# Work smarter, not harder

## Fulfilling your cardiac safety requirements without a Thorough QT (TQT) study

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# Cardiac Safety in drug development

## WHY it matters?

- All drugs, regardless of therapeutic indication, enter the bloodstream and will circulate through the heart
- There is therefore a risk that all drugs may affect the heart

## WHAT are the risks?

- Myocardial Infarctions (Vioxx, Avandia)
- Valvular damage (fen-phen)
- Atrial and ventricular arrhythmias
- Hypertension
- Heart failure
- ECG effects - QRS prolongation, **QT prolongation**

## HOW can we monitor for these risks?

- **ECG** (office or remote), arrhythmia monitoring (**Holter, patch**), **blood pressure** monitoring (clinic, home, ABPM), cardiac imaging (**echo, MRI**, etc.)
- ECG is non-invasive and very cost effective
  - Protect individual subject safety: exclude high risk patients (baseline), and detect potential drug-related (or unrelated) changes
  - Protect the development program: exclude or detect and characterize any drug-related changes; high quality data reduces risk for false positive safety signals



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# ICH E14 Requirements – a historical perspective

## QT prolongation risk is one specific concern

- Prolonged QT interval has long been know (1960s) to potentially trigger serious ventricular arrhythmias, specifically Torsades de Pointes (TdP)
- **Seldane** – 1st "nonsedating" antihistamine – small excess incidence of sudden death; taken off the market (1997). This eventually resulted in **ICH E14 guidance**, requiring all drugs to undergo rigorous QT testing (Thorough QT Study), October 2005
  - More than 400 TQT studies have been performed
  - Total cost for a TQT has ranged from $1.5m to ~$20m
- Cardiac safety considerations, including QT Prolongation, has become the leading cause for drugs to be abandoned in development or withdrawn from the market
- IQ-CSRC Study, led by iCardiac, demonstrated ability to get TQT-like results within existing **Phase I SAD / MAD** studies and guidance was updated in December 2015 enabling **c-QT modeling**

## In addition to assessing QT interval, ECG is useful for general screening for other cardiac safety concerns

- Treatment-emergent rhythm changes, myocardial infarction, morphology changes

All drugs in clinical development must undergo a careful evaluation of potential ECG effects



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# Evolution of ICH E14 Guidelines

The ICH E14 Guidance provides recommendations to **sponsors on the design, conduct, analysis, and interpretation of clinical studies** to assess the potential of a drug to delay cardiac repolarization. This assessment typically includes testing the effects of new compounds on the QT interval as well as other cardiovascular adverse events/morphology changes.

**MAY 2005**

**ICH Harmonized Guideline Finalized**

**JUNE 2008**

**The first set of Q&As** was finalized to clarify questions on ECG methodology, gender in QT studies, positive controls, and study design

**APRIL 2012**

**The second set of Q&As** was developed and approved by the Steering Committee to further clarify questions on ECG methodology, gender in QT studies, and ECG monitoring in late-stage clinical trials

**MARCH 2014**

**The third set of Q&As removed the TQT requirement** for large molecules and allowed for more flexible study designs for drugs where conventional thorough QT study might not be feasible

**DECEMBER 2015**

**Q&A** was revised as a result of a study led and supported by iCardiac (Clario) demonstrating that small studies can detect mild QT prolongation using C-QTc analysis, potentially eliminating the need for a separate TQT study

