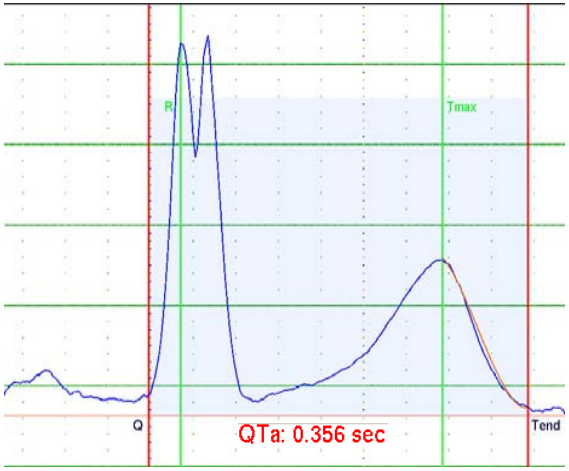
QTinno™ Overview

- NewCardio 3-Dimensional software for measuring and adjudicating all timing intervals and voltage/amplitude parameters

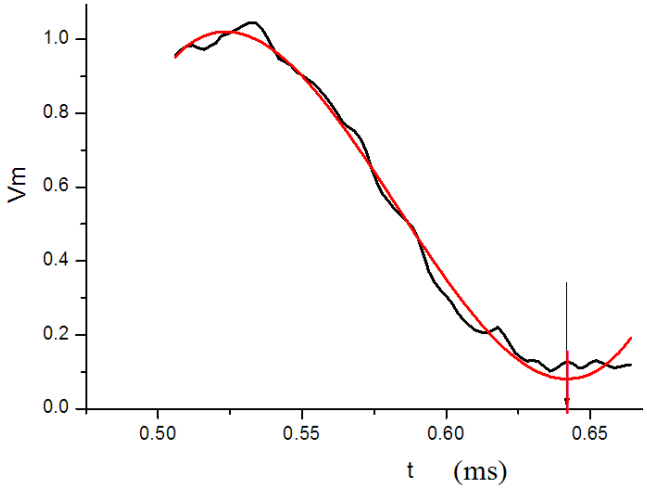
- Key features include:
  - All measurements made on the heart **Vector Magnitude lead**
  - **Novel, proprietary algorithms** for accurate and precise fiducial point placement
  - **Full automation** with intelligent self-validation algorithms to ensure reliability
  - **Confidence Factor**™ identifies and flags problematic ECGs for possible human overread
  - **Analysis of all readable P-QRS-T complexes** in each ECG or Holter recording
  - **Continuous quantitative assessment** of ventricular repolarization
  - **No change in ECG practice**; accepts all files from standard ECG Equipment

Key Features of QTinno Engine

- Use of Vector Magnitude Virtual Lead
  - Produces single “virtual” ECG lead with full electrical information
  - from *all* 12 leads and *all complexes in an ECG*
  - improves signal-to-noise ratio over standard 12-lead ECG



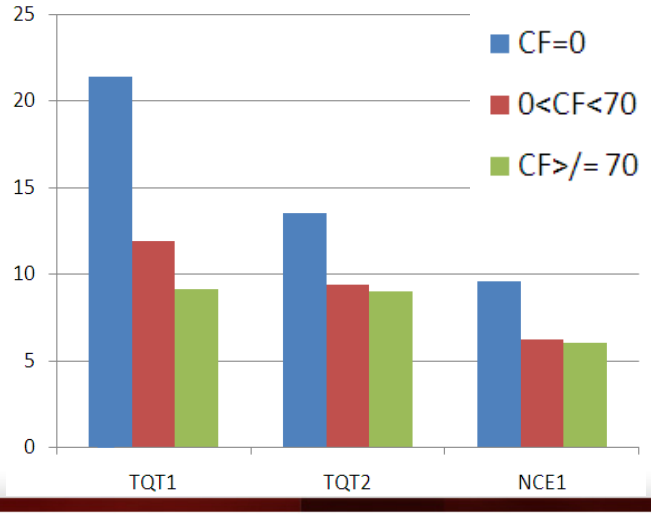
- Proprietary, iterative curve fitting algorithms optimize fiducial point accuracy and precision
  - Least-square fit of 3rd-order polynomial to VM data
  - Multiple iterations done to optimize fitting
  - Minimum of fitted function represents T_{end}
  - Approach is noise-resistant and baseline-independent



