# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 21-513

# Statistical Review(s)

# Memorandum of Statistical Review

Date: November 17, 2004

To: Mark Hirsch, M.D., HFD-580, Division of Reproductive and Urologic Drug Products

Re: NDA 21-513 (Serial 000, dated June 16, 2004)
Sponsor: Novartis Pharmaceuticals Corp.
Product: Enablex® (darifenacin hydrobromide) Extended-Release Tablets
Indication: Treatment of overactive bladder
Goal Date: December 23, 2004

The Sponsor submits this application as complete response to the October 2, 2003 approvable action letter sent by the Division of Reproductive and Urologic Drug Products. This memo addresses QT Study DAR328 using data submitted on September 17, 2004.

Study DAR328 is a single center, double blind, parallel group, placebo and active controlled, multiple dose study in healthy volunteers. The objective of the study is to determine the effect of 6-day, once daily darifenacin administration (to steady state) on QTcF interval (the Fridericia's formula corrected QT interval) in poor and extensive CYP2D6 substrate metabolizers. The treatment groups studied are placebo, darifenacin 15 mg qd, darifenacin 75 mg qd, and Avelox 400 mg qd. The drug-placebo comparison is of the form:

$$[(\text{drug } QTcF_{t\_max \text{ on day-6}}) - (\text{drug } QTcF_{baseline})] - [(\text{placebo } QTcF_{day\text{-}6}) - (\text{placebo } QTcF_{baseline})]$$

The drug $QTcF_{t\_max \text{ on day-6}}$ value is computed by taking the average of the 3 QTcF measurements at each subject's t_max on day-6. The placebo $QTcF_{day\text{-}6}$ value is computed by taking the average of 3 QTcF measurements at 13 different time points on day-6 (a time-averaged value). The drug and placebo $QTcF_{baseline}$ values are computed by taking the average of 3 QTcF measurements at 13 different time points at baseline. A 90% confidence interval for drug minus placebo is computed from estimates from an ANCOVA model with treatment fixed effect and baseline QTcF as the covariate. This study was prospectively designed with statistical and clinical input from the Division.

The Sponsor has conducted the study as recommended by the Division and the QT results in Table 4-5 on page 14 of the submission, shown below, have been recalculated and verified by the statistical reviewer. In general, these results for QTcF show that Avelox 400 mg has a QT prolongation effect, and that the upper bounds of the 90% confidence interval for the difference from placebo are 3.2 mm for darifenacin 15 mg and 2.2 mm for darifenacin 75 mg.

Sonia Castillo, Ph.D.
Mathematical Statistician
HFD-715

**Table 4-5 Treatment comparison vs placebo based on change from baseline PD endpoints**

| Day | PD Endpoint | Conduct interval (ms) | Comparison | DF | Estimate | Standard Error | p-value | 90% CI for difference |
|---|---|---|---|---|---|---|---|---|
| 6 | E_tmax | QT | DAR328 15mg - Placebo | 87 | 4.9 | 3.4 | 0.154 | (-10.6, 0.8) |
| | | | DAR328 75mg - Placebo | 84 | -8.2 | 4.0 | 0.046 | (-14.9, -1.5) |
| | | | Avelox 400mg - Placebo | 87 | 20.5 | 3.7 | <0.001 | ( 14.3, 26.6) |
| | | QTcF | DAR328 15mg - Placebo | 87 | -0.4 | 2.2 | 0.842 | ( -4.1, 3.2) |
| | | | DAR328 75mg - Placebo | 84 | -2.2 | 2.6 | 0.400 | ( -6.6, 2.2) |
| | | | Avelox 400mg - Placebo | 87 | 11.6 | 2.4 | <0.001 | ( 7.6, 15.5) |
| | | QTcB | DAR328 15mg - Placebo | 87 | 2.5 | 2.5 | 0.309 | ( -1.6, 6.6) |
| | | | DAR328 75mg - Placebo | 84 | 2.0 | 2.7 | 0.470 | ( -2.5, 6.5) |
| | | | Avelox 400mg - Placebo | 87 | 6.4 | 2.8 | 0.022 | ( 1.9, 11.0) |
| | | QTcI | DAR328 15mg - Placebo | 87 | 1.0 | 2.4 | 0.694 | ( -5.0, 3.1) |
| | | | DAR328 75mg - Placebo | 84 | -3.4 | 2.9 | 0.248 | ( -8.2, 1.5) |
| | | | Avelox 400mg - Placebo | 87 | 10.6 | 2.5 | <0.001 | ( 6.4, 14.8) |
| | | QRS | DAR328 15mg - Placebo | 87 | 0.1 | 1.0 | 0.888 | ( -1.6, 1.9) |
| | | | DAR328 75mg - Placebo | 84 | 0.6 | 0.9 | 0.517 | ( -0.9, 2.1) |
| | | | Avelox 400mg - Placebo | 87 | 0.6 | 0.9 | 0.547 | ( -1.0, 2.1) |

