A TQT Study Confirms Early PK/PD Modeling That a Supratherapeutic Dose of Omarigliptin, a Once-Weekly DPP-4 Inhibitor, Does Not Prolong the QTc Interval

Daniel Tatosian[1], Nadia Cardillo Marricco[2], Xiaoli Shirley Glasgow[1], Bruce DeGroot[2], Katherine Dunnington[2], Laura George[1], Isaias Noel Gendrano[1], Amy O. Johnson-Levonas[1], Dennis Swearingen[2], and Eunkyung Kauh[1]

[1]Merck, Kenilworth, NJ; [2]Celerion, Lincoln, NE

Abstract

Background: Omarigliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor being developed as a once-weekly treatment for type 2 diabetes. Plasma concentration-QTc analysis was performed using data from the first-in-human single-ascending dose trial, and predicted a clinically insignificant 2.8 msec QTc prolongation at 10 μM, a concentration ~15-20-fold higher than the therapeutic C_{max}.

Methods: This double-blind, double-dummy, randomized, placebo- and active-comparator-controlled, 3-period, balanced crossover study definitively evaluated the effects of a supratherapeutic omarigliptin dose on the QTc interval. A population-specific correction of QT interval (QTcP) was used for the primary analysis. Healthy subjects (n=60) received treatments separated by ~28-day washout: A) single-dose 25 mg omarigliptin on Day 1, single-dose 175 mg omarigliptin on Day 2; B) placebo on Day 1, single-dose 400 mg moxifloxacin on Day 2; C) placebo on Days 1 and 2. Day 2 QTcP intervals were analyzed. The primary hypothesis was supported if the 90% confidence intervals (CIs) for the least squares mean differences between omarigliptin 175 mg and placebo in QTcP interval change from baseline were all <10 msec at every postdose time point on Day 2.

Results: The upper bounds of the 90% CIs for the true mean differences (omarigliptin-placebo) in QTcP change from baseline for omarigliptin 175 mg were <10 msec at all postdose time points on Day 2.

Conclusions: A supratherapeutic dose of omarigliptin does not prolong the QTcP interval to a clinically meaningful degree relative to placebo, confirming the results of the earlier concentration-QTc analysis. These results support the early usage of first-in-human concentration-QTc analysis as a valid approach to assess QTc risk.

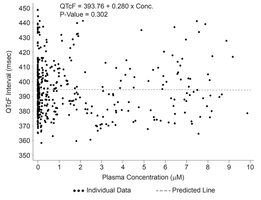
Background

- Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released by neuroendocrine cells of the intestine in response to a meal. These hormones lower blood glucose concentrations by increasing insulin (for GLP-1 and GIP) and decreasing glucagon levels (for GLP-1) in a glucose-dependent manner.
- Incretins are rapidly degraded in the blood stream by the enzyme dipeptidyl peptidase-4 (DPP-4).
- DPP-4 inhibitors are oral anti-hyperglycemic agents used for the treatment of type 2 diabetes (T2DM) that act by prolonging, and thereby augmenting, the action of incretin hormones.
- Omarigliptin (MK-3102) is a long-acting, oral DPP-4 inhibitor currently in Phase III development for the treatment of T2DM as a once-weekly dosing regimen with the potential to improve treatment adherence.
- Since some non-antiarrhythmic drugs may delay cardiac repolarization leading to increased risk of cardiac arrhythmias and death, drug regulatory agencies mandate that every novel drug candidate undergo an evaluation to assess the potential to prolong the QT/QTc interval in healthy human subjects.

Background: Exploratory QT Prolongation Risk Assessment: Protocol 001 (First-in-Human Study).

- Design: double-blind, randomized, placebo-controlled, multiple period, alternating panel, rising single oral dose study in healthy male subjects.
- Matched plasma omarigliptin sample collection and triplicate QT collection by 12-lead ECG.
- QT corrected using Fridericia method.
- Analysis: linear concentration-QTc model developed and evaluated to assess likelihood for QT prolongation at varying concentrations.

Figure 1. Background: Exploratory Assessment of Concentration-QTc Data in First-in-Human Study



- Exploratory concentration-QTc model results:
  - The slope in the linear QTc vs. omarigliptin concentration model was estimated to be not statistically significant (95% CI of slope contains zero), with point estimate and 95% CI of 0.2797 (-0.2523, 0.8117) msec/μM (**Figure 1**).
  - The point estimate predicts an approximate 2.8 msec prolongation at exposures up to 10 μM (approximately 15-20 fold above the clinical C_{max} in patients with mean ~600 nM), which is below the level of regulatory concern and suggests low likelihood of QT risk at clinical or supratherapeutic doses.

