# How CiPA might be implemented in clinical development and regulatory approaches

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# Disclaimer

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# QTc Evaluation in Drug Development

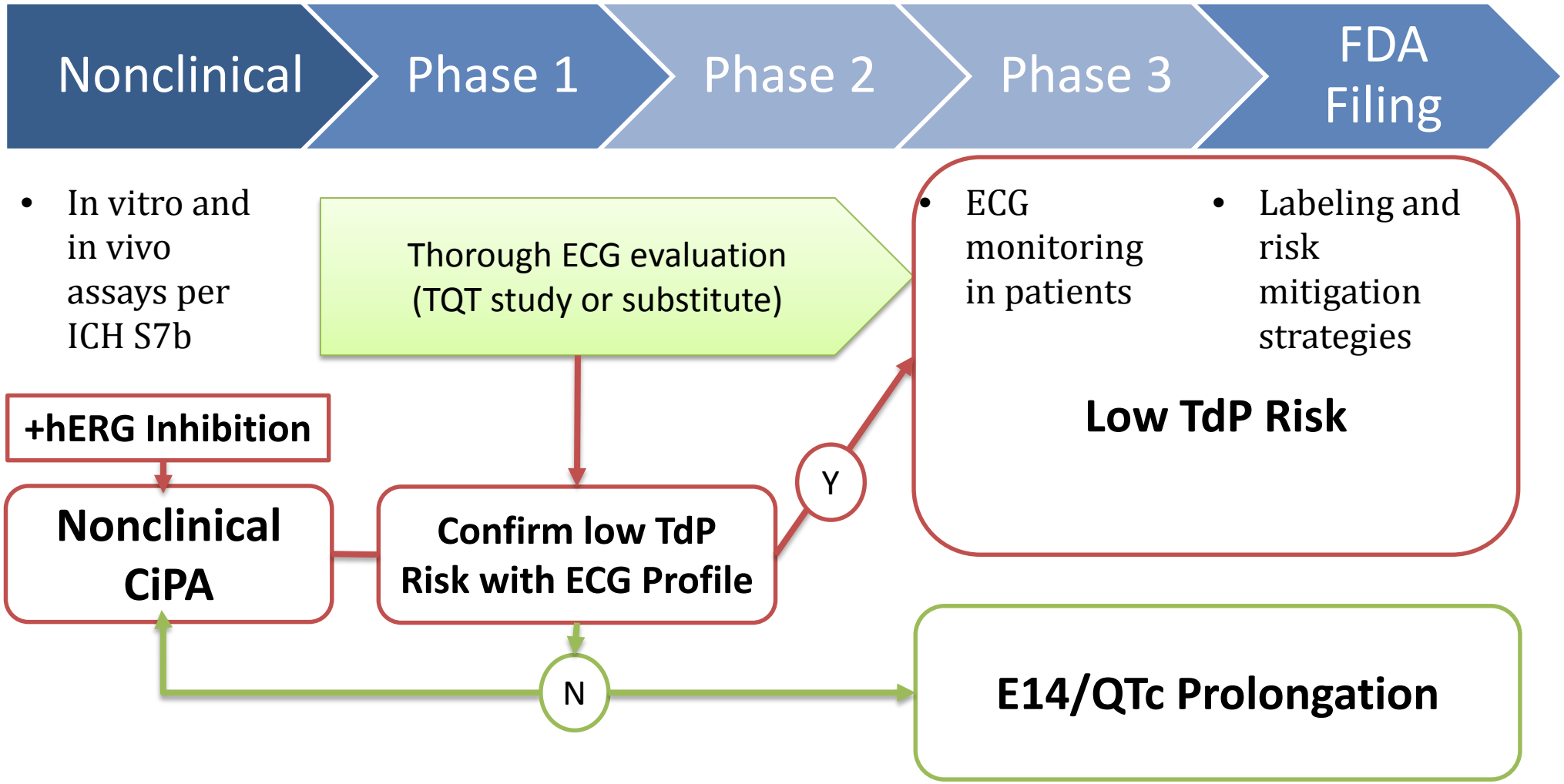

- In vitro and in vivo assays per ICH S7b

Thorough QT evaluation (TQT study or substitute)