**FEBRUARY 2022**

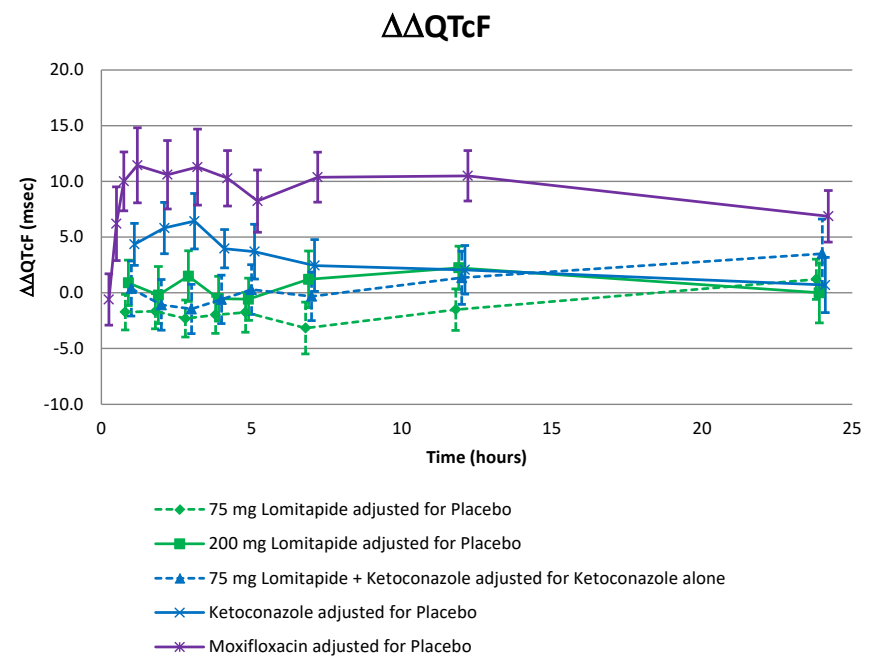
**Brings together S7B/E14 Q&As into one document**

1. Q&A 5.1 allows lower safety margin for clinical data to claim absence of a QT effect
2. Q&A 6.1 applies to oncology, stronger claim for absence of effect

*Provided standardized hERG and in-vivo assays are negative*

# TQT results for 2 approved drugs

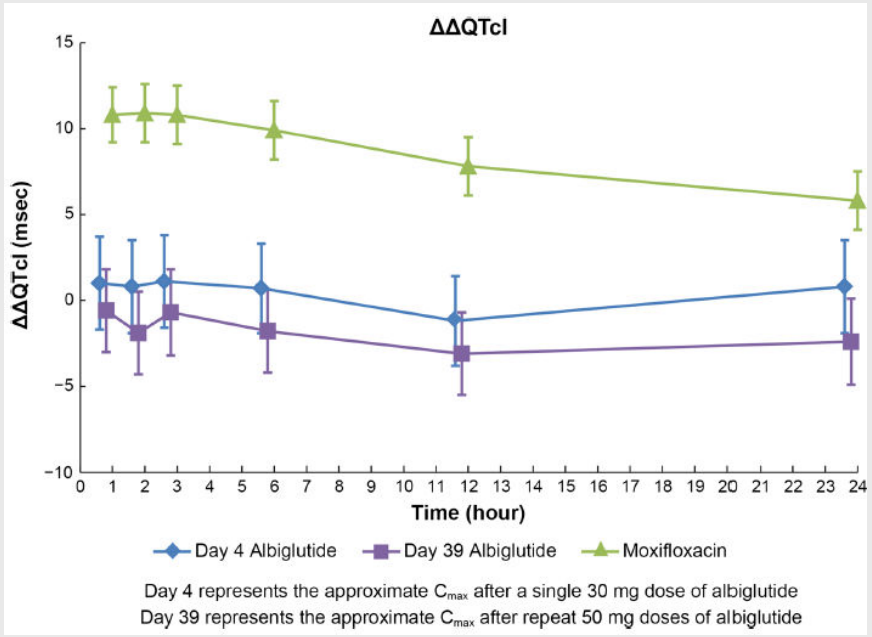
## Lomitapide




54 subjects, 5-way SD (incl. keto), XO study
**Precision: Mean SD of ΔQTcF 6 to 7 ms**

Darpo et al. ANE 2013; Doi: 10.1111/anec.12103

## Albiglutide




85 subjects, 4 treatment, parallel with nested XO study, 39 days of dosing
**Precision: Mean SD of ΔQTcI = 6.1 ms**

Darpo et al. Diabetes Ther. 2013; Doi: 10.1007/s.13300-014-0055-1



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# 2015: The journey towards more efficient ECG evaluation started

## The ICH E14 Q&A (R3) revision enabled sponsors to replace the TQT study with ECG data from FIH studies

1. Extensive experience had been gained by applying C-QTc analysis on data from TQT studies and patient data over the last 20 years.
2. The results of the IQ-CSRC study, performed by industry, FDA and Clario, demonstrated that small studies can detect mild QT prolongation using C-QTc analysis.