Role of Confidence Factor™

- Internal assessment of quality and reliability is a mandatory feature of automated ECG analysis - otherwise, user must choose between 2 undesirable options: (1) accept automated results on a "black box" basis, or (2) overread all results
- Confidence Factor assigns each ECG a CF score of 0 to 100 based on:
  - ECG signal quality, including excessive noise, missing leads, etc
  - Measurement quality, including goodness of fit, heart rate variability, etc
  - Currently, CF<70 flags an ECG for possible overread (about 1-5% of early-phase studies)

Mean Std Dev of Difference Between QTinno and Core Lab, by CF Category



QTinno™ Performance in Clinical Validation Studies

Comparison Between Methods (QTinno – Core Lab)

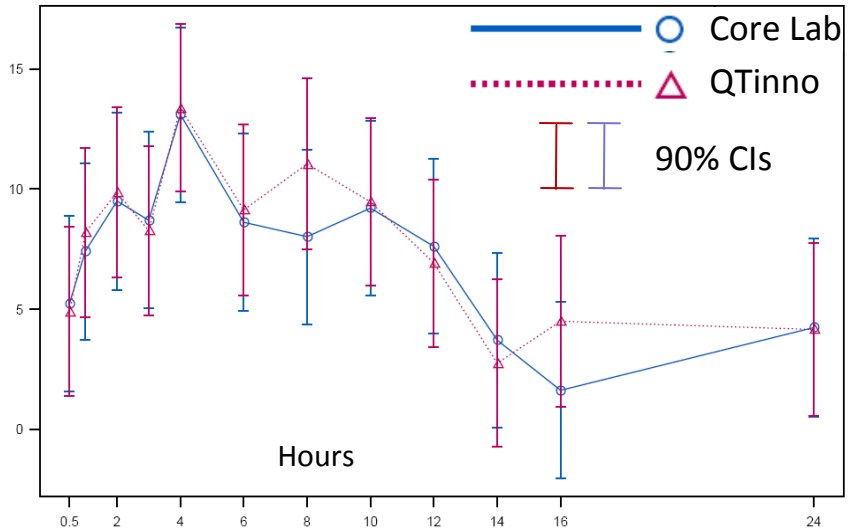
Study	CPU time	Diff in Mean ΔQTcF	STD of Diff, Raw QTcF	Categorical Analysis	ECGs flagged for overread by QTinno
NCE1 (n=1963)	<10 min	<0.1 ms	<7 ms	Highly concordant	<2 %
NCE2 (n=7039)	<30 min	<1 ms	<8 ms	Highly concordant	<2 %
NCE3 (n=2523)	<15 min	<1 ms	<10 ms	Highly concordant	<10% (high-noise dataset extracted from Holters)
TQT1 (n=10,880)	< 30 min	<0.1 ms	<8 ms	Highly concordant	<5%
TQT2 (n=17,506)	< 60 min	<1 ms	<8 ms	More outliers reported by Core Lab than by QTinno	<1%
TQT3 (n=29,547)	< 120 min	Analysis in Progress			
TQT4 (24 Hr Holters , 72 pts)	< 60 min per Holter	Analysis in Progress			