Objectives

- To definitively evaluate the potential for a single supratherapeutic dose of omarigliptin 175 mg to prolong ventricular polarization as per the International Conference on Harmonization (ICH) E14 Guidance document.
- To evaluate the safety and tolerability of omarigliptin administered at a supratherapeutic dose in normal healthy volunteers.

Methods

Study Design

- This was a 2-dose randomized, double-blind, double-dummy, placebo- and positive-controlled, 3-period, balanced crossover study assessing the effect of single-dose omarigliptin 25 mg (therapeutic dose) and 175 mg (supratherapeutic dose) on QT/QTc interval.
- There were three treatment periods, and each subject received the following study treatments in a randomized order:
  - Treatment A: Single-dose omarigliptin 25 mg on Day 1, followed by single-dose omarigliptin 175 mg on Day 2 plus placebo to moxifloxacin on Day 2
  - Treatment B: Matching placebo to omarigliptin (25 mg) on Day 1, followed by single-dose moxifloxacin 400 mg plus placebo to omarigliptin (175 mg) on Day 2
  - Treatment C: Matching placebo to omarigliptin (25 mg) on Day 1 and matching placebos to both omarigliptin (175 mg) and moxifloxacin (positive control) on Day 2
- A washout of ≥ 4 weeks separated dosing periods, based on preliminary half-life estimates of 50-100 hours for omarigliptin.

Subjects

- Healthy non-smoking adult males and females between 18 and 45 years of age (inclusive) with a body mass index (BMI) ≤30 kg/m^2 and QTcF interval <450 msec (males) and <470 msec (females) with QRS duration <120 msec and PR interval <200 msec.

Treatments

- A single dose of study drug was administered orally the morning of Days 1 (omarigliptin 25 mg or placebo) and 2 (omarigliptin 175 mg or moxifloxacin 400 mg or placebo), following a 10-hour overnight fast, with 240 mL of water.
- Water consumption was restricted for 1 hour prior to and 1 hour after study drug administration.
- A standard lunch and dinner were provided at approximately 4 and 10 hours postdose, respectively, on each study drug administration day.
- A snack was provided approximately 7 and 13 hours postdose on each study drug administration day.
- Subjects fasted from all food between meals and snacks.

ECG Assessments

- Subjects were confined to the study site during each dosing period until at least 24 hours after the final dose for that treatment period, and no strenuous activities were permitted.
- Subjects rested in a semi-recumbent position for at least 10 mins prior to and 5 mins after each prescribed ECG extraction time point.
- Continuous 12-lead digital ECG data were obtained over 24 hours on Days 1 and 2 within each treatment period using Mortara H12+ Digital Holter Recorders (Mortara Instrument, Inc., Milwaukee, WI, USA). ECG data were recorded on compact flash memory cards, then extracted and analyzed by a central, blinded ECG laboratory (Quintiles Phase I Services, Inc., Durham, NC, USA).
- ECG "snapshots" at each protocol-specified timepoint were extracted automatically, and quality control checks were performed by trained Holter specialists.
- For each subject, at each timepoint, three to five consecutive QT values were measured and mean interval values were calculated.
- In addition to QT, measurements for RR, HR, PR, and QRS intervals were performed.
- Derivation of QTcF, QTcB, T-wave and U-wave morphologies, ECG rhythms, and overall clinical interpretation (normal, abnormal) was determined by Quintiles.

Pharmacokinetics

- Within each treatment period, on both study Days 1 and 2, blood samples were collected from predose through 23.5 hours postdose for omarigliptin concentration assay and from predose through 4 hours postdose for moxifloxacin assay.
- $AUC_{0\text{-}23.5hr}$, C_{max}, and T_{max} were determined for omarigliptin using samples collected on Day 2 of Treatment A (ie, single-dose 25 mg omarigliptin on Day 1 followed by a single-dose omarigliptin 175 mg and placebo to moxifloxacin on Day 2).
- The Day 1 omarigliptin and the Days 1 and 2 moxifloxacin samples were archived, and were to be analyzed only in the event that the primary hypothesis failed.

