Final Concept Paper

E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Additional Q & As document

***15* March 2010**

Endorsed by the Steering Committee on 13 April 2010

Type of Harmonizations Action Proposed

- **To generate an additional Q and A document** addressing some of the limitations of the current guideline within 1 year. [Phase-1]
- **To create an ICH working group that will initiate collaborative data gathering and analyses** in all ICH regions in order to address in an ongoing manner additional questions identified that could lead to enhancement of the current guideline (either by re-opening it or by additional set of Q & As). [Phase-2]

Statement of the Perceived Problem

There are differences in the way the ICH E14 guideline is interpreted and implemented within the ICH regions with varied experience and expertise. These have led to lack of clarity and unresolved debate regarding a number of aspects of the S7B and E14 documents that has raised points that will need to be clarified. In addition, there have been advances in knowledge, experience, and technology since E14 was issued in 2005. These differences across ICH regions has had considerable impact on the sponsors in addressing this issue of evaluation of effect on cardiac repolarisation with lack of clarity and unresolved debate. This scenario leads to an inefficient and less effective evaluation of the potential for QT prolongation that is not harmonized across the regions. It also raises the spectre that the "risk-averse industry" shelving a number of potentially valuable agents in early development purely based on the potential for QT prolongation between 5-10 ms (ΔΔQT- placebo & baseline corrected).

Issues to be Resolved

The E14 adhoc expert group which met in St. Louis, Missouri in October 2009 has proposed a set of issues that require resolution and it is proposed that these be attended to in a phased manner.

Phase-1:

This initial phase will attempt to clarify a number of issues for which there is already considerable consensus across the regions but which are not explicated clearly in the ICH E14 guideline or the subsequent Q&As document that was generated. The following issues will be clarified in this Phase:

- Use of Concentration-Response Relationships (CRR) in a TQT study
- Use of CRR and alternative designs of Phase I studies to enhance the evaluation of QTc
- Enhanced clarity around gender
- Approach to validating new technologies for ECG acquisition and analysis (automated interpretation of intervals)
- Clarification of approach to evaluating adequacy of HR correction
- Clarification of approach to evaluating QTc in late stage clinical development

Phase-2:
The second Phase of this working group will address several fundamental issues and questions (listed below) that, if resolved, would require a substantial revision of ICH E14. At the present time, however, a productive discussion of these issues requires additional data collection and discussion. The following issues and questions have been identified and are proposed to be addressed by the working group in a 1-3 year time frame.

- Evaluate alternative statistical methods for analyzing continuous QTc data?
- What data and quality control metrics would provide sufficient confidence in the TQT study to remove the requirement for a positive control? What alternative positive controls are acceptable and how should they be evaluated?
- Are there important differences in QTc responses across different ethnic groups?
- Does the preclinical evaluation (S7B) of QT risk reflect the outcome of the TQT study?
- Can we enhance the preclinical evaluation (S7B) of QTc and gain greater confidence that a TQT study is not necessary?
- How well can existing and enhanced Phase I data predict a negative TQT study? (e.g., Can a clearly defined PK-QTc relationship in Phase I at supra-therapeutic exposures exclude the need for a TQT study?)
- Can we identify methods of integrating Phase I data in the context of the S7B evaluation that would provide sufficient confidence to exclude the need for a TQT study?

Background to the Proposal

The ICH E14 guidance provides recommendations to sponsors concerning the design, conduct, analysis, and interpretation of clinical studies to assess the potential of a drug to delay cardiac repolarization. This assessment should include testing the effects of new agents on the QT/QTc interval as well as the collection of cardiovascular adverse events. The investigational approach used for a particular drug should be individualized, depending on the pharmacodynamic, pharmacokinetic, and safety characteristics of the product, as well as on its proposed clinical use.

E14 was signed off as a *Step 4* document in May 2005. At the time of sign-off, it was recognized that this document would require maintenance as the science evolved over time. Since 2005, a number of advances relating to knowledge, understanding of the hERG channel blockade, hERG channel traffic inhibition, potential utility of concentration-QT effect relationship in the TQT study. The concentration-effect (QT/QTc) relationship has been explored in phase-I studies during drug development and the statisitical methodolgies utilized have also improved. Facilities for analyses of QT/QTc intervals from continous recording over time, offer a unique and more advanced understanding of the QT dynamics in preference to that of analyzing the QT interval at timed intervals. The statistical methodologies for analysis of both TQT studies and continous QT data are progressing, but these not been systematically analysed in the context of regulatory submissions with E14 providing little opportunity. These advances in experience, and technology will need to be incorporated and reflected in the guidance document with out being either restrictive or prescriptive. It is therefore proposed that the working group evaluate these in order to enhance the existing guidance.

At the ICH Steering Committee meeting held in Yokohama on June 6-11, 2009, the Steering Committee endorsed the establishment of an Informal E14 Discussion Group to assess the E14 guideline in view of experience gained. The SC disbanded the E14 IWG and requested the Secretariat to close the E14 mail box; and agreed to the organization of an Informal Discussion Group in St. Louis, Missouri, October 2009. The ICH E14 Informal Discussion Group met for three days in St. Louis and discussed the status of the implementation of ICH E14 in the different regions. The different levels of implementation of ICH E14 resulted in significant differences in experience, data collection, research activity, and expertise across the regions with regard to issues related to QT/QTc. The group recognized that there have been significant advances in knowledge, experience, and technology since E14 was issued in 2005.

Type of Expert Working Group and Resources

Based on the proposal to evaluate the proarrhythmic risk in accordance to existing guidance for both pre-clinical (S7B) and clinical aspects (E14), it is proposed that an Implementation Working Group (IWG) be set up to advance the work anticipated to resolve the issues. In order to limit the size of the IWG and based on the ICH SC recommendations, the IWG will be composed primarily of clinical members who will interact ex-committee with their preclinical safety colleagues in the region and inform the IWG of their deliberations. However, given the translational aspects of one of the questions (related to the use of PK-PD modelling) members representing the preclinical sciences with an expertise on PK-PD modelling will be encouraged to participate in the IWG.

Constitution of the group

While the representation from each ICH region is dependent on the regional authorities wishes and their choice, the current ICH E14 Informal Discussion Group (constituated of the six ICH parties and the Observers) has the advantage and experience of working together in order to effectively arrive at a consensus opinion and produce the expected output. We therefore request that this group form the basis of the Informal Discussion Group with recruitment of additional expertise as necessary.

Timing

The anticipated time scale is as follows;
Phase -1

1. Concept paper — Spring 2010 (anticipated Concept paper adoption by ICH SC)
2. Draft Q & As for Phase-1 — Jun 2010 (Face to face at ICH mtg in Tallinn, Estonia)
3. Finalise Phase-1 Q & As — Nov 2010 (Face to face if necessary in Japan)

Phase -2
Other questions will need additional work and might lead to a revision of the E14 Guideline. It includes discussion of alternative statistical methods for analyzing QTc data, alternative positive controls, pre-clinical evaluation (S7B) to reflect the outcome of TQT study. Those efforts should result in an enhanced evaluation of QT in drug development and further improvement of harmonization across the regions. Based on feedback from the ICH SC, The IWG will develop an additional Concept Paper for future activities for SC discussion once Q&As will have progressed.