**Today:**

- In many FIH studies, serial ECG monitoring paired with PK sampling is implemented
  - In SAD/MAD, depending on the anticipated PK profile and selected doses
  - Collection and storage of ECG waveforms enables the sponsor to make an informed decision on when and what to analyze
- The majority of TQT studies are performed with C-QTc analysis and with reduced sample size (n=24 to 28) as compared to previous studies based on ‘by time point analysis’ (IUT)

# Can phase I ECG data replace the need for a dedicated TQT Study?

**The vast majority of drugs that cause TdP do this based on a concentration dependent effect on the QT interval**

- Exposure response analysis, also referred to as **concentration-QT modeling**, is therefore biologically an appropriate means to quantify the relationship
  - Steady state Cmax is the most critical timepoint to assess change from baseline QTc

**If studied carefully in healthy subjects, a small change (i.e., 10 ms) in QTc in relationship to drug exposure, can be detected**

- This small effect is a surrogate for TdP risk when the drug is provided to a much larger population that will include at-risk individuals

**Early QT assessment in phase I has several distinct advantages:**

- Sponsor acquires definitive data earlier in development than a typical TQT, informing portfolio decision making early on
- Data can be acquired within the standard phase I SAD/MAD design without any study design modifications
- Cost of intensive phase I ECG collection and statistical analysis is a fraction of the cost for a dedicated TQT study
- Substantial regulatory precedent now exists for acceptance of this approach



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# The IQ-CSRC Study

**Objective:** Evaluate whether QT assessment in the early phase clinical study paradigm can replace or serve as an alternative to the traditional Thorough QT Study

Designed and executed as a **collaboration** between the IQ-consortium, CSRC, and FDA

**Prospective** study in HVs with design characteristics similar to a standard FIH study:

- 20 male and female HVs, 3 treatment periods
- Study drugs:
  - **5 QT-positive drugs**: ondansetron, quinine, dolasetron, moxifloxacin, dofetilide
  - **1 QT negative drug**: levocetirizine
  - Placebo
- Two dosing days:
  - Day 1 target 10-12 ms QTc effect
  - Day 2 15-20 ms QTc effect
- ECG analysis methodology: iCardiac's EPQT method

Results From the IQ-CSRC Prospective Study Support Replacement of the Thorough QT Study by QT Assessment in the Early Clinical Phase

B Darpo[1,2*], C Benson[3†], C Dota[4*], G Ferber[5], C Garnett[6*], CL Green[7], V Jarugula[8‡], L Johannesen[9], J Keirns[10†], K Krudys[11], J Liu[11], C Ortemann-Renon[12*], S Riley[13], N Sarapa[14†], B Smith[2], RR Stoltz[15], M Zhou[2] and N Stockbridge[16]

The QT effects of five "QT-positive" and one negative drug were tested to evaluate whether exposure–response analysis can detect QT effects in a small study with healthy subjects. Each drug was given to nine subjects (six for placebo) in two dose levels; positive drugs were chosen to cause 10 to 12 ms and 15 to 20 ms QTcF prolongation. The slope of the concentration/ΔQTc effect was significantly positive for ondansetron, quinine, dolasetron, moxifloxacin, and dofetilide. For the lower dose, an effect above 10 ms could not be excluded, i.e., the upper bound of the confidence interval for the predicted mean ΔΔQTcF effect was above 10 ms. For the negative drug, levocetirizine, a ΔΔQTcF effect above 10 ms was excluded at 6-fold the therapeutic dose. The study provides evidence that robust QT assessment in early-phase clinical studies can replace the thorough QT study.