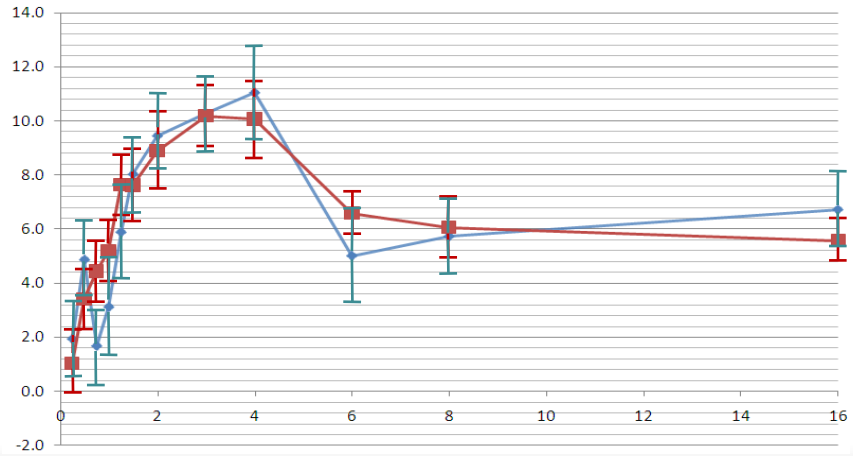
Comparison of 2 TQT Studies - Methods

- **TQT1 Study**
  - Pharma-sponsored dataset from parallel-group TQTS; 10,880 ECGs from moxi and placebo arms
  - QTinno fully automated results generated in blind fashion, then analyzed and compared by Pharma physician-scientists to manual Core Lab measurements
- **TQT2 Study**
  - Unblinded CSRC dataset from crossover TQTS; 17,506 ECGs from moxi and placebo arms
  - QTinno fully automated results internally compared to Core Lab results

Comparison of 2 TQT Studies – ddQTcF by Hour

Mean ddQTcF





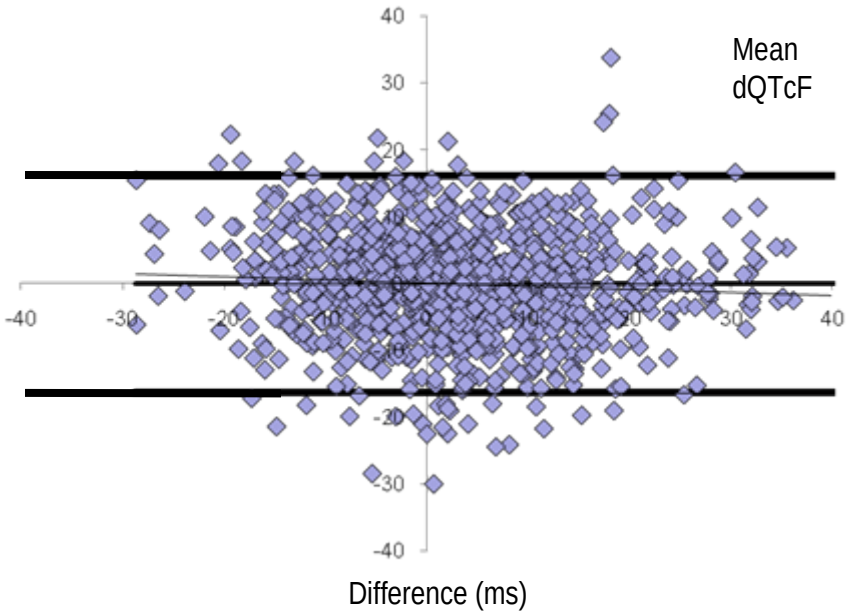
- **TQT1 Study**
  - Both Core Lab and QTinno show typical moxi ddQTcF curve
  - Less than 1 ms difference in point estimates at 7 of 11 time points
  - 90% CIs for QTinno and Core Lab virtually identical in width

- **TQT2 Study**
  - Both Core Lab and QTinno show typical moxi ddQTcF curve
  - Less than 1 ms difference in point estimates at 7 of 12 time points
  - 90% CIs consistently narrower for QTinno relative to Core Lab

