decisions to their particular circumstances.

Some forms of asymptomatic high-grade and/or complex ventricular arrhythmia may occur in normal individuals but, because of day-to-day variability, may not be evident during subject screening. Unless there is a clear association between ventricular arrhythmia and drug exposure, or a clear dose-response or exposure-response relationship, asymptomatic, nonsustained, monomorphic VT is often benign and of little clinical significance; and its detection need not automatically lead to termination of a subject or a halt to dose escalation.

Potential stopping criteria for individual subjects in case of multiple dosing (in addition to other protocol-specified criteria and also assuming the study will be supplemented with ECGs obtained for concentration-QT analysis) include the following:

- NSVT (potential criterion);
- Sustained VT and ventricular fibrillation;
- Significant QTc prolongation (eg, $QTc \geq 500$ milliseconds) postdosing;
- Adverse events (when subject is off continuous ECG monitoring but exposed to the drug) such as unexplained syncope that might suggest ventricular arrhythmias;
- Development of ECG abnormalities that could mimic ventricular arrhythmias, such as supraventricular arrhythmia with aberrant conduction, and/or render it more difficult to monitor for arrhythmias.

Potential stopping criteria for dose escalation or the entire study include the following:

- Confirmed significant QTc prolongation, ventricular ectopy, or NSVT in one or more subjects on the drug in a pattern (either in the specific cohort or in the entire study) suggestive of drug-relatedness;
- Adverse events potentially due to ventricular arrhythmia occurring in one or more subjects on the drug in a pattern suggestive of drug-relatedness;
- New preclinical or clinical data that suggest significantly increased risk of ventricular arrhythmia at the study planned drug exposures.

Case studies

As a means to illustrate prior points where consensus approaches could be useful, the following 3 hypothetical case vignettes have been created. These cases do not represent a regulatory opinion or guidance on how to address these specific issues.

Case study 1

During a phase I repeat-dose study of a known sodium channel blocker, a 23-year-old subject with no significant medical/family history or concomitant medications/electrolyte abnormalities developed electrocardiographic QRS duration increase from a baseline measurement of 80 milliseconds to a value of 160 milliseconds. This was followed by polymorphic ventricular ectopy and then ventricular fibrillation, which occurred at T_{max} . The patient was successfully resuscitated. Result of a cardiac workup including an echocardiogram, stress test, and cardiac catheterization was negative. The development program for this drug was terminated because the causal relationship of the drug to the serious adverse event was considered likely and predictable on the basis of its known activity as a sodium channel blocker.

Case study 2

During a phase I repeat-dose study of a drug with no known nonclinical cardiovascular effects, a single subject (30 subjects were studied) developed a 5-beat run of asymptomatic monomorphic VT at a heart rate of 140 beat/min while sleeping. The morphology of the NSVT was a negative QRS complex in V_1 and positive in lead aVF. Results of the subject's baseline ECG and ECG immediately after the event were normal. The electrolytes and drug screen were nonrevealing. Findings of a subsequent stress test and echocardiogram were normal. A follow-up Holter monitor several days after the last dose revealed frequent PVCs and 2 short runs of NSVT with morphology similar to that during the trial and consistent with RVOT ventricular ectopy.

It was the determination of the sponsor/investigator that this represented an underlying benign ventricular

arrhythmia, and development of the drug continued as planned. A screening 24-hour Holter monitor was added to evaluate potential study candidates to further reduce the possibility of including additional subjects with similar benign arrhythmias from participating in the early clinical program.

Case study 3

During a phase I repeat-dose study of a drug with a nonclinical *bERG* signal (but a negative dog telemetry study), a subject receiving the drug had an 8-beat run of asymptomatic monomorphic NSVT. Single-lead telemetry was being used, so full morphology was not available. Cardiac evaluation was nonrevealing. Telemetric monitoring was extended from 24 hours to 5 days for the remainder of the study. Two additional subjects receiving the drug developed short runs of asymptomatic, monomorphic NSVT; cardiac evaluations for them were also nonrevealing. A fourth subject receiving placebo developed 6 beats of NSVT; no cardiac abnormalities were detected in this instance. The ratio of placebo-treated to drug-treated individuals was 1:3 for this study. Although there appeared to be a “balanced” ratio of observed arrhythmias in treated and placebo individuals, only 16 subjects were evaluated. Therefore, there was an incidence of ventricular arrhythmias of 25% in each treatment arm (ie, drug and placebo), which is significantly higher than that reported in the medical literature.

At this point, a proposal was presented to the regulators regarding potential continuation of the clinical development program. The proposal included enhanced baseline evaluation, more conservative inclusion/exclusion and discontinuation criteria relative to screening Holter monitoring and echocardiographic findings, and more extensive telemetry monitoring. Although none of the arrhythmias had potentially serious characteristics, it was not possible to exclude a proarrhythmic effect. Given that this drug was being developed to treat a serious medical illness with no alternatives, it was felt that expansion of the clinical development program would be needed (ie, larger subject numbers) to determine if there was a drug-induced proarrhythmic effect. Ultimately, after several hundred subjects were enrolled in the clinical trials, the incidence of observed asymptomatic ventricular arrhythmias decreased to 4% with an equal ratio in placebo and treated individuals. Subsequently, it was felt that the high frequency of arrhythmias in the initial study may have been due to detection of “background baseline” arrhythmias with prolonged telemetry monitoring and, therefore, that it did not represent a clinically significant issue.

