# Integrated Nonclinical Risk Tables

Integrated nonclinical risk assessment is recommended under the following scenarios:

* ICH E14 Q&A 5.1:
  + When the high clinical exposures have been achieved in the clinical ECG assessment, but a sufficient multiple has not been obtained (i.e., 2x high clinical exposure) to waive the positive control.
* ICH E14 Q&A 6.1:
  + Support the interpretation of low proarrhythmic risk for a product that cannot be evaluated in a conventional QTc study designed to exclude a 10-ms mean increase in ∆∆QTc.
  + Products with confounding heart rate effects that could impact accurate determination of the QTc.

# References

ICH Guidelines:

<https://database.ich.org/sites/default/files/E14_Guideline.pdf>

<https://database.ich.org/sites/default/files/E14_Q%26As_R3_Q%26As.pdf>

<https://database.ich.org/sites/default/files/E14-S7B_QAs_Step4_2022_0221.pdf>

ICH Training Materials:

<https://database.ich.org/sites/default/files/ICH_E14-S7B_TrainingMaterial_2022_0407.pdf>

<https://database.ich.org/sites/default/files/ICH_E14-S7B_TrainingMaterial_ExamplesSupplementalFile_2022_0331.pdf>

# Table 1-B. In vitro hERG Assay Evaluation

|  |  |  |
| --- | --- | --- |
| Analyte: Parent; Protocol Number | | |
| Best Practice Element | **Deviation / Issue** | **Impact of Deviation / Issue** |
| Temperature (35–37°C) |  |  |
| Voltage Protocol1 |  |  |
| Recording Quality2 |  |  |
| IC50 Calculation3 |  |  |
| Concentration Verification4 |  |  |
| Positive Control5 |  |  |
| Negative Control6 |  |  |
| Good Laboratory Practice |  |  |
| **Table 1-B Notes** 1: Approximate the appropriate elements of a ventricular action potential; evoked at adequate frequencies  2: Adequate voltage control; stability at baseline; steady state inhibition  3: Justification if 50% could not be achieved, selective blocker at high concentration, residual background current subtracted  4: Validated analytical method; samples collected from cell chamber; samples collected from satellite or real experiments; concentration-response relationship with nominal or measured concentrations  5: Positive control is one of the “reference drugs” under Q&A 1.2; two or more concentrations 20-80% block; positive control within expected range  6: Vehicle-control included, includes all non-compound materials in the test solution  *Abbreviations: °C: degrees Celsius; IC50: half maximal inhibitory concentration; µM: micromolar* | | |

# Table 1-C. In vitro Assay Results

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Investigational Drug | | | | | | |
|  | In Vitro Assay1 | High Clinical Cmax,ss (ng/mL) 2 | Protein Binding, %3 | Mol Wt (g/mole) | hERG IC50 (µM) / (μg/mL)4 | Safety Margin5 |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| hERG Safety Margin Threshold Defined by Reference Drugs6 | | | | | | |
| Reference Drugs | In Vitro Assay | Critical Concentration (ng/mL) | Protein Binding, % | Mol Wt (g/mole) | IC50 Distribution (µM) | Safety Margin |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Threshold | | | | | |  |
| Table 1-C Notes 1: In vitro assay protocol evaluated for best practice in Table 1-B.  2: For the investigational product, include high Clinical Exposure scenario is defined as in ICH E14 Q&A 5.1, i.e., Cmax,ss achieved when the maximum therapeutic dose is administered in the presence of the intrinsic or extrinsic factor (organ impairment, drug-drug interaction, food effect, etc.) that has the largest effect on increasing Cmax,ss. Shown as mean (95% CI).  3: If the protein binding is higher than 99%, use 99% when calculating the free fraction (ICH S7B Q&A 1.2).  4: If the concentration range did not allow for estimating IC50, provide the % block and highest concentration studied, e.g., 10% (1 µM).  5: Safety margin calculated as the IC50 normalized to the drug’s estimated high clinical concentrations (ICH S7B Q&A 1.2). 95% CI computed using the CI of the high clinical Cmax. Shown as mean (95% CI).  6: Considerations to use the preestablished hERG safety margin threshold for Investigational drug:   * The Investigation drug and reference drugs are evaluated under the same experimental protocol. * The concurrent positive control for hERG assay is one of the reference drugs used to derive the threshold. * The IC50 of positive control, computed from two or more concentrations achieving 20–80% block, is similar to the expected range of IC50 values of reference drug evaluated under the same experimental protocol. * Directly compare the lower 95% confidence bound of the hERG safety margin of parent and/or metabolite to safety margin threshold. * If the hERG safety margins of the parent and/or metabolite are higher than the pre-established threshold, then the in vitro assay indicates a low risk for QT prolongation due to direct hERG block.   *Abbreviations: C: concentration; CC: critical concentration; CI: confidence interval; Cmax,ss: maximum concentration at steady state; g: gram; IC50: half maximal inhibitory concentration;* *μM: micromolar; Mol: molecular; N: number; PK: pharmacokinetic; ss: steady state; TdP: torsade de pointes; Tmax: time of Cmax; Wt: weight* | | | | | | |

