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↑ > 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: 425 ms – C: 452 ms – 465 ms
- **Mozos I et al 2011**: 38 patients with cirrhosis
  - QTc↑ 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

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

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%)

<table>
<thead>
<tr>
<th>QTcF</th>
<th>ECG Machine Read Value</th>
<th>Centrally Evaluated (Assuming Same Percentages)</th>
</tr>
</thead>
<tbody>
<tr>
<td>451-470</td>
<td>428</td>
<td>~137</td>
</tr>
<tr>
<td>471-500</td>
<td>291</td>
<td>~57</td>
</tr>
<tr>
<td>&gt;500</td>
<td>43</td>
<td>~2</td>
</tr>
</tbody>
</table>

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