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The Effect of Exenatide on QTc Interval in Healthy Subjects

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ABSTRACT

The effect of exenatide on cardiac repolarization as assessed by QT interval was investigated in this single-dose, randomized, positive and placebo-controlled, double-dummy, double-blinded, three-period crossover. The relationship of QT and glucose/insulin concentrations was also explored, as literature suggests glucose lowering may prolong QT. Healthy male and female subjects (N=70) with a normal baseline ECG (QTc <450 ms) underwent an initial tolerability screening. Subjects received 10 µg SC exenatide (maximum therapeutic dose) on up to 3 consecutive days; those who withdrew consent, or experienced severe GI events were excluded from ECG assessment. Subjects who passed the tolerability screening (N=62, 39 males/ 23 females, mean age 38 y, mean BMI 26.5 kg/m^2) received exenatide (10 µg SC), placebo, and moxifloxacin (400 mg oral) on separate occasions in a randomized crossover separated by washout periods of approximately 5 d. Twelve-lead ECGs in triplicate and blood samples for exenatide, glucose and insulin concentration were collected predose and at 1, 2, 3, 4, 5.5, and 10 h postdose. For the primary analysis, QT intervals were corrected for heart rate using Fridericia's method (QTcF) and were analyzed as the change from predose measurement. Based on time-matched QTcF, exenatide 10 µg did not prolong QT compared with placebo as the upper bound of the 2-sided 90% CI for the largest time-matched mean difference from placebo was <10 ms. No subject had QTc >450 ms or QTc change from baseline >30 ms with exenatide dosing. Moxifloxacin (positive control) increased QTc (maximum 14.14 ms at 3 h postdose). Although the QTcF change was not clinically relevant, a small, positive relationship (slope 0.02, 95% CI [0.01, 0.03]) was observed for plasma exenatide and placebo-adjusted change in QTcF. This observation may be confounded by exenatide's glucose lowering effect. A negative relationship (slope -1.45, 95% CI [2.18, -0.73]) was seen for QTcF change from baseline and glucose, with higher QTcF values occurring at lower glucose concentrations. This study demonstrates that a single 10 µg dose of exenatide did not prolong the QTc interval.

BACKGROUND

- Exenatide, the first in a class of antidiabetic agents known as glucagon-like peptide-1 receptor agonists, improves glycemic control in patients with type 2 diabetes by enhancing insulin secretion in a glucose-dependent fashion, suppressing elevated glucagon secretion, slowing gastric emptying, and enhancing satiety[1,2]
- Repeat-dose studies in monkeys and short- and long-term clinical studies as well as postmarketing data, found no evidence of QT prolongation with exenatide treatment. In vitro assessment of the human ether-a-go-go-related gene (hERG) channel found no statistically significant blockade at ≤91 µM exenatide (1.8 million-fold the human mean peak concentration)
- Literature data have shown that changes in glucose homeostasis may affect the QT interval[3, 4, 5], therefore, this study explores the influence of potential physiological covariates such as glucose and insulin on the QTc interval
- This study was designed to assess the effect of exenatide on cardiac repolarization according to the recommendations in the International Conference on Harmonisation (ICH) E14 guidance "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs"

Objectives

- **Primary:**
  - To determine, in healthy subjects, that a single 10 µg dose of exenatide does not differ from placebo in the mean change from predose in 12-lead ECG corrected QT (QTc) interval measurements
- **Secondary:**
  - To evaluate the relationship between plasma exenatide concentrations and QTc interval in healthy subjects
  - To explore the influence of potential physiological covariates such as plasma insulin, plasma glucose, and potassium on QTc interval in healthy subjects

Subjects and Methods

- This was a randomized, placebo-controlled, double-dummy, double-blinded, three-period crossover study conducted at two sites
- Subjects were overtly healthy males or females (of non-child-bearing potential), between the ages of 18 and 65 years, with a body mass index between 19 and 35 kg/m^2
- Subjects were excluded if they had an abnormality in the 12-lead ECG that would increase the risk of participating in the study, such as a Bazett's corrected QT (QTcB) interval >450 ms, or evidence or history of Long QT Syndrome, or significant active cardiac disease, or with symptoms of angina pectoris or transient ischemic attacks within the previous 6 months