# Table 1-D. In Vivo QT Assessment

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| QT Study | | | | | | | | | | |
| Exposure | | | |  | | | | | | |
| Design1 | | | |  | | | | | | |
| *Species:* | | | |  | | | | | | |
| Historical Sensitivity: | | | |  | | | | | | |
| ECG collection | | | |  | | | | | | |
| ECG reading methodology | | | |  | | | | | | |
| PK Collection | | | |  | | | | | | |
| Analysis Methods: | | | |  | | | | | | |
|  | Data reduction method | | |  | | | | | | |
|  | Analysis methodology | | |  | | | | | | |
|  | HR correction method | | |  | | | | | | |
| ECG Findings | | | |  | | | | | | |
| Summary Findings | | | | | | | | | | |
| *Moiety & Dose* | | *QTcI Effect Size (ms* ± SE*) 2* | *Parent concentration at 3 h (ng/mL)3* | | *Cmax-total*  *(ng/mL) 4* | *Cmax-free*  *(ng/mL) 5* | *Protein Binding: Species (%) 6* | *High Clinical Cmax,ss (ng/mL) 7* | *Exposure Ratio 8* |
|  | |  |  | |  |  |  |  |  |
|  | |  |  | |  |  |  |
|  | |  |  | |  |  |  |
| *MDD9* | |  | | | | | | | |
| Table 1-D Notes 1: Study design indicates crossover or parallel, sample size, species and historical MDD for positive control under same study design. MDD is a statistical indication of the smallest effect size that can be determined in a QT study.  2: Indicate unit of effect size: Δ from vehicle (ms). Reference drug effects should be reported in same units  3: Indicate the drug exposure (e.g., mean; total drug) obtained at each dose group in QTc study animals  4: Indicate total drug level (e.g., mean) from a PK study (either in QTc study animals or separate animals)  5: Indicate free (unbound) drug levels (corrected for protein binding in the animal species)  6: Indicate protein binding in the animal species used for the QTc study. If protein binding is higher than 99%, use 99% when calculating the free fraction.  7: For the investigational product, include high clinical exposure as defined in ICH E14 Q&A 5.1, i.e., Cmax,ss achieved when the maximum therapeutic dose is administered in the presence of the intrinsic or extrinsic factor (organ impairment, drug-drug interaction, food effect, etc.) that has the largest effect on increasing Cmax,ss.  8: Exposure ratio is the ratio of mean Cmax,free: mean High Clinical Cmax,ss free  9: MDD is calculated from the ANOVA model, *e.g.,* MDD = ta=0.05,df\*sqrt(2)\*Residual/sqrt(N=4)  *Abbreviations: ANOVA: analysis of variance; CI: confidence interval; Cmax: maximal concentration; Cmax,ss: steady state maximal concentration; df: degrees of freedom; h: hour; kg: kilogram; MDD: minimal detectable difference; mL: milliliter; ms: millisecond; ng: nanogram; PK: pharmacokinetic; QTcI: individual heart rate correction* | | | | | | | | | | |