Future directions

Additional nonclinical and clinical research is needed to better understand the risks to subjects as well as the biological plausibility of ventricular arrhythmias attrib-

able to a drug during clinical development. Better nonclinical models with good predictivity for clinical events need to be established. In addition, larger data sets of Holter or telemetry data on healthy subjects in a phase I setting would help to accurately determine the baseline rates of arrhythmias in this population. Partnerships between industry, academia, and regulators to evaluate continuous ECG waveform data and novel cardiac safety end points are important to further our understanding of cardiac safety in drug development, including when to conduct intensive cardiac monitoring in early phase clinical studies.

An appropriate study to determine the true incidence of spontaneous ventricular arrhythmias (especially tachyarrhythmias) and other forms of arrhythmia in selected healthy subjects in a phase I environment, the environment of interest here, has not been conducted. Such a study or data set, or perhaps a series of studies, would lead to more definitive approaches. Such a study or studies, prospective in nature, could have the following characteristics:

- Sponsors: Ideally, a group of interested pharmaceutical companies.
- Location: Several phase I units considered representative of the varieties of size, experience, location, bed layout, and other physical attributes typical of phase I units.
- Enrollment: Ideally, a large, genetically, ethnically, and sociologically diverse group of healthy subjects would be enrolled under a single set of inclusion and exclusion criteria.
- Duration of monitoring: Monitoring should be continuous and last for 4 to 7 days. If possible, subjects would return to the phase I unit weeks or months later for a second episode of confinement and recording.
- Electrocardiography: Twelve-lead recordings would be obtained with either Holter or telemetry equipment capable of reliable data capture and storage. Use of a single manufacturer's system would be preferable. Recordings would be obtained during confinement; subjects would be managed as they typically would be in an early phase study, including rest period and blood draws; and mock therapy in the form of a placebo would be administered.
- Centralized data: A single commercial or academic core ECG laboratory or data warehousing facility would collect the data and make provisions for its analysis.
- Data analysis: A summary of the incidence of all types of arrhythmias and their diurnal, day-to-day, and long-term variability would be produced. Potentially influential cofactors would be evaluated, including sex, age, ethnicity, unit characteristics (eg, bed

layout, location, size), study activities (eg, blood drawing, rest, meals), and time of year.

It should be noted that a study of this type would be expensive and logistically demanding and, if carried out, will not be completed for some time. In the interim, therefore, an analysis of existing data could be very helpful. Such a study, retrospective in nature, might be designed as follows:

- Sponsors: Interested pharmaceutical companies, phase I units, and core ECG laboratories.
- Data source: Multiple pharmaceutical companies, phase I units, and core ECG laboratories in possession of appropriate continuous 12-lead ECG data.
- Eligible data: Any study in which healthy subjects participated under phase I confinement would be eligible for inclusion in this study if appropriate screening criteria had been used, 12-lead continuous recordings were obtained and are available, and at least 2 days of monitoring without administration of an active drug was performed. In most cases, this type of data will be limited to a control/placebo group. If feasible, data obtained with a single manufacturer's device would be preferable.
- Centralized data: A single commercial or academic core ECG laboratory or data warehousing facility would collect the data and make provisions for its analysis; or, at a minimum, a universal case report form would be used to compile existing data evaluated by multiple ECG laboratories.
- Data analysis: A summary of the incidence of all types of arrhythmias and their diurnal, day-to-day, and long-term variability would be produced. Potentially influential cofactors would be evaluated, including sex, age, ethnicity, unit characteristics (eg, bed layout, location, size), study activities (eg, blood drawing, rest, meals), and time of year.
- The information obtained from either of these data sets would have substantial influence on the design, conduct, and overall strategy for drug development and, ultimately, on the safety and efficacy of new drugs. In addition, this work would greatly improve our clinical understanding of the nature and incidence of arrhythmias in healthy subjects, potentially resulting in improved arrhythmia management in clinical medicine.

Concluding remarks

As cardiac safety continues to be a primary safety and regulatory concern in drug development, increased cardiac monitoring will be used and ventricular ectopy and arrhythmias will very likely be observed more frequently in early phase development. Although complex ventricular arrhythmia is relatively rare, these events will continue to be observed during phase I trials; and the

biologic plausibility that the event is drug related will continue to come into question. If an event occurs while a healthy subject is taking a drug but is not replicated off drug, it cannot always be reflexively assumed that the event is related to the drug.

Certain factors—such as the underlying frequency of events in healthy people in general; the morphology, frequency, and length of the ventricular event; the preclinical cardiac risks of the investigational product; the PK/PD relationship of the drug to the event; the concomitant changes on the ECG; and the underlying risk factors in the individual—need to be considered. When events of potential clinical concern are seen in a subject, the appropriate workup and follow-up need to be undertaken to ensure the safety of that individual subject and the safety of the study population. The risks to the individual subject include underlying unidentified cardiac disease and/or the proclivity for drug-induced arrhythmias.

Despite these considerations, it must be borne in mind that if few ventricular events are observed during drug development, it cannot simply be assumed that the investigational drug is safe. The appropriate workup and additional evaluation of the drug need to be addressed so that drugs with true cardiac safety risks are identified and that drugs with promising therapeutic benefit are not unnecessarily terminated. Consistent approaches are needed to the identification (and treatment where necessary) of events occurring in individual subjects and to the evaluation of any consequences of such events for continuing the clinical development program. The CSRC hopes that this paper will facilitate discussions of this issue among all stakeholders that may lead to the further development of, and general agreement upon, such approaches.

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