Comparison of 2 TQT Studies – Method Differences in dQTcF

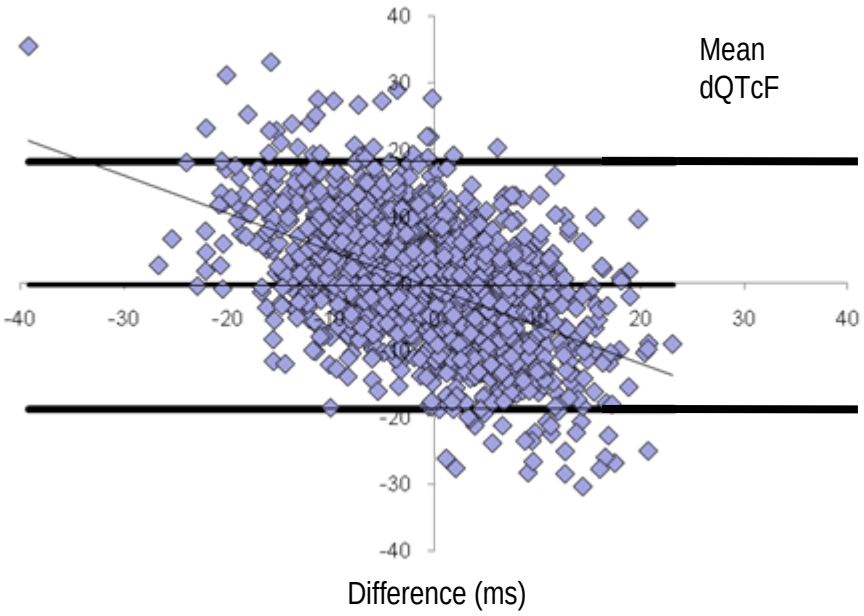
Bland-Altman Analysis
Core Lab vs. QTinno Automated