1. E_tmax, E_mean, and E_max are for the interval at PK tmax, for the time-average value, and for the maximum of intrasubject intervals from 13 ECG timepoints from the evaluation Day
2. Estimate, Standard Error, p-value, and 90% confidence interval are determined from ANCOVA model with Treatment as factor, and baseline value as covariate. Separate ANCOVA for each comparison.

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/s/
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Sonia Castillo
11/17/04 04:02:36 PM
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Mike Welch
11/18/04 11:19:05 AM
BIOMETRICS

# Statistical Consultation – Protocol Review

| | |
|---|---|
| **IND #:** | 45,457 |
| **Applicant:** | Novartis Pharmaceuticals Corp. |
| **Name of Drug:** | Enablex (darifenacin hydrobromide) Tablets |
| **Indication:** | Treatment of overactive bladder |
| **Documents Reviewed:** | Phase 3 Protocol, Serial No. 177 |
| **Date received:** | 10 / 27 / 03 |
| **Medical Reviewer:** | Mark Hirsch, M.D., HFD-580 |
| **Statistical Reviewer:** | Sonia Castillo, Ph.D., HFD-715 |

*This submission contains a proposed Phase 3 QTc protocol entitled "A double blind, double dummy, parallel group, placebo, and active controlled, multiple-dose study to evaluate the effects of darifenacin on cardiac safety in poor and extensive CYP2D6 substrate metabolizers." This protocol is submitted to fulfill a requirement in the approvable letter sent by the agency to the sponsor.*

## Statistical Reviewer's Comments for the Sponsor:

1. Please prespecify one of the QT correction formulae as the one to be used in the primary analysis. Any other correction formulae analyses should also be submitted as secondary analyses.

2. The QT data used for analyses needs to come from the darifenacin $T_{max}$ timeframe.

3. The sample size needs to be calculated based on the anticipated difference from baseline between darifenacin and placebo.

4. Sample size calculations need to use a two-sided test with significance level of 5% or a 95% two-sided confidence interval assumption.

5. Any 95% confidence intervals that are presented should be two-sided.

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/s/
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Sonia Castillo
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A letter with these statistical comments about QTC study design were sent to the sponsor by HFD-580 on 12-4-03. This document was entered into DFS on 2-26-04.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# STATISTICAL REVIEW AND EVALUATION

| | |
|---|---|
| **NDA:** | 21-513 |
| **Name of Drug:** | ENABLEX (darifenacin hydrobromide) Extended Release Tablets (7.5 / 15 mg) |
| **Indication:** | [ ] |
| **Sponsor:** | Novartis Pharmaceutical Corp. |
| **Documents Reviewed:** | Study Reports and the data submitted to Electronic Document Room: |
| | Paper Volumes (December 3, 2002) 1.1 - 1.55 |
| | \\CDSESUB1\N21513\N_000\2002-12-03 |
| | \\CDSESUB1\N21513\N_000\2003-04-16 |
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| | \\CDSESUB1\N21513\N_000\2003-08-19 |
| | \\CDSESUB1\N21513\N_000\2003-08-21 |
| **Date Received:** | December 6, 2002 |
| **Project Manager:** | Jean King, HFD-580 |
| **Clinical Reviewer:** | Zili Li, M.D., HFD-580 |
| **Clinical Team Leader:** | Mark Hirsch, M.D., HFD-580 |
| **Statistical Reviewer:** | Sonia Castillo, Ph.D., HFD-715 |
| **Statistical Team Leader:** | Michael Welch, Ph.D., HFD-715 |
| **Biometrics Director:** | Edward Nevius, Ph.D., HFD-715 |

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|---|---|
| **Key Words:** | Clinical studies, NDA review |

## TABLE OF CONTENTS

# 1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

The effectiveness of darifenacin 7.5 mg and 15 mg in decreasing the number of incontinent episodes per week and number of micturitions per day (symptoms of overactive bladder) has been demonstrated.

