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Research paper

Challenges in implementing and obtaining acceptance for J-Tpeak assessment as the clinical component of CiPA

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ABSTRACT

Introduction: This paper is based on a presentation held at the Annual Safety Pharmacology Society meeting in September 2017, at which challenges for the clinical component of CiPA were presented. FDA has published an automated algorithm for measurement of the J-Tpeak interval on a median beat from a vector magnitude lead derived from a 12-lead ECG. CiPA proposes that J-Tpeak prolongation < 10 ms can be used for drugs with a QTc effect < 20 ms to differentiate between safe and unsafe delayed repolarization and to reduce the level of ECG monitoring in late stage clinical trials.

Methods: We applied FDA's algorithm, complemented with iCOMPAS, to moxifloxacin and dolasetron data from the IQ-CSRC study with 9 subjects on active and 6 on placebo. The effect on QTcF and corrected J-Tpeak (J-Tpeak_c) was analyzed using concentration-effect modeling.

Results: There was a good correlation between QTcF and J-Tpeak_c prolongation after oral dosing of 400 mg moxifloxacin with placebo-adjusted, change-from-baseline (ΔΔ) J-Tpeak_c of ~12 ms at concentrations that caused ΔΔQTcF of ~20 ms. On dolasetron, J-Tpeak_c was highly variable, no prolongation was seen and an effect on ΔΔJ-Tpeak_c > 10 ms could be excluded across the observed plasma concentration range.

Discussion: In this limited analysis performed on the IQ-CSRC study waveforms using FDA's automated algorithm, J-Tpeak prolongation was observed on moxifloxacin, but not on dolasetron, despite clinical observations of proarrhythmias with both drugs. Challenges for the implementation of the J-Tpeak interval as a replacement or complement to the QTc interval, include to demonstrate that the proposed clinical algorithm using a J-Tpeak threshold of 10 ms, can be used to categorize drugs with a QT effect up to ~20 ms as having low pro-arrhythmic risk.

1. Introduction

At the Annual Safety Pharmacology Society meeting in Berlin in September 2017, a session was held presenting non-clinical, clinical and regulatory opportunities and challenges of the Comprehensive Proarrhythmia In-vitro Assay (CiPA) project (https://www.safetypharmacology.org/AM2017/). This brief report covers the presentation addressing challenges in regard to acceptance and implementation of the clinical component, i.e., using the J-Tpeak interval duration as a novel and improved biomarker to assess proarrhythmic risk of drugs in development. The assumption is that the reader has an overall understanding of the non-clinical parts of CiPA and the proposal that the project may lead to revision of ICH S7B non-clinical and E14 clinical guidance (Johannesen et al., 2014; Johannesen et al., 2016, b; Vicente et al., 2018; Vicente, Hosseini, Johannesen, & Strauss, 2017).

1.1. Background

In 2013, when the CiPA project was initiated, definitive assessment of a drug's effect on the QTc interval was typically performed in a so-called thorough QT (TQT) study. This study, performed in healthy subjects, was a key component in the International Conference of Harmonisation (ICH) E14 clinical guidance document from May 2005 (ICH E14, 2005), for evaluation of ECG effects of all new drugs. The TQT study has been successful in terms of detecting drugs with a QT effect and thereby avoiding the introduction of new medicines with an unknown QT liability to the market. The TQT study is however resource intensive (Bouvy, Koopmanschap, Shah, & Schellekens, 2012), based on a relatively conservative threshold of the QT effect (10 ms) and the requirement that the effect is evaluated at several post-dosing timepoints ('by timepoint' analysis). The study thereby has low power to exclude small effects and must be relatively large (Zhang & Machado,

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2008). Moreover, the TQT study needs to include a positive control and placebo, in addition to a supratherapeutic dose of the drug, and is therefore in most cases a designated, stand-alone study.