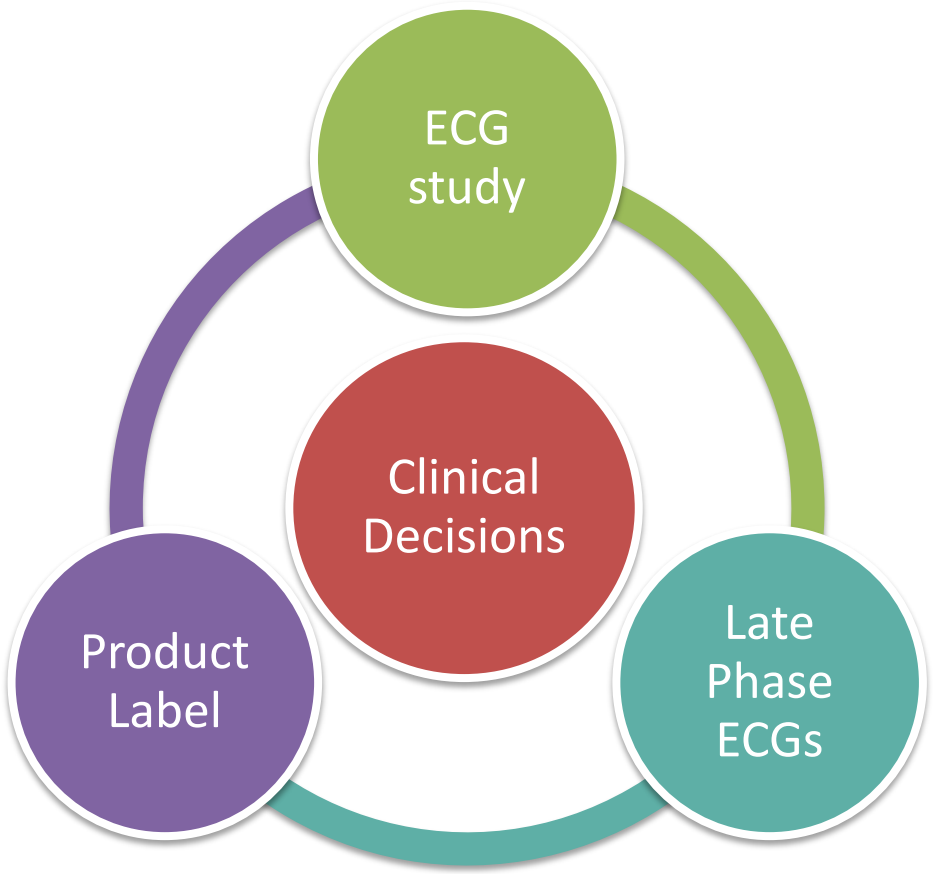
- ECG monitoring in patients
- Labeling and risk mitigation strategies