Efficacy is based on two foreign and two U.S./Canadian multi-center, double-blind, randomized, placebo-controlled, parallel-group studies comparing the safety and efficacy of darifenacin (7.5 mg and 15 mg) and placebo in women and men over 18 years of age over 12 weeks of treatment. Efficacy is based on calculation of the difference from baseline in the average number of incontinent episodes per week and average number of micturitions per day compared to placebo. Table 1.1 presents the decrease from baseline in these endpoints for all treatments for all studies.

**Table 1.1**
**Summary of the Decrease from Baseline in the Average Number of Incontinent Episodes per Week and the Average Number of Micturitions per Day at Week 12 of Treatment for All Studies**

| | Average Number of Incontinent Episodes per Week* | | | Average Number of Micturitions per Day* | | |
|---|---|---|---|---|---|---|
| | Darifenacin 7.5 mg | Darifenacin 15 mg | Placebo | Darifenacin 7.5 mg | Darifenacin 15 mg | Placebo |
| ***Study A1371001 (U.S., Canada)*** | | -11.4 | -9.0 | | -1.9 | -1.2 |
| **Study A1371002 (Foreign)** | -8.1 | -10.4 | -5.9 | -8.5 | -10.7 | -5.8 |
| **Study A1371041 (Foreign)** | -9.0 | -10.4 | -7.6 | -1.6 | -1.7 | -0.8 |
| | Darifenacin 7.5 mg/15 mg | | | Darifenacin 7.5 mg/15 mg | | |
| **Study A1371047 (U.S., Canada)** | -8.2 | | -6.0 | -1.9 | | -1.0 |

Source: Statistical Reviewer's listing.
*All darifenacin doses demonstrated statistically significant differences from placebo ($p<0.05$) for both endpoints in all studies except for the average number of micturitions per day in Study A1371001. Also see Tables 4.2 and 4.3.

# 2 BACKGROUND AND INDICATION

The sponsor has submitted an application that contains 94 clinical studies comprised of 25 studies in subjects with overactive bladder, 48 studies in healthy volunteers, and 21 studies in special populations or other indications. Three of the 25 studies in subjects with overactive bladder (A1371001, A1371002, and A1371041) are the pivotal studies and one in subjects with overactive bladder is supportive (A1371047). These studies were designed to assess the clinical efficacy of darifenacin on the symptoms of overactive bladder. Table 2.1 presents a brief summary of each of the four studies addressed in this review.

The sponsor's proposed indication is:

[redacted]

Since the sponsor is seeking approval of the 7.5 mg and 15 mg dosages, this review will focus on those dosages and not address other dosages or tolterodine.

**Table 2.1**
**Brief Summary of Clinical Studies for Darifenacin**

| Study Number (Dates Conducted) | Number of Centers (Location) | Patient Population | Treatment[1] | Sample Size (Entered Study) | Male / Female (%) | Design[2] | Duration of Treatment |
|---|---|---|---|---|---|---|---|
| A1371001 (3-28-00 to 8-29-01) | 66 (U.S., Canada) | Males and females at least 18 years of age with symptoms of overactive bladder (UUI) for at least 6 months prior to entry in the study | 15 mg darifenacin<br>30 mg darifenacin<br>2 mg tolterodine<br>placebo | 112<br>230<br>223<br>115 | 21 / 79<br>17 / 83<br>17 / 83<br>10 / 90 | DB, R, PC, PG, MC, DD | 12 weeks |
| A1371002 (12-16-99 to 2-28-01) | 62 (Europe, Israel) | | 7.5 mg darifenacin<br>15 mg darifenacin<br>30 mg darifenacin<br>placebo | 108<br>107<br>115<br>109 | 13 / 87<br>14 / 86<br>14 / 86<br>17 / 83 | DB, R, PC, MC | 12 weeks |
| A1371041 (1-10-02 to 9-17-02) | 57 (Europe, S. America, S. Africa, Israel) | | 3.75 mg darifenacin<br>7.5 mg darifenacin<br>15 mg darifenacin<br>placebo | 53<br>230<br>115<br>164 | 17 / 83<br>13 / 87<br>15 / 85<br>16 / 84 | DB, R, PC, PG, MC | 12 weeks |
| A1371047 (5-5-02 to 1-11-03) | 66 (U.S., Canada) | | 7.5/15 mg darifenacin<br>placebo | 268<br>127 | 15 / 85<br>17 / 83 | DB, R, PC, PG, MC, UDA | 12 weeks |