Design

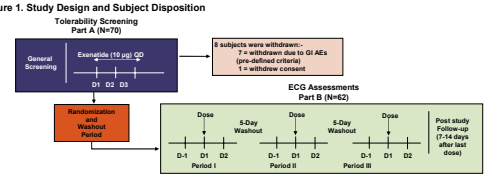
- Part A, subjects underwent a 3-day tolerability screen to exclude those who were particularly sensitive to GI side effects with exenatide (10 µg). Pre-defined withdrawal criteria were: (1) withdrawal due to nausea and vomiting (2) severe nausea (inability to eat a meal) or (3) more than one episode of vomiting
- Part B, (the ECG assessment phase), subjects received single doses of 10 µg exenatide, 400 mg moxifloxacin, and placebo, in a double blind, double dummy fashion, on three separate occasions
- All study drugs in Parts A and B were administered to the subjects in the morning after an overnight fast (lunch served at 4.5 h post dose)
- Electrocardiograms were performed in triplicate at approximately 1-minute intervals and centrally overread in a blinded fashion (-15 min, 1, 2, 3, 4, 5.5, 10 h postdose)
- On each dosing day blood samples were collected (-15 min, 1, 2, 3, 4, 5.5, 10 h postdose) for exenatide, glucose and insulin concentrations to evaluate changes in these parameters occurring at the time of ECG recordings
- Moxifloxacin 400 mg was included to establish assay sensitivity. It is a well-characterised fluoroquinolone antibiotic known to prolong the QT interval and generally accepted as a positive control in Thorough QT (TQT) studies

Statistical Analyses

- The primary QT correction for heart rate was performed according to the method of Fridericia (QTcF)
- The primary analysis was a mixed effects ANOVA with change in QTcF interval from the predose measurement (ΔQTcF) as the dependent variable, and treatment, time, period, sequence, and time-by-treatment interaction as fixed effects; random effects were subject, the subject-by-treatment interaction, and subject-by-time interaction
- Assay sensitivity was established if the time-matched mean difference between moxifloxacin and placebo was significantly different from 0 at a two-sided 0.05 significance level at one or more time points, adjusted for multiplicity using a resampling-based test
- Categorical analysis: Frequency of observations where QTcF>450 ms, or ΔQTcF >30 ms or ΔQTcF >60 ms for each treatment
- Relationship to drug or glucose concentrations: linear mixed-effects model with placebo-adjusted ΔQTc exenatide or moxifloxacin period (ΔQTc), as the dependent variable and time-matched plasma concentration of exenatide (or glucose) as a covariate and subject as a random effect

Study Design and Subject Disposition

Figure 1. Study Design and Subject Disposition



RESULTS

Table 1. Patient Baseline Characteristics

	Part A N=70	Part B N=62
Sex, n (%) male	43 (61.4)	39 (62.9)
Age, years	38.0 ± 14.3	37.7 ± 14.0
Weight, kg	80.4 ± 13.1	80.4 ± 13.5
Body mass index, kg/m^2	26.54 ± 3.64	26.53 ± 3.77

Data are means ± standard deviations

Table 2. Statistical Comparison of Mean Changes from Predose in QTcF[a] Intervals Between 10 µg Exenatide and Placebo

	Least Squares Mean Change from Predose		
Time (h)	10 µg Exenatide (N=62)	Placebo (N=62)	Difference (90% CI) Exenatide-Placebo
1	3.58	-0.36	3.93 (1.74, 6.13)
2	5.32	-0.49	5.81 (3.62, 8.00)
3	4.46	0.44	4.02 (1.82, 6.22)
4	2.65	0.95	1.70 (-0.49, 3.90)
5.5	0.55	-0.70	1.25 (-0.94, 3.45)
10	-3.18	-4.45	1.27 (-0.92, 3.47)

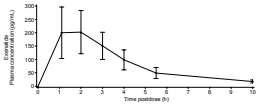
[a] *ANOVA model: Change in QTc = TIME + TREATMENT + TREATMENT*TIME with random effects for SUBJECT, SUBJECT*TIME + SUBJECT*TREATMENT*

Table 3. Frequency of 12-Lead ECG QTc Intervals >450 ms and Changes from Predose in QTc Intervals >30 ms and >60 ms at All Timepoints

	Number (%) of Subjects		
Treatment	QTcF Intervals >450 ms	ΔQTcF (change from Predose >30 ms)	ΔQTcF (change from Predose >60 ms)
10 µg exenatide N=62	0 (0)	0 (0)	0 (0)
Placebo N=62	1 (1.6)	0 (0)	0 (0)
400 mg moxifloxacin N=62	7 (11.2)	4 (6.4)	0 (0)

PHARMACOKINETICS

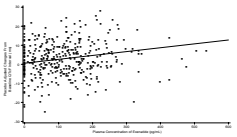
Figure 2. Arithmetic Mean (±SD) Plasma Concentrations of Exenatide Following a Single Dose of 10 µg Exenatide



Mean peak concentration of 208 pg/mL occurred approximately 2 hours post-dose

PHARMACOKINETIC/PHAMACODYNAMIC EVALUATIONS

Figure 3. Scatterplot of Changes from Predose in QTcF Interval Versus Plasma Exenatide Concentrations Following a Single 10 µg Dose