Based on experience over the years, it seems that the TQT study is very sensitive and may result in 'false' positives results in regard to the feared outcome, the proarrhythmic event (Malik & Stockbridge, 2012; Stockbridge, Morganroth, Shah, & Garnett, 2013). The CiPA project raises the concern that the focus of the current ICH S7B/E14 paradigm on hERG inhibition and QTc prolongation may lead to the premature discontinuation of potentially efficacious drugs without an actual proarrhythmic risk (Vicente et al., 2018). A clearly defined goal of CiPA is therefore to improve identification of drugs with a true proarrhythmic liability and to replace the TQT study with a less demanding clinical ECG evaluation, with the objective to confirm the absence of unexpected ECG effects for drugs with a negative non-clinical evaluation (Sager, Gintant, Turner, Pettit, & Stockbridge, 2014; Vicente et al., 2018).

At the time of the initiation of the CiPA project (2013), efforts were already underway to obtain acceptance for concentration-QTc (C-QTc) modeling to replace the 'by timepoint' analysis, described in ICH E14, in the evaluation of drug-induced QT effects. This was largely based on increasing experience with C-QTc analysis applied to all TQT studies under review by FDA's Interdisciplinary Review Team for QT studies (IRT) (Garnett et al., 2008; Tornoe et al., 2011). If C-QTc analysis were to be applied to ECG data derived from studies routinely performed as part of clinical development, e.g., the First-in-Human study, this would represent a more efficient approach, and would also have other potential advantages, such as improved understanding of ECG liabilities early in clinical development (Darpo & Garnett, 2013; Rohatagi, Carrothers, Kuwabara-Wagg, & Khariton, 2009; Shah & Morganroth, 2012).

To evaluate the concept of detecting mild QT prolongation in small sized studies using C-QTc analysis, a prospective study was designed and conducted collaboratively between the Cardiac Safety Research Consortium, the Consortium for Innovation and Quality in Pharmaceutical Development and FDA (the IQ-CSRC study) (Darpo et al., 2014). Five mildly QT prolonging drugs with known proarrhythmic potential were selected from a list provided by FDA, and administered to healthy subjects in an incomplete block design with 9 subjects on active and 6 on placebo. Two doses of each drug were given, chosen to cause QTc prolongation of 9 to 12 ms and 15 to 20 ms. The study successfully detected the QT effect of the lower dose for all 5 drugs by demonstrating a statistically significant slope of the C-QTc relationship and that the upper bound of the 90% confidence interval (CI) of the predicted effect exceeded 10 ms. A QTc effect exceeding 10 ms could also be excluded with a negative drug, levocetirizine.

Based on regulators' increasing confidence in C-QTc analysis and on the results of the IQ-CSRC study, ICH E14 was revised in December 2015, through an amended Q&A section (ICH E14 Questions & Answers (R3) December 10, 2015) and this revision is now endorsed in all regions. The TQT study can thereby be waived if C-QTc analysis is applied to routine clinical pharmacology studies, such as the First-in-Human (FIH) study, provided that sufficiently high, supra-therapeutic plasma concentrations have been achieved (Garnett et al., 2018; Murphy et al., 2017; Nelson et al., 2015). In Fig. 1, an example of a negative QT assessment is shown, in which a QT effect exceeding 10 ms could be excluded throughout the observed plasma concentration range. In cases where a TQT study has to be performed, based on the sponsor's choice or when sufficiently high plasma concentrations of the drug cannot be achieved, C-QTc analysis allows a substantial reduction of the sample size. The power to exclude a 10 ms QT effect can be retained with C-QTc analysis with approximately half the number of subjects (n = 24 to 28) (Liu, 2016), as compared to the conventional 'by timepoint' analysis (n = 44 to 48) (Zhang & Machado, 2008).