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# Results

## Primary analysis

- Results were presented to the **ICH E14** Discussion group and were subsequently **endorsed**
- Revised E14 now states that both the **intersection-union test** and the **concentration response analysis** can be used to estimate the maximum effect of a drug on the QTc interval
- Upper bound of the two-sided 90% CI should be <10 ms
- Early QT assessment with cQT modeling is now a **fully accepted alternative** to the TQT study
- Separate positive control is not required if a sufficient exposure multiple is achieved

| Drug | Slope, mean ms per ng/mL | LB 90% CI | UB 90% CI | Treat-ment effect ms | Cmax Day 1, ng/mL | Projected QTc effect mean, ms | LB 90% CI* | UB 90% CI* |
|---|---|---|---|---|---|---|---|---|
| | | | **Positive drugs (Day 1)** | | | | | |
| **Ondansetron** | 0.033 | ***0.025*** | 0.042 | 0.2 | 284 | 9.7 | 6.2 | ***12.8*** |
| **Quinine** | 0.004 | ***0.0034*** | 0.0047 | -3.0 | 3623 | 11.6 | 6.8 | ***17.1*** |
| **Dolasetron** | 0.021 | ***0.013*** | 0.028 | 3.1 | 211 | 7.4 | 3.0 | ***11.0*** |
| **Moxifloxacin** | 0.0065 | ***0.0059*** | 0.0072 | 2.3 | 1862 | 14.5 | 10.5 | ***17.7*** |
| **Dofetilide*** | 22.2 | ***18.9*** | 25.6 | 1.1 | 0.42 | 10.5 | 6.3 | ***14.9*** |
| | | | | | | | | |
| | | | **Negative drug (Day 2)** | | | | | |
| **Levocetirizine** | 0.0014 | ***-0.0013*** | ***0.0041*** | 0.7 | 1005 | 2.1 | -2.3 | ***6.1*** |

**: Slope from linear model for comparison.*
*Predicted effect for dofetilide using Emax model: 11.6 ms; 90% CI 7.0 to 16.0*

FDA has independently analyzed and confirmed the results



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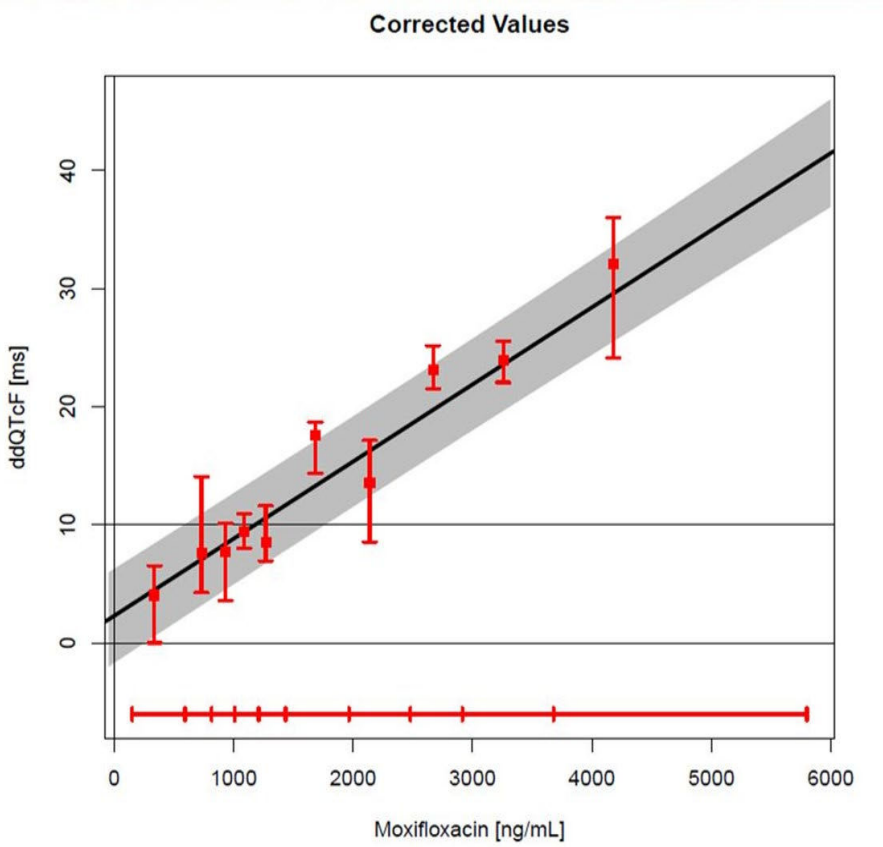
# The IQ-CSRC Study