Slope (95% CI) from linear mixed effects model = 0.02 (0.01, 0.03) [p-value <0.001]
Regression line from linear mixed effects model

PHARMACOKINETIC/PHAMACODYNAMIC EVALUATIONS

Figure 4. Mean Plasma Concentrations of Glucose Following Single Doses of 10 µg Exenatide and Placebo

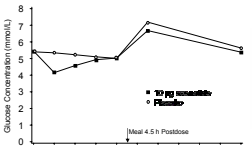


Figure 5. Mean Plasma Concentrations of Insulin Following Single Doses of 10 µg Exenatide and Placebo

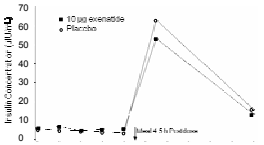
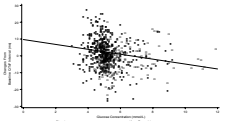
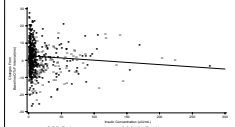


Figure 6. Scatterplot of Changes from Predose in QTcF Interval Versus Plasma Glucose Concentrations Following Single doses of 10 µg Dose Exenatide and Placebo



Slope (95% CI) from linear mixed effects model = -1.45 (-2.18, -0.73) [p-value <0.001]
Regression line from linear mixed effects model

Figure 7. Scatterplot of Changes from Predose in QTcF Interval Versus Plasma Insulin Concentrations Following Single Doses of 10 µg Exenatide and Placebo



Slope (95% CI) from linear mixed effects model = -0.03 (-0.06, 0.00) [p-value = 0.085]
Regression line from linear mixed effects model

Safety and Tolerability

- The majority of adverse events were mild in severity, and no severe or serious adverse events were reported
- No hypoglycemic episodes were reported during the study
- There were no clinically significant changes in any laboratory parameters, vital signs data, or safety 12-lead ECGs for individual subjects following 10 µg exenatide administration

Table 4. Part B (ECG Assessment Phase): Frequency of Drug-related Adverse Events

	Number of Adverse Events [Number (%) of subjects with Adverse Events]		
MedDRA Preferred Term	10 µg Exenatide (N=62)	Placebo (N=62)	400 mg Moxifloxacin (N=62)
Nausea[a]	18 [17] (28%)	1 [1] (2%)	1 [1] (2%)
Headache	6 [6] (10%)	2 [2] (3%)	3 [3] (5%)
Dizziness	5 [5] (8%)	2 [2] (3%)	2 [2] (3%)
Vomiting[a]	9 [3] (5%)		
Lethargy	3 [3] (5%)		
Diarrhoea[a]	1 [1] (2%)	1 [1] (2%)	
Dry mouth[a]			2 [2] (3%)
Dysgeusia		1 [1] (2%)	1 [1] (2%)
Fatigue	1 [1] (2%)	1 [1] (2%)	
Chills	1 [1] (2%)		
Depressed mood			1 [1] (2%)
Disorientation	1 [1] (2%)		
Dyspepsia[a]			1 [1] (2%)
Feeling cold	1 [1] (2%)		
Hiccups	1 [1] (2%)		
Somnolence			1 [1] (2%)
Overall Total	**47 [27] (44%)**	**8 [8] (13%)**	**12 [9] (15%)**

Abbreviations: MedDRA = Medical Dictionary of Regulatory Activities; N =number of subjects studied
[a] *Gastrointestinal disorders*

SUMMARY AND CONCLUSIONS

- A single 10 µg dose of exenatide did not differ from placebo in the mean change from predose in 12-lead ECG QTcF interval in healthy subjects, as the upper bound of the one-sided 95% CI was <10 ms
- Following a single 10 µg dose of exenatide, no individual subjects had an absolute QTcF interval >450 ms or a change from baseline in QTc interval >30 ms
- There were no safety concerns, in terms of vital signs and clinical laboratory evaluations, following administration of 10 µg exenatide. The majority of adverse events reported were mild in severity, and no severe or serious adverse events were reported
- There was a slight positive correlation between plasma exenatide concentrations and changes from baseline in QTcF interval following a single dose of 10 µg exenatide in healthy subjects; this finding was considered to be of no clinical concern
- There was a slight negative correlation between plasma glucose concentrations and changes from baseline in QTcF interval in healthy subjects administered single doses of 10 µg exenatide and placebo; this finding was considered to be of no clinical concern
- There was no relationship between the other physiological covariates, plasma insulin and serum potassium, and changes from baseline in QTcF interval in healthy subjects
- This study in healthy subjects met the criteria described by ICH E14 guidance as a 'negative QT/QTc study.'

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Sponsored by Amylin Pharmaceuticals, Inc. and Eli Lilly and Company