Source: Statistical Reviewer's listing.
[1] Darifenacin is taken once daily, tolterodine is taken twice daily
[2] DB = Double-blind, R = Randomized, PG = Parallel Group, MC = Multicenter, PC = Placebo Controlled, DD = Double Dummy, UDA = Upward Dose Adjustment

# 3 STUDY DESIGN

## 3.1 Study Description

The primary objective of each study is to assess the clinical efficacy of darifenacin on the symptoms of overactive bladder. Each study is designed as a multicenter, double-blind, randomized, placebo-controlled, parallel group study of darifenacin in subjects with overactive bladder. In Study A1371047, all subjects started on 7.5mg daily and upward dose adjusted to 15 mg daily darifenacin (for darifenacin subjects) or placebo (for placebo subjects) after 2 weeks provided the subject met the following two criteria:

- The subject and Investigator are not satisfied with the efficacy of the current dose, and
- The current dose is well tolerated.

Table 2.1 presents the treatment subjects were randomized to receive in a double-blind fashion for each study.

After a two-week washout period for those on prohibited medication, subjects entered a two week run-in period. Study A1371001 had a 14-day medication-free run-in period and the other three studies had a 14-day single-blind placebo run-in period. Studies A1371001 and A1371002 collected data during the entire 14-day run-in period and the other two studies collected data for the last 7 days of the 14-day run-in period. Following the run-in period, eligible subjects were randomized to receive double-blind treatment for 12 weeks. Inclusion criteria include the following:

1. Male and female subjects, aged 18 years and over;
2. Subjects must have symptoms of overactive bladder for at least 6 months;
3. Subjects must exhibit all of the following symptoms of overactive bladder during the run-in period (this information was collected using an electronic patient diary during the run-in period):
   - incontinence – at least 10 (5 for studies A1371041 and A1371047), but no more than 100 (50 for study A1371041 and no upper limit for study A1371047) incontinent episodes over the run-in period.
   - frequency of micturition – at least 8 times per 24 hours, on average, over the run-in period.
   - urgency (strong desire to void) – at least once per 24 hours, on average, over the run-in period.

All efficacy variables were recorded with electronic patient diaries that were completed by the subjects daily for the 2-week (1-week Study A1371041) periods directly preceding visits 4, 5 and 6 (i.e., during treatment weeks 1-2, 5-6, and 11-12).

## 3.2 Primary Objective and Efficacy Variables

The primary objective of each study is to assess the clinical efficacy of darifenacin on the symptoms of overactive bladder. The primary efficacy variable is the average number of incontinent episodes per week. One secondary efficacy variable that is of interest to the medical reviewer is daily frequency of micturitions and will be reported below.

## 3.3 Statistical Analysis Plan

All studies use a two-sided test at the 5% significance level to test treatment differences against placebo, except for study A1371001, which uses a 2.5% significance level. The sponsor used a step down procedure to assess the efficacy of the darifenacin groups against placebo for all studies except study A1371001, which used a step down procedure to assess the efficacy of the darifenacin groups against placebo and against tolterodine. The ITT data set consists of all randomized subjects who have taken at least one dose of trial medication and who have a baseline efficacy assessment.

The primary endpoint is the average number of incontinent episodes per week, $F = 7 \times (T/D)$, where T = the total number of incontinent episodes recorded in the diary at the time point of interest and D = the number of days in the diary at the time point of interest. The secondary endpoint of interest to the medical reviewer is the average number of micturitions per day.

For Studies A1301001 and A1371002, the change from baseline in the average number of incontinent episodes per week is analyzed comparatively using a Wilcoxon (Mann-Whitney) rank sum test and last observation carried forward (LOCF) for missing Week 12 data. Differences between treatments are summarized by the Hodges-Lehmann point estimate with associated 97.5% confidence intervals for Study A1371001 and 95% confidence intervals for Study A1371002. The secondary endpoint of the change from baseline in the average number of micturitions per day is analyzed at week 12 in the same way.

For Studies A1371041 and A1371047, the change from baseline in the average number of incontinent episodes per week is analyzed comparatively using stratified Wilcoxon rank-sum test (van-Elteren's test) with locally best weights (per stratum-dose combination) and normal approximation and last observation carried forward (LOCF) for missing Week 12 data. The secondary endpoint of the change from baseline in the average number of micturitions per day is analyzed at week 12 in the same way. The data are stratified into three discrete groups defined by baseline severity for each endpoint.

