

Exclusion of patients based on ECG criteria

The incidence of ECG abnormalities, in particular QTc prolongation, is high in patients with severe liver disease

- **Bal J-S et al 2003:** 409 + 162 cirrhotic patients
 - ✓ QTc \uparrow > 440 ms observed in 40% and 56% (QTcB)
- **Genovesi S et al 2009:** 48 patients with Child Pugh A to C
 - ✓ QTc prolonged with severity: A- C: 425 ms – 452 ms – 465 ms
- **Mozos I et al 2011:** 38 patients with cirrhosis
 - ✓ QTc \uparrow in 71% (QTmax); QTcB: 465 ms, increased with severity
- **Patel D et al 2014:** 51 patients who underwent LT
 - ✓ QTcF shortened after LT

Conclusion:

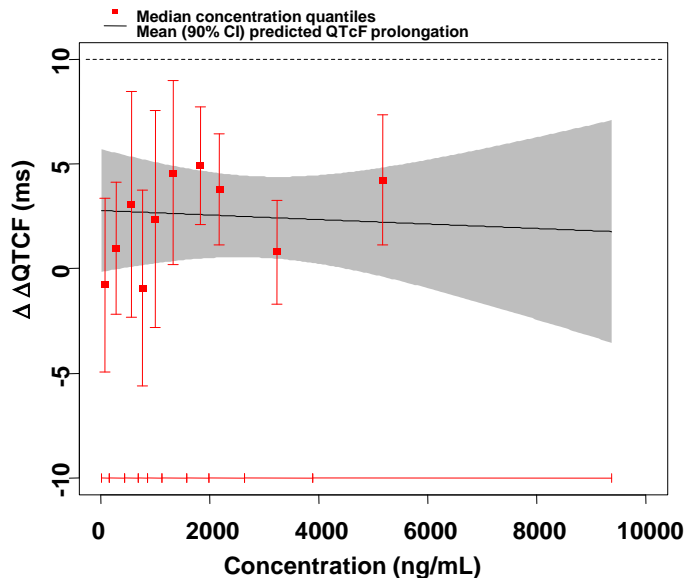
- QT prolongation is common in cirrhotic patients
 - Inappropriate correction methods (QTcB) often used
 - Little data on other ECG abnormalities (e.g. conduction, BBB)

How to reduce exclusion of patients based on ECG criteria

Two approaches to reduce exclusion of patients based on ECG criteria:

- Definitive characterization of the drug's ECG effects early in development (e.g. FiH)
 - ✓ Will allow inclusion of patients with standard ECG criteria, i.e. without focus on QTc interval
- Efficient and accurate 'alert-triggered' central evaluation of screening ECGs
 - ✓ Will reduce the number of excluded patients based on ECG misinterpretation

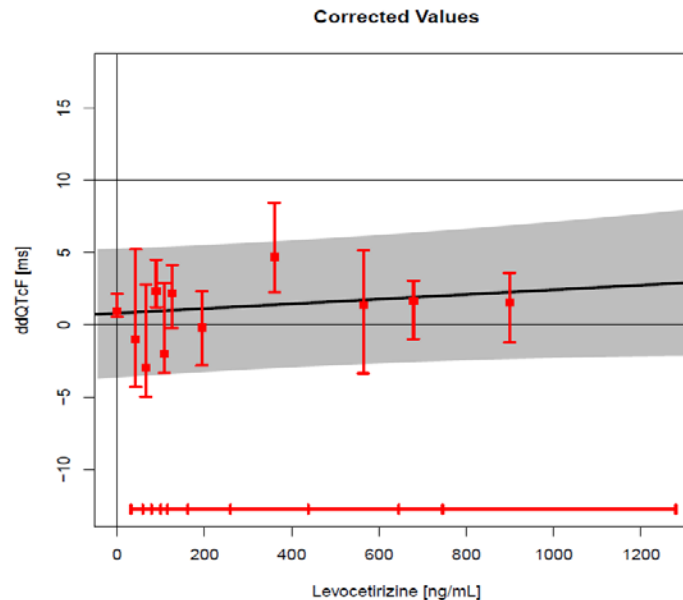
Early ECG assessment replaces the TQT study



SAD study with selisistat

Westerberg G et al.

Br J Clin Pharm 2015; 79: 477-91



IQ-CSRC study - Validation study with FDA

Darpo B et al. CPT 2015; 97: 326-35

Dynamic ECG centralization

- 12-lead ECGs are recorded and automatically uploaded to central ECG laboratory
- Screening ECGs meeting alert criteria (only) reviewed within defined timeline
 - Alert criteria
 - based on machine readout (at ECG laboratory)
 - or triggered 'for-cause' by site
 - ECG interval evaluation within 2 to 4 hours
 - Allows quick correction of most common machine errors
 - Cardiologist interpretation within 24 hours
 - Full interpretation for definitive screening assessment
- Alert review are done per defined requirements, i.e. flexible
- Process allows for timely and efficient evaluation of screening ECGs and will minimize inappropriate patient exclusion

Examples of Improved Results

- 2 studies that reported both machine read QTcF values and Central ECG lab (iCardiac) values were reviewed
- A total of 4,586 ECGs were reviewed
- ECGs were looked at for QTcF values exceeding 450, 470 and 500msec in all ECGs

Dynamic ECG Centralization: Case Study

<i>Alert Range (QTcF)</i>	<i># of ECGs within alert range with Machine Read Value*</i>	<i># of ECGs within normal range after central ECG read*</i>
451-470	409	131 (32%)
471-500	118	23 (19.5%)
>500	24	1 (4%)
Total	551	155 (28.1%)

Central ECG lab review significantly reduces chance of unnecessary patient exclusion due to QT criteria.

* Average of all ECGs in study: Machine Read=422 ms vs Central Read=408 ms

Case Studies

- Study 1: 426 QTcF Alerts based on 3,512 ECGs (12.2%)
- Study 2: 336 QTcF Alerts based on 2,913 ECGs (11.6%)

QTcF	ECG Machine Read Value	Centrally Evaluated (Assuming Same Percentages)
451-470	428	~137
471-500	291	~57
>500	43	~2

- If Dynamic ECG Centralization were to be used and same error rate occurred, 196 of 772 (25%) ECGs would be true alerts