Statistical Analysis

- The proarrythmic potential of omarigliptin was assessed by evaluating QT intervals at predefined timepoints (25 min, 15 min, and 7 min predose, and 0.5, 1, 2, 3, 4, 6, 10, 16, and 23.5 hours postdose on both study days).
- Baseline was defined in each period as predose (ie, any measurements taken prior to administration of drug on Day 1).
- Change from baseline was computed as postdose on Day 2 minus predose for all analyses.
- QTcF was found to inadequately correct the QT for heart rate based on a regression analysis. Therefore, a population-specific rate correction for QT ($QTcP = QT/RR^{slope}$) was used as the primary correction parameter used to assess the primary objective and hypothesis. Results based on QTcF were also calculated.
- A repeated measures mixed model appropriate for a 3-period crossover design was used to analyze QTcP change from baseline. The model included the following fixed factors: period, treatment, time, and treatment-by-time interaction; a double compound symmetry covariance structure was assumed.
- The within-subject correlation across periods was modeled by specifying subject as a random effect.
- The within-subject correlation across time points within a period was modeled by specifying the subject-by-period interaction as the repeated measure with residual compound symmetry. Carryover was investigated and tested at α = 0.10. All other tests were performed at α = 0.05.
- Least-squares means (LS means) and 2-sided 90% CIs (equivalent to 1-sided upper 95% CIs) for the true mean difference (omarigliptin – placebo) in QTcP change from baseline (dQTcP) was provided at each prespecified time point postdose on Day 2.
- If the largest upper bound of the 95% one-sided CI for the mean difference in QTcP from time-matched baseline ECG recordings between omarigliptin and placebo was < 10 msec, then omarigliptin was considered to have no potential for QT/QTc prolongation.
- A relationship between omarigliptin plasma concentrations and the cardiodynamic response was explored through visual inspection of the plot of time-matched individual change from baseline in QTcP (delta QTcP, dQTcP) versus Day 2 plasma omarigliptin concentrations.

Safety and Tolerability Assessments

- Assessment of safety and tolerability was based on repeated evaluations of adverse experiences and clinical assessments (semi-recumbent vital sign measurements, 12-lead safety ECGs, physical examinations, and safety laboratory tests [chemistry, hematology, and urinalysis]) at scheduled time points.

Results

Patient Characteristics

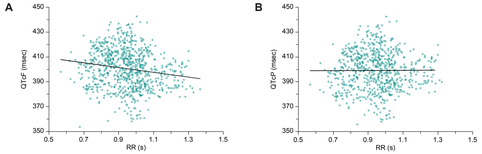
Table 1. Baseline demographics for the entire cohort of randomized subjects, categorized by gender

	All subjects (n=60)	Male (n=30)	Female (n=30)
Race, n (%)			
White	7 (11.7%)	4 (13.3%)	3 (10.0%)
Hispanic	47 (78.3%)	23 (76.7%)	24 (80.0%)
Black	4 (6.7%)	2 (6.7%)	2 (6.7%)
Asian	1 (1.7%)	1 (3.3%)	0
Native American	1 (1.7%)	0	1 (3.3%)
Age, mean, yr (range)	33 (18-45)	32 (22-45)	33 (18-45)
Height, mean, cm (range)	163.1 (146.0-186.0)	168.8 (154.0-186.0)	157.3 (146.0-170.0)
Weight, mean, kg (range)	70.5 (50.3-91.0)	76.8 (60.8-91.0)	64.2 (50.3-83.2)
Body mass index, kg/m^2	26.4 (19.1-30.4)	26.9 (20.4-30.4)	25.9 (19.1-29.5)

Appropriateness of QT Correction Methodology

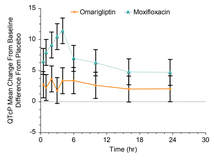
- Per protocol, Fridericia's correction to QT was made and the appropriateness of the correction factor was assessed by simple linear regression of QTcF versus RR interval using placebo and drug-free data.
- The estimated slope was -0.0207 with a 95% CI of (-0.0294, -0.0120) which excluded zero (**Figure 2A**). Thus, Fridericia's correction was found to be inadequate for correcting QT for HR.
- The Population-Specific Rate Correction Method was investigated and yielded a slope of -0.0013 with a 95% CI of (-0.0099, 0.0074) which included zero (**Figure 2B**). Thus, the Population-Specific Rate Correction Method was used as the primary measure of change in QT interval in this study, as this method was found to adequately correct QT for HR.

Figure 2. (A) QTcF (msec) versus RR (sec) and (B) QTcP (msec) versus RR (sec) following the administration of placebo on Days 1 and 2 (n=59)



Cardiodynamic Results

Figure 3. Mean placebo-adjusted change from baseline in QTcP versus placebo on Day 2 (bars represent 90% CI)