TQT1



Mean difference = -0.1 ms
Std Dev = 8.1 ms

TQT2



Mean difference = 0.0 ms
Std Dev = 9.8 ms

Comparison of 2 TQT Studies: Categorical (Outlier) Analysis for dQT/dQTcF

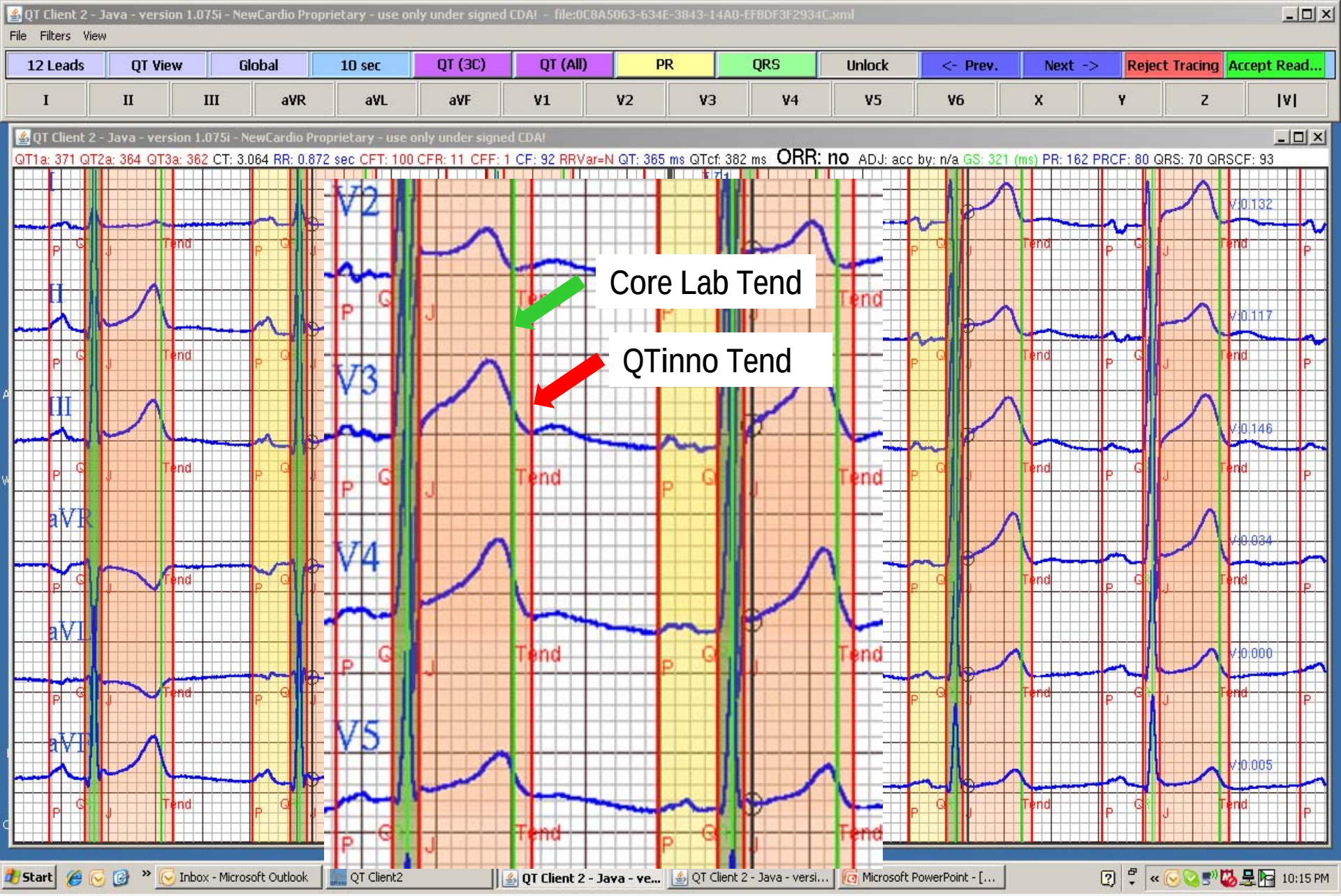
TQT1 Study

			Number of Subjects by Category				
			<30 ms	30-60 ms	60-90 ms	>90 ms	Total
dQT	Plac	Core Lab	437	27	5	0	469
		QTinno	434	28	6	1	469
	Moxi	Core Lab	458	45	7	0	510
		QTinno	452	48	9	1	510
dQTcF	Plac	Core Lab	466	3	0	0	469
		QTinno	466	3	0	0	469
	Moxi	Core Lab	495	15	0	0	510
		QTinno	489	21	0	0	510

TQT2 Study

	Number of Subjects by Category			
	<30 ms	30-60 ms	>60 ms	Total
Core Lab	1396	40	1	1437
QTinno	1403	24	0	1437
Core Lab	1385	76	0	1461
QTinno	1425	36	0	1461
Core Lab	1434	3	0	1437
QTinno	1437	0	0	1437
Core Lab	1434	27	0	1461
QTinno	1459	2	0	1461

- Shows substantial agreement between Core Lab and QTinno in both categorical analysis and distribution of dQT/dQTcF, for both Placebo and Moxifloxacin groups


QT Client 2 - Java - version 1.075i - NewCardio Proprietary - use only under signed CDA!
File Filters View
12 Leads QT View Global 10 sec QT (3C) QT (All) PR QRS Unlock <- Prev. Next -> Reject Tracing Accept Read...
I II III aVR aVL aVF V1 V2 V3 V4 V5 V6 X Y Z |V|
QT1a: 371 QT2a: 364 QT3a: 362 CT: 3.064 RR: 0.872 sec CFT: 100 CFR: 11 CFF: 1 CF: 92 RRVar=N QT: 365 ms QTcf: 382 ms ORR: no ADJ: acc by: n/a GS: 321 (ms) PR: 162 PRCF: 80 QRS: 70 QRSCF: 93
Core Lab Tend
QTinno Tend
Start
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Residual Variability Obtained from Fitting a Mixed Model to dQTcF by Method