**E14/QTc Prolongation**

# Proarrhythmic Risk Evaluation in Drug Development



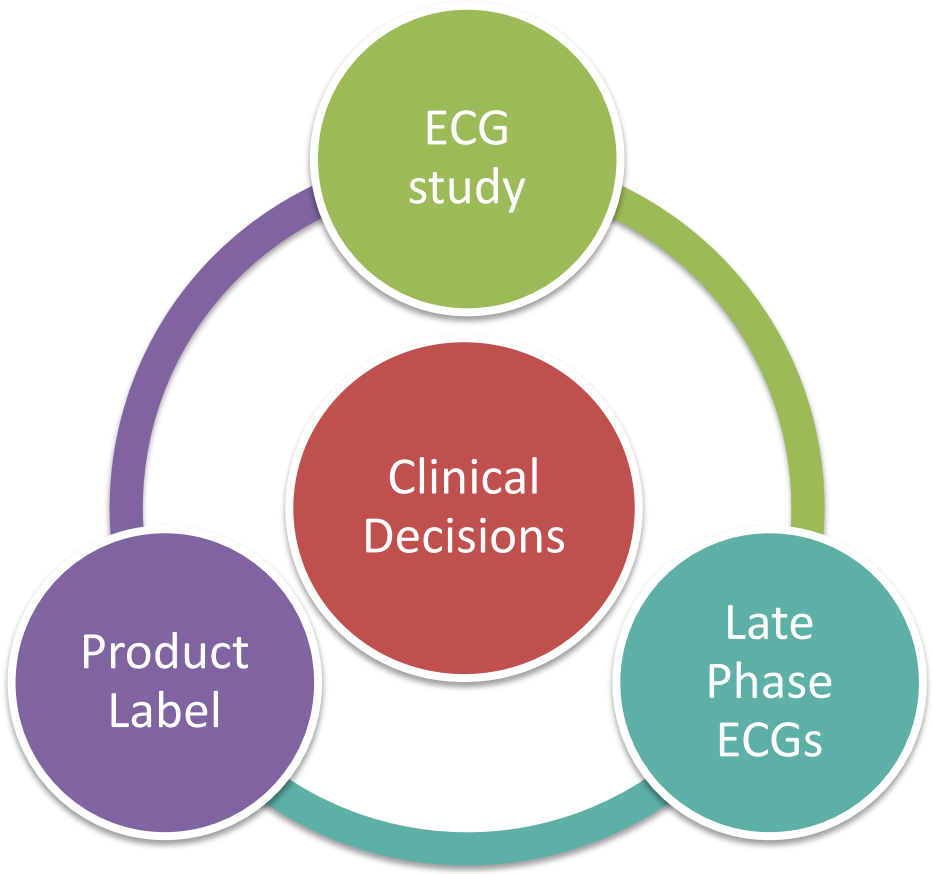
# Clinical Questions with CiPA Implementation




**ECG study design, analysis and interpretation for a drug that inhibits multiple cardiac ion channels**

- Can the SAD study provide sufficient data to characterize the ECG profile for drugs with nonlinear exposure-response relationships?
- How to confirm a “low proarrhythmic risk” drug using the ECG profile?
- How to detect “unanticipated effects” in the clinical ECGs?

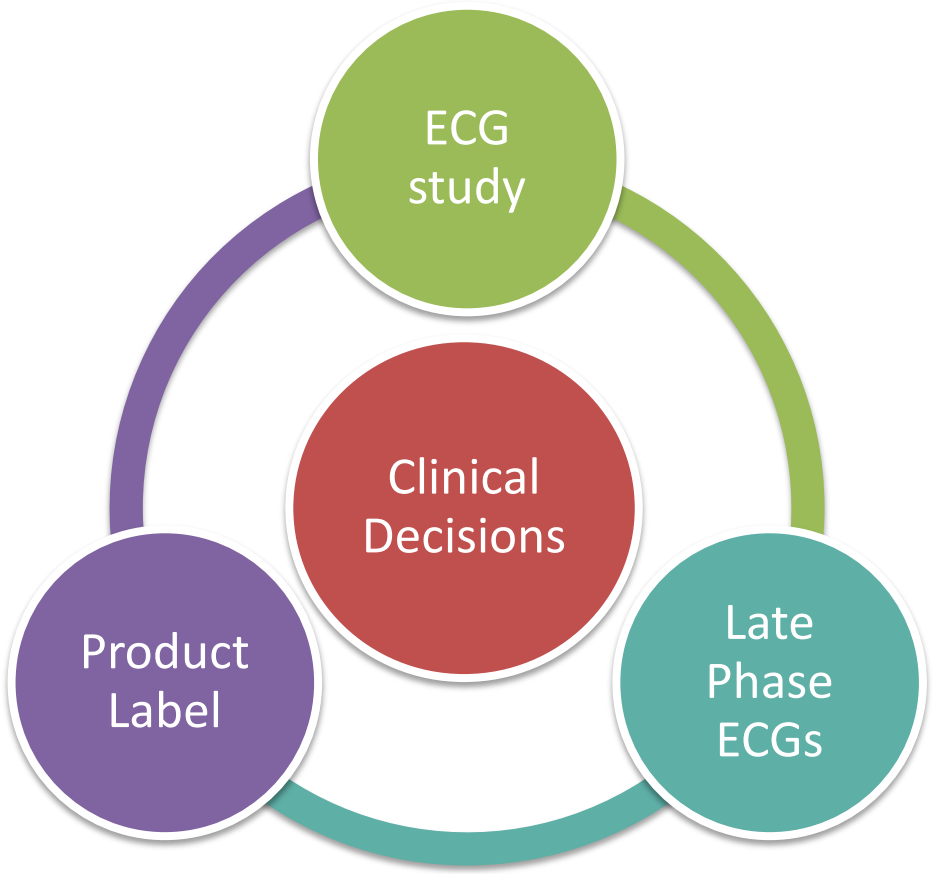
# Clinical Questions with CiPA Implementation




