Technosphere® QT Study

To date there have been no data to suggest cardiovascular effects in animals or humans that would be attributed to Technosphere® particles. Following careful review with FDA, it was agreed to thoroughly assess Technosphere as the New Chemical Entity in Technosphere Insulin.

To definitively assess the potential for QT prolongation, 48 healthy subjects were randomly assigned a sequence in a crossover trial to receive one of the four treatment regimens: Technosphere (FDKP) 20mg, Technosphere (FDKP) 40 mg, placebo and moxifloxacin (positive control) 400 mg.

A centralized, independent ECG reading lab was used to read the ECGs with interpretation by a high-resolution manual on-screen caliper method with annotations to minimize inter-reader variability. The central ECG laboratory was blinded to subjects and their treatment. All treatments included a single baseline of the mean of 18 ECGs just before each dose of treatment. The study protocol was prospectively reviewed by the FDA and complied with "E14 Guidance to Industry: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Drugs for Non-Antiarrhythmic Drugs.

The validity of this trial was demonstrated by the following:

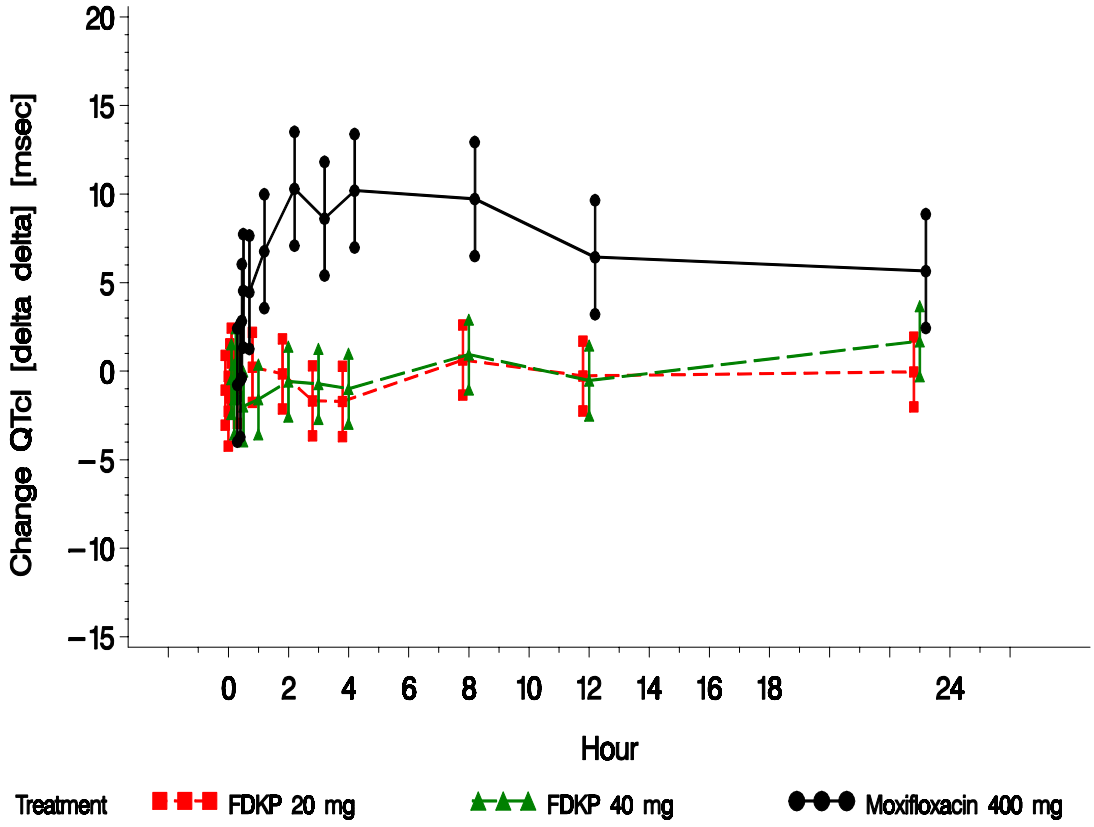
- The moxifloxacin positive control group showed the expected small change in QTc duration.
- The placebo group's change from baseline was within 3 ms for QTcI and shows that the spontaneous factors for QTc change were very well controlled.

The results of this ECG trial showed no signal of any effect on heart rate, AV conduction or cardiac depolarization as measured by the PR and QRS interval durations. There were no new clinically relevant morphological changes.

The effect of Technosphere on cardiac repolarization using the QTcI interval and the pharmacokinetic-pharmacodynamic relationships demonstrated no signal.

It was concluded by the independent analysts that this trial was well conducted and valid (assay sensitivity being reached and placebo group showing control of background QTc variability), and the results of this Thorough ECG Trial demonstrated that Technosphere had no effects on heart rate, PR and QRS interval duration or cardiac morphology. The effects on cardiac repolarization by the preponderance of data, including a careful pharmacodynamic-pharmacokinetic analysis also show that Technosphere has no effect on cardiac repolarization.

Figure: Time-Matched Placebo-Corrected QTcI Mean Change from Baseline Estimates from Mixed Model Analysis of Variance: ECG Population



Time-Averaged Analysis of Mean Changes from Baseline for ECG Parameters: ECG Population

Parameter	Treatment Group			
	Therapeutic (n = 47)	Supratherapeutic (n = 48)	Moxifloxacin 400 mg (n = 48)	Placebo (n = 47)
Heart rate, bpm	2.2	2.0	2.2	1.3
PR, ms	-2.6	-1.2	-2.3	-2.7
QRS, ms	-0.2	-0.3	-0.0	-0.2
QT, ms	-6.8	-5.8	-0.5	-4.6
QTcI, ms	-2.7	-2.5	3.3	-2.2
QTcF, ms	-2.2	-1.5	4.2	-1.4
QTcB, ms	0.1	0.6	6.6	0.1

bpm = beats per minute; ECG = electrocardiogram; ms = milliseconds; QTcI = individualized QT interval corrected; QTcB = QT interval corrected by the Bazett formula; QTcF = QT interval corrected by the Fridericia formula.

Data Source: Appendix **Error! Reference source not found.**, Tables 1 through 7.