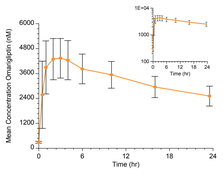


- The time-matched baseline-corrected QTcP interval difference between the omarigliptin 175 mg and placebo groups was substantially below the threshold of regulatory concern on Day 2, confirming the result of the exploratory concentration-QTc analysis from Protocol 001 (**Figure 3**).
  - The upper bound of the 95% CI for the between-group difference between omarigliptin and placebo was less than 10 msec at all postdose time points (range of 3.89 to 5.76 msec).
  - The maximum placebo-adjusted least-squares difference during the postdose observation period was 3.66 msec with a 90% CI of (1.56, 5.76).
- Since the Day 2 data confirmed that a single supratherapeutic dose of omarigliptin does not prolong the QTc interval to a clinically significant degree, the ECG data for Day 1 postdose were not extracted from Holter recordings.
- As expected, treatment with moxifloxacin lengthened the QT/QTc interval analyzed by QTcP, confirming the sensitivity of this study (**Figure 3**).
  - From hours 1 through 4 postdose, the lower bound of the 95% CI for the between-group difference between moxifloxacin and placebo (in change from baseline QTcP) (i.e., from Day -1 to Day 2) was greater than 5 msec.
  - The mean placebo-adjusted difference was greater than 10 msec from 3 to 4 hours postdose (range of 10.5 to 11.4 msec).
- The results of QTcF were similar to those seen with QTcP: treatment with moxifloxacin led to increased QT/QTc interval length, whereas treatment with omarigliptin 175 mg did not.

Pharmacokinetic Results

- The geometric mean C_{max}, $AUC_{0\text{-}23.5hr}$, and median T_{max} for omarigliptin on Day 2 after administration of 25 mg dose on Day 1 and 175 mg dose on Day 2 were 4,540 nM, 75.8 μM*hr and 2.11 hr, respectively (**Figure 4**).
- The mean C_{max} provides an approximate 8-fold margin to the C_{max} at the 25 mg dose under evaluation in Phase III.

Figure 4. Arithmetic mean (±standard deviation) plasma concentration-time profile of omarigliptin on Day 2 after administration of a single therapeutic dose (25 mg) on Day 1 and a single supratherapeutic dose (175 mg) on Day 2. Treatment A, n=54 (insert = semi-log scale)



Safety and Tolerability Results

Table 2. Number (%) of subjects with adverse experiences by System Organ Class category presented by treatment group

	Omarigliptin (n=55)		Moxifloxacin (n=54)		Placebo (n=54)	
	n	%	n	%	N	%
Subjects with ≥1 adverse experiences	15	27.3	17	31.5	17	31.5
Eye disorders	0	0	2	3.7	1	1.9
Gastrointestinal disorders	2	3.6	4	7.4	4	7.4
General disorders and administration site conditions	1	1.8	1	1.9	0	0
Immune system disorders	0	0	1	1.9	0	0
Infections and infestations	1	1.8	0	0	0	0
Investigations	1	1.8	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	1	1.9	1	1.9
Nervous system disorders	5	9.1	4	7.4	3	5.6
Psychiatric disorders	1	1.8	0	0	0	0
Reproductive system and breast disorders	0	0	1	1.9	3	5.6
Respiratory, thoracic, and mediastinal disorders	0	0	2	3.7	0	0
Skin and subcutaneous tissue disorders	7	12.7	6	11.1	10	18.5
Surgical and medical procedures	1	1.8	0	0	0	0

- There were no clinically meaningful differences between the treatment groups in the incidences of adverse events within any of the SOC categories (**Table 2**).
- The most common individual adverse experiences were contact dermatitis (at the ECG electrode sites), headache, and constipation.
  - There were no clinically meaningful differences between the treatment groups in the incidences of these specific adverse events.
- There were no deaths in this study.
- There were no consistent changes of clinical relevance in blood chemistry, vital signs, or physical examinations across any of the treatments.

Conclusions

- The results of this thorough QT/QTc study confirmed the results from a concentration-QTc analysis conducted in the first-in-human study: treatment with omarigliptin 25 mg on Day 1 and 175 mg on Day 2 did not have a clinically meaningful effect on the QT/QTc interval on Day 2 at various time points over 23.5 hours postdose.
  - The mean difference between omarigliptin and placebo in change in QTcP interval from baseline was substantially less than the protocol-defined threshold for identifying a prolongation effect.
  - When QTcF was analyzed, the same conclusion was reached: omarigliptin did not adversely effect the QT/QTc interval.
  - The peak plasma concentrations observed in this treatment exceeded the peak clinical concentrations for 25 mg under study in Phase III by approximately 8-fold.
- The results of the moxifloxacin treatment met the positive control criteria.
- Omarigliptin at single doses of 25 mg and 175 mg was well tolerated, and there was no identifiable safety signal.
- Based on these results, no clinically relevant prolongation of the QT interval is expected in the population intended to be prescribed omarigliptin.