## Need for late phase ECG monitoring

- Is ECG monitoring needed for "low risk" drugs that moderately prolong the QTc interval at clinical exposures?
- Does the drug affect other ECG intervals?

# Clinical Questions with CiPA Implementation




## Communicating Risk in Product Label

- Low risk: What is the proarrhythmic risk when used with other QT-prolonging drugs?
- Low risk:  What is the proarrhythmic risk when used in high risk patients (i.e., those with congenital long QT, electrolyte imbalances, structural heart disease )?
- Intermediate vs. high risk: is there a difference in product labels?

# CiPA Use in Clinical Development

## Current scenarios*

- Replacing an uninterpretable TQT study for a drug with large heart rate increases (>20 bpm) at therapeutic doses
- Supporting late phase ECGs when a TQT study can not be conducted because of safety concerns with healthy volunteers and feasibility concerns in patients.

## Possible future scenarios

- Supplementing Phase 1 ECG evaluation when exposure margin is not large enough to waive positive control
- Oncology safety evaluation
- Influencing the intensity of ECG monitoring in late phase trials
- Aligning product labels with proarrhythmic potential

*FDA has requested CiPA with these scenarios

# Oncology Drugs: A Good Place to Implement CiPA?

**Problem:**

- Without placebo controls and large exposure margins, QTc assessments are designed to exclude large increases (>20 ms)
- QTc outliers in late phase clinical studies are difficult to interpret with confounding QT prolonging drugs and co-morbid conditions of patient

| Example Drugs | QTc prolongation magnitude (12.2) | C-QTc Relationship? | QTc ARs or SAEs cited in labeling? | W&P? |
|---|---|---|---|---|
| **Afatinib** | No large changes in the mean QTc interval (>20 ms) | No | No | No |
| **Eribulin** | 11 ms (UCL: 19.5 ms) | No | No | Yes |
| **Pazopanib** | No large changes in the mean QTc interval (>20 ms) | No | Yes, including TdP | Yes |