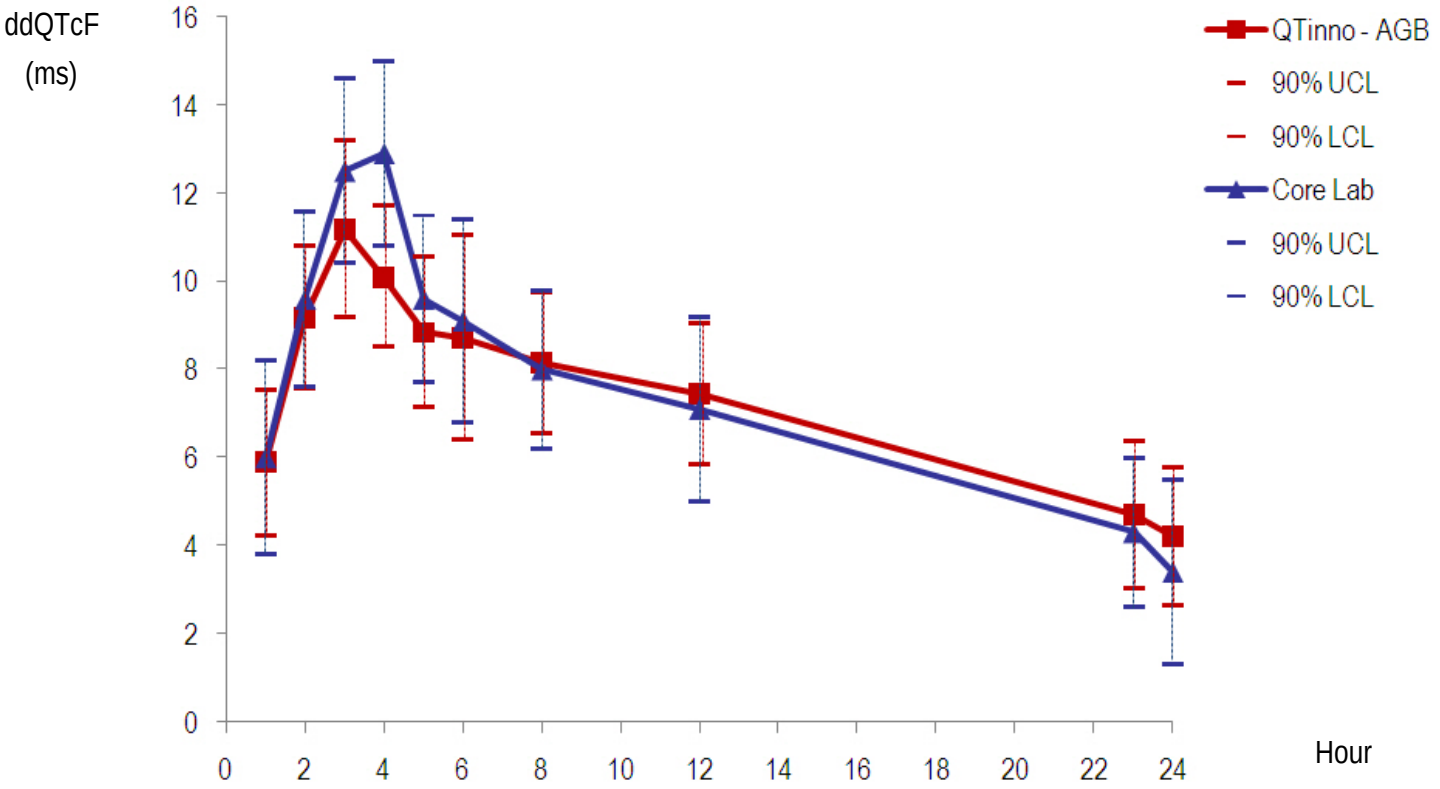
Study	Method	Intrinsic Variability (ms)	
		Between-Subject	Within-Subject
TQT1	Core Lab	7.4	8.8
	QTinno	7.9	8.1
TQT2	Core Lab	3.8	10.7
	QTinno	3.2	6.7

- Mixed Statistical Model with factors for day, time, age, gender, treatment and all interactions

