Background
Shire pharmaceuticals wished to gain FDA approval for use of guanfacine in attention-deficit/hyperactivity disorder. Studies showed that the drug was effective, but regulatory and safety concerns were raised following a thorough QT study that showed placebo-adjusted upper 90% CI for QTc prolongation were 9.3 and 20.7 msec at therapeutic and supratherapeutic dose levels of 4 and 8 mg/kg, respectively. Guanfacine was known to produce a centrally mediated reduction in heart rate and blood pressure. Previous studies have demonstrated that QTc can produce erroneous arrhythmia liability indications for drugs that elicit this type of response.

Evaluating Arrhythmogenic Risk
Based on the QTc prolongation findings, FDA requested that Shire perform a retrospective dynamic QT beat-to-beat analysis (QTbtb). ECG restitution was employed to assess the risk related to the observed QT prolongation. ECG restitution is a technique that quantifies cardiac stress that can lead to arrhythmia vulnerability by assessing the ability of the heart to recover from one beat to the next. Restitution measures changes in QT interval (working phase of heart) in response to each preceding TQ interval (resting phase of heart) at every heart rate (RR interval) to quantify the stress on the heart and identify conditions where the likelihood of a re-entry arrhythmia is increased. Restitution and dynamic QT beat-to-beat (QTbtb) analysis can circumvent many of the limitations of QTc as a biomarker of arrhythmia vulnerability. QTbtb has shown to differentiate changes in QT interval duration due to heart rate or autonomic state from impaired repolarization. Dynamic QTbtb analysis compares QT intervals to individual cardiac cycles from all normal autonomic states at similar RR intervals, thereby eliminating potential sources of error from the use of QT correction functions. Since QTbtb compares all treatment related beats to similar beats under all baseline autonomic conditions, it can identify when abnormal autonomic states or impaired repolarization exist that may lead to increased arrhythmia vulnerability. However, under these same conditions, QTc breaks down as a cardiac risk biomarker and can produce either a false positive or false negative indication of cardiac risk.

Study Design
Sixty healthy subjects using 24-hour Holters were examined in a 3-arm, placebo- and positive-controlled, double-blind crossover study for effects on beat-to-beat QT, TQ, and RR intervals. Dynamic beat-to-beat and ECG restitution analyses were performed following beat-to-beat derivation of RR and QT intervals from the continuous ECG recordings.

Results
ECG restitution analyses indicated that, at all time points, a disproportionate effect to increase the TQ interval (rest) occurred more in relationship to each QT interval lengthening resulting in a placebo-adjusted reduced QT/TQ ratio of 21% after 4 mg and 31% after 8 mg (both antiarrhythmic responses). Additionally, the percentage of time and magnitude of stress on the heart, as measured by the upper limits of the QT/TQ ratio, were reduced with guanfacine by 22% to 24%. In contrast to guanfacine, the positive control moxifloxacin, did not show a significant improvement in any restitution parameters but reflected a trend toward proarrhythmia with an increase in the QT/TQ ratio of up to 11%.

Conclusions
These results indicate that guanfacine causes a stabilizing effect on cardiac restitution that helps reconcile the clinical evidence for a lack of arrhythmia liability despite apparent increases in typical QT/QTc prolongation measures. Beat-to-beat and ECG restitution analyses may be more appropriate methodologies for risk assessment when QTc interval is affected by changes in autonomic state or heart rate.

Shire received FDA approval in 2009. To date, more than 3 million prescriptions have been filled with a clean history of cardiac safety.