## Moxifloxacin C-QTc analysis




Red bars denote observed median (IQR) ΔΔQTcF within each concentration decile

| Slope, mean ms per ng/mL | LB 90% CI | UB 90% CI | Treatment effect (intercept) ms | Cmax Day 1, ng/mL |
|---|---|---|---|---|
| 0.0065 | **0.0059*** | 0.0072 | 2.3 | 1862 |

| Predicted QTc effect mean, ms | LB 90% CI | UB 90% CI | *Criteria* |
|---|---|---|---|
| 14.4 | 10.6 | **17.9**** | Met |

***The positive slope is statistically significant.**

****QTc effect above 10 ms at the Cmax of Day 1 cannot be excluded.**

Darpo B et al. Results From the IQ-CSRC Prospective Study Support Replacement of the thorough QT Study by QT Assessment in the Early Clinical Phase. CPT 2015: 97: 326





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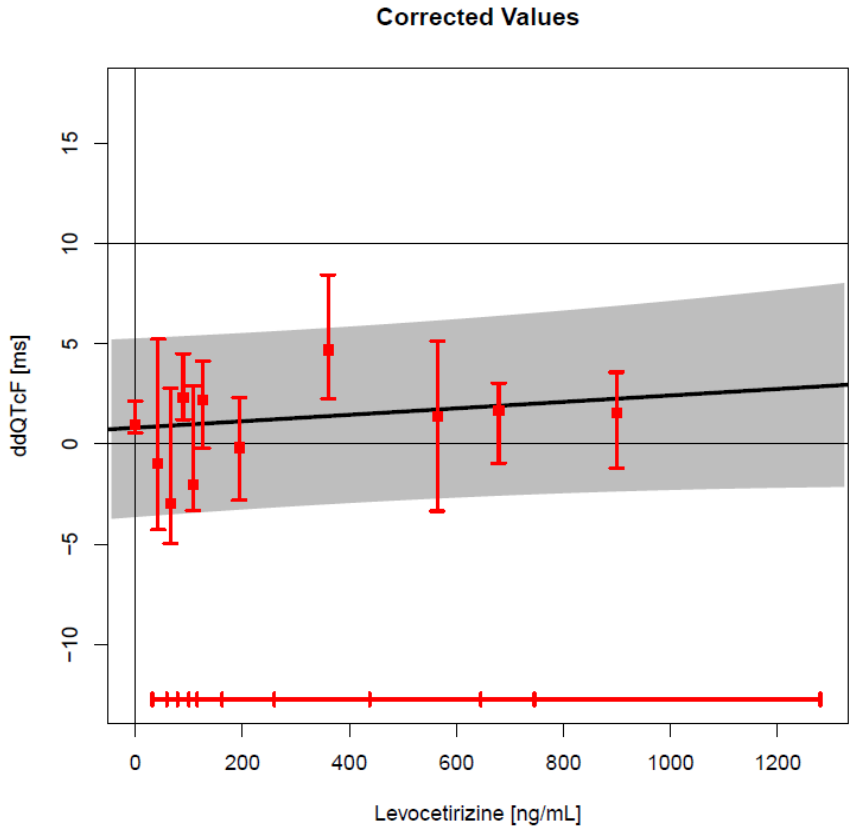
# The IQ-CSRC Study