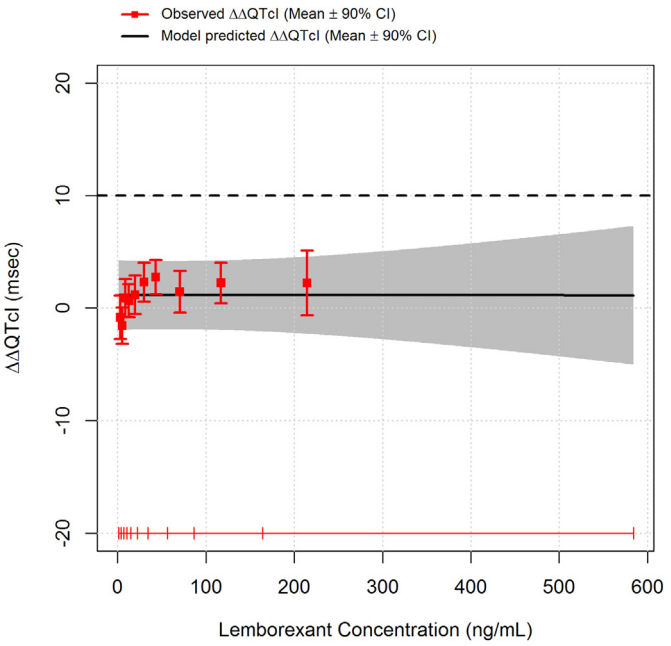

Fig. 1. Concentration-QTc analysis applied to pooled data from 2 multiple-ascending studies with lemborexant. The goodness-of-fit graphs shows observed change-from-baseline QTcF, adjusted for the placebo effect, within deciles of lemborexant plasma concentration (red bars; mean ± 90% CI) and the predicted QT effect using the C-QTc model (black line with grey shaded area; mean ± 90% CI). Achieved plasma concentrations provided an 8-fold margin above levels considered clinically relevant, based on the maximum dose tested in phase 3 clinical trials. Given the negative QT assessment, this development program was allowed to proceed into pivotal trials without a TQT study in EU, Japan and USA.
From Murphy et al. Concentration–Response Modeling of ECG Data From Early-Phase Clinical Studies as an Alternative Clinical and Regulatory Approach to Assessing QT Risk — Experience From the Development Program of Lemborexant. J Clin Pharmacology 2017; 57: 96–104. Reproduced with permission from the publisher (John Wiley & Sons).

1.2. The J-Tpeak interval as a novel and improved biomarker for proarrhythmic risk

The current standard for ECG assessment is therefore widely different as compared to when the CiPA project was initiated. A novel approach for clinical assessment must therefore be shown to be better than what is presently done, i.e., provide the same level of safety and represent a more efficient approach for drug developers. To this end, FDA has through a series of publications proposed that a novel ECG biomarker, the duration of the J-Tpeak interval provides a better differentiation of the proarrhythmic risk, especially for drugs with effects on several cardiac ion channels, and that this interval can replace or complement the QTc interval (Johannesen et al., 2014; Johannesen et al., 2016, b; Vicente et al., 2015; Vicente, Hosseini, Johannesen, & Strauss, 2017). The J-Tpeak interval corresponds to the duration between the J point defined as the end of the QRS complex and Tpeak, which is the apex of the T-wave under normal configuration. The J-Tpeak interval is therefore, by definition, a sub-interval of the QT interval. More specifically, it is proposed that for CiPA 'low risk' drugs with QT prolongation < 20 ms, J-Tpeak prolongation < 10 ms would be threshold of clinical concern and serve as a qualifier with impact on the level of ECG monitoring in late stage clinical trials (Vicente et al., 2018) (Fig. 2). CiPA 'low-risk' drugs can be defined as drugs with equal or greater late sodium or calcium block compared to hERG inhibition (Crumb Jr, Vicente, Johannesen, & Strauss, 2016; Vicente et al., 2018; Vicente, Hosseini, Johannesen, & Strauss, 2017). The full understanding of the electrophysiological meaning of the J-Tpeak interval and clinical