# Example Clinical Implementation

## Example 1

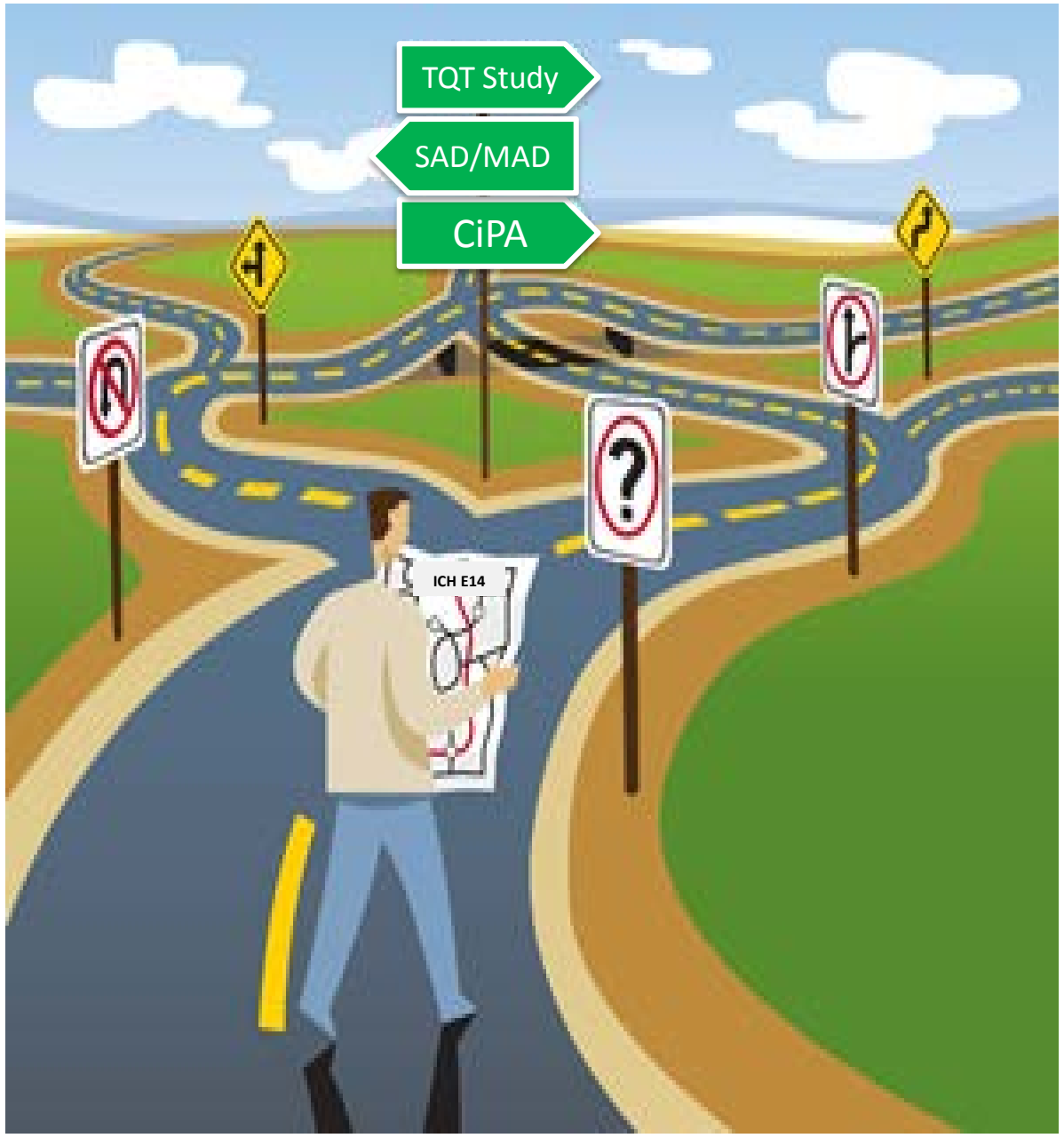
- Drug found to be multi-ion channel blocker with low TdP risk in CIPA conducted prior to FIH study
- What to do?
  - Collect intensive ECGs in the SAD & MAD studies. Evaluate ECG biomarkers using dose- and concentration-ECG analyses.
  - At highest clinical exposure scenario, evaluate drug's effect on QTc, J-$T_{peak}$, and $T_{peak,end}$.
  - Confirm *in silico* Low TdP Risk score and there are no unanticipated effects
  - Continue with clinical development with modified ECG monitoring (if applicable)

## Example 2

- Drug was found not to inhibit hERG and CIPA was not conducted prior to FIH study; however, concentration-dependent QTc prolongation was observed in FIH study.
- What to do?
  - Continue clinical development with ECG monitoring according to E14 Q&A 7.1
  - Perform CIPA, test for off-target QTc effects, test for active metabolites

# Conclusion

- FDA's interdisciplinary review team (IRT) has requested a CiPA approach to support clinical ECGs when a TQT study was not feasible or interpretable.
- Identify clinical scenarios where CiPA can be implemented to gain experience with the approach and to answer outstanding questions.
- If a sponsor would like to use a CIPA approach in their drug development program, contact the IRT via the Clinical Division


TQT Study
SAD/MAD
CiPA
ICH E14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