## Levocetirizine C-QTc analysis




Red bars denote observed median (IQR) ΔΔQTcF within each concentration decile

| Slope, mean ms per ng/mL | LB 90% CI | UB 90% CI | Treatment effect (intercept) ms | Cmax Day 1, ng/mL |
|---|---|---|---|---|
| 0.0014 | **-0.0013** | **0.0041** | 0.7 | 1005 |

| Predicted QTc effect mean, ms | LB 90% CI | UB 90% CI | *Criteria* |
|---|---|---|---|
| 2.1 | -2.3 | **6.1*** | Met |

***QTc effect above 10 ms can be excluded at the geometric mean Cmax on Day 2**

Darpo B et al. Results From the IQ-CSRC Prospective Study Support Replacement of the thorough QT Study by QT Assessment in the Early Clinical Phase. CPT 2015: 97: 326





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# The TQT study waiver process





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# The “TQT Waiver”

**What does it take to obtain a waiver for the traditional TQT study?**

- cQT analysis must exclude a drug-related effect on QTc of 10 ms at a **sufficient multiple of the clinically relevant exposure**
- The **upper bound of the 90% CI** of the predicted effect, using exposure response analysis, must be **below 10 ms**

**Exposure requirement - twice the ‘high clinical exposure’**

- Must fact in DDI effects, food effect, hepatic and renal impairment
- Lack of a positive control in phase I SAD/ MAD designs necessitates this margin to clinical exposure
- This is the single most common reason a phase I PK-matched ECG analysis may not be able to serve alone to support a waiver request

**E14 / S7B revision in Feb 2022 now addresses the role for non-clinical data in the setting that this margin is not achieved**

- Concept of ‘**Double negative**’ in vivo and in vitro results was introduced



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# February 2022 - Revised E14/ S7B Q&A Document

Until recently, the role of **non-clinical assays** has been to ensure that NCEs can be safely taken into humans in the First-in-Human (FIH) trial

The revised S7B/E14 Q&A document (February 2022) states that non-clinical assays, when performed in a robust, standardized way, can be used to **support clinical ECG data**:

- **Revised E14 5.1: ECG evaluation in FIH trials:**
  - When concentration-QTc analysis is applied to data from a First-in-Human (FIH) trial with intention to 'waive' the request for a formal TQT study, achieved concentrations in the FIH study must *exceed* therapeutic concentrations:
  - The required **2-fold margin can now be reduced** if supported by negative standardized *in vivo* and *in vitro* non-clinical assays
  - This further promotes the use of FIH data to replace the traditional TQT study

- **Revised E14 6.1: Applicable when high exposures cannot be safely achieved in healthy subjects:**
  - If a small QTc effect (< 10 ms) can be excluded in a patient study with the highest recommended dose, the sponsor can claim 'low proarrhythmic liability' if supported by double negative non-clinical assays
  - Favorable labeling advantage over the more common "no large effect" statement

# Special circumstances to consider

**Scenarios in which concentration-effect modeling may not be feasible**

- Drugs that exhibit significant **hysteresis** (QTc effects do not temporally align with PK profile)
- Non-hERG related mechanisms of QT prolongation (i.e. **hERG channel trafficking** effects)
- Active **metabolite** which blocks hERG and exhibits a different PK profile than parent