Holter-Based TQT Study Design

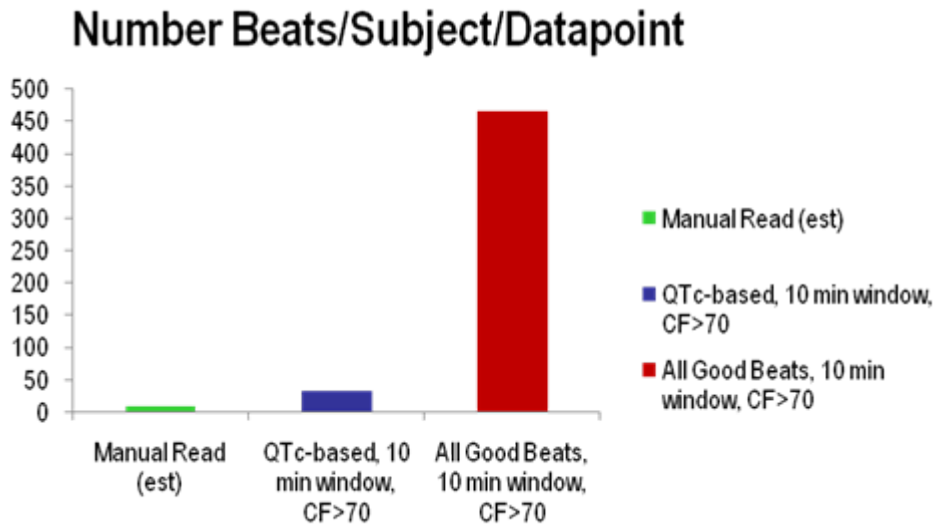
- Moxi and Placebo arms from a recent Pharma-sponsored TQTS
- Continuous 12-Lead Holter recordings on 71 healthy volunteer subjects
- Crossover design; all subjects have 1 day on placebo and 1 day on moxi
- Baseline for both placebo and moxi days – average of hrs -1, -0.5, and 0 for all subjects
- Ten predetermined time points for 12-lead ECG extraction – hrs 1, 2, 3, 4, 5, 6, 8, 12, 23, 24
- Extraction performed within 5 min of predetermined time point, after 10 min of supine rest

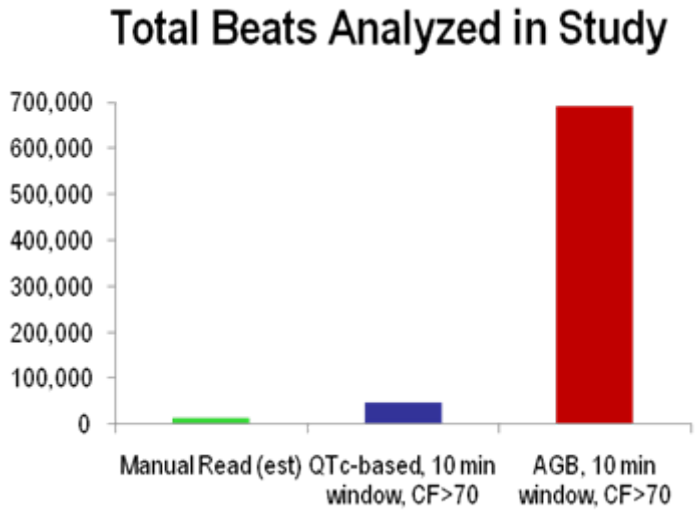
Hourly ddQTcF by Measurement Method



- All 3 QTinno measurement methods produced acceptable and similar ddQTcF moxi curves, with All Good Beats (shown) having the narrowest CIs
- Results closely comparable to Core Lab results

"All Good Beats" vs QTc-Based Selection: Effect on Number of Beats Analyzed





- Using QTc-based 10 min Screening Window, 30 sec Measurement Window, CF>70 cutoff results in an average of 31 beats analyzed per subject per datapoint
- Using "All Good Beats", 10 min window, CF>70 cutoff results in 466 beats analyzed per subject per datapoint
- This may be an advantage for AGB that contributes to substantially lower 90% CIs than QTc-based selection

Residual Variability Obtained from Fitting a Mixed Model to dQTcF by Method

Method	Intrinsic Variability (ms)	
	Between-Subject	Within-Subject
Core Lab	TBD	6.9
QTinno (RR-based selection)	3.9	6.2
QTinno (QTc-based selection)	4.3	6.0
QTinno (All Good Beats)	3.5	5.4

- Mixed Statistical Model with factors for day, time, age, gender, treatment and all interactions

Summary and Conclusions

- NewCardio automated analysis yields acceptable ddQTcF moxi curves for all measurement approaches
  - “All Good Beats” appears to yield better data than either QTc-based or RR-based screening with 30 or 60 sec measurement windows
  - Cutoff of CF>70 is superior to CF>0 cutoff, for QTc-based or RR-based screening, but CF cutoffs were approximately equal for All Good Beats
  - For All Good Beats, larger measurement windows appear superior to smaller, and leftward-shifted measurement windows appear superior to rightward-shifted windows
- NewCardio automated analysis performs well on measurement of non-QT IDMs, such as RR, PR, and QRS intervals