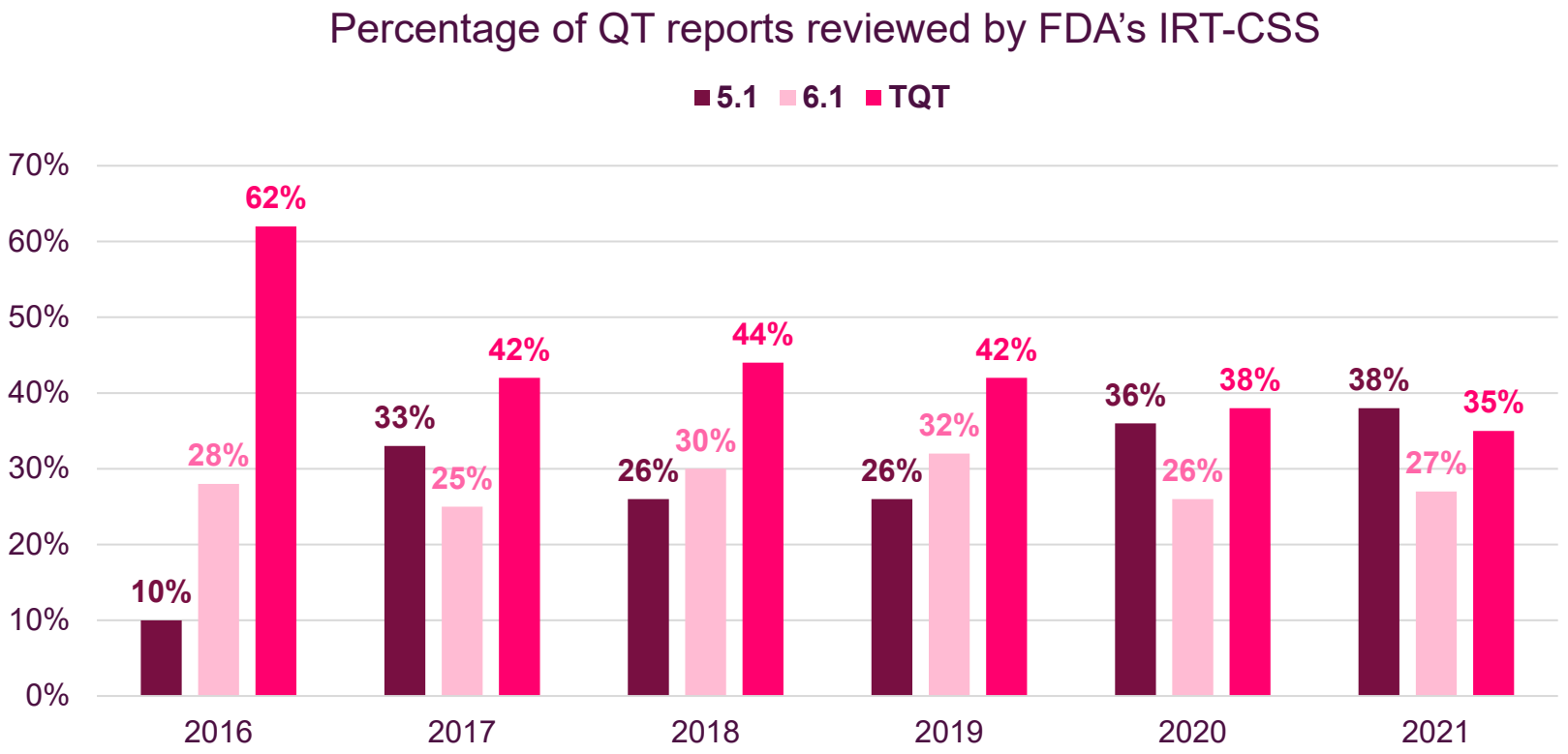
**Drugs not tolerated at supratherapeutic exposures**

**Drugs unable to be safely administered to healthy volunteers (at any exposure)**

**Drugs with long dose titration requirements for tolerability, or prolonged time to steady state**

# Number of FIH studies with definitive ECG evaluation has steadily increased since 2015

## Proportion of TQT vs. 5.1 (FIH) and 6.1 (oncology) studies




On average, 55 studies per year

Graph kindly provided by Dr. Garnett, FDA





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# Conclusions

- Early QT assessment is now a fully accepted way to confidently exclude a clinically relevant effect on the QT interval for a new drug
- Revised S7B/E14 Q&A (February 2022) will further encourage use of early clinical studies
  - (e.g., FIH) to obtain ECG data that may obviate the need for a TQT study
- Critically important to proactively liaise with non-clinical laboratories to ensure that hERG and non-rodent in-vivo assays meet best practices
  - Request historical data from assays using same experimental procedures
- The TQT study will not completely disappear and will remain as a viable option in select cases
- Overall, QT assessment can be done more effectively:
  - Potential ECG effects of an NCE will be known earlier
  - ECG assessment can be performed as part of routine SAD/MAD studies or in small tailored studies



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# Thank you for your time

If you have any additional questions, please contact:

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