For the primary endpoint, clinically meaningful strata are defined as follows - mild: <14 incontinence episodes per week, moderate: ≥14 and <21 incontinence episodes per week, and severe: ≥21 episodes per week. Strata for the secondary endpoint are determined using the 33$^{rd}$ and 66$^{th}$ percentiles of the baseline distribution of the endpoints as cut-points to create three baseline severity groups.

The estimated difference between darifenacin and placebo of the change from baseline at Week 12 is calculated using the Hodges-Lehmann point estimate, stratified by baseline severity using the same strata as the stratified Wilcoxon rank-sum test, along with corresponding 95% confidence intervals.

# 4 STUDY RESULTS

## 4.1 Study Enrollment, Randomization, Disposition, and Demographics

Table 4.1 presents the number of randomized subjects and the disposition of the subjects for all four studies. A greater percentage of darifenacin 15 mg subjects (7.8% to 17.9%) discontinued study than darifenacin 7.5 mg subjects (4.4% to 8.3%). The primary reasons for study discontinuation in all studies for all treatments are adverse events and other reasons not related to study treatment. Discontinuations due to adverse events ranged from 22.2% to 69.2% for all darifenacin doses and from 25% to 37.5% for placebo. Discontinuations due to other reasons not related to study treatment ranged from 15.4% to 55.6% for all darifenacin doses and from 36.4% to 58.3% for placebo.

**Table 4.1**
**Summary of Subject Disposition for**
**Studies A1371001, A1371002, A1371041, and A1371047**

| | Darifenacin 7.5 mg | Darifenacin 15 mg | Placebo |
|---|---|---|---|
| **Study A1371001 (U.S., Canada)** | | | |
| Randomized | | 112 | 115 |
| Treated (ITT) | | 112 | 115 |
| Completed* | | 92 (82.1) | 104 (90.4) |
| All Discontinuations* n (%) | | 20 (17.9) | 11 (9.6) |
| Discontinued Due to Adverse Events** n (%) | | *8 (40.0)* | *4 (36.4)* |
| Withdrew because of Insufficient Clinical Response | | *1 (5.0)* | *2 (18.2)* |
| Protocol Violations | | *1 (5.0)* | *1 (9.1)* |
| Other Reasons not Related to Study Treatment | | *10 (50.0)* | *4 (36.4)* |
| **Study A1371002 (Europe, Israel)** | | | |
| Randomized | 108 | 107 | 109 |
| Treated (ITT) | 108 | 107 | 109 |
| Completed | 99 (92.7) | 93 (86.9) | 101 (92.7) |
| All Discontinuations* n (%) | 9 (8.3) | 14 (13.1) | 8 (7.3) |
| Discontinued Due to Adverse Events** n (%) | *2 (22.2)* | *6 (42.8)* | *3 (37.5))* |
| Withdrew because of Insufficient Clinical Response | *1 (11.1)* | *2 (14.3)* | *2 (25.0)* |
| Protocol Violations | *1 (11.1)* | *2 (14.3)* | - |
| Other Reasons not Related to Study Treatment | *5 (55.6)* | *4 (28.6)* | *3 (37.5)* |
| **Study A1371041 (Europe, S. America, S. Africa, Israel)** | | | |
| Randomized | 229 | 115 | 164 |
| Treated (ITT) | 229 | 115 | 164 |
| Completed | 219 (95.6) | 106 (92.2) | 152 (92.7) |
| All Discontinuations* n (%) | 10 (4.4) | 9 (7.8) | 12 (7.3) |
| Discontinued Due to Adverse Events** n (%) | *3 (30.0)* | *3 (33.3)* | *3 (25.0)* |
| Withdrew because of Insufficient Clinical Response | *2 (20.0)* | *2 (22.2)* | *1 (8.3)* |
| Protocol Violations | *2 (20.0)* | *1 (11.1)* | *2 (16.7)* |
| Other Reasons not Related to Study Treatment | *3 (30.0)* | *3 (33.3)* | *6 (50.0)* |

| | Darifenacin 7.5 mg / 15 mg | |
|---|---|---|
| **Study A1371047 (U.S., Canada)** | | |
| Randomized | 269 | 129 |
| Treated (ITT) | 268 | 127 |
| Completed* | 242 (90.3) | 115 (90.6) |
| All Discontinuations* n (%) | 26 (9.7) | 12 (9.4) |
| Discontinued Due to Adverse Events** n (%) | *18 (69.2)* | *4 (33.3)* |
| Withdrew because of Insufficient Clinical Response | *2 (7.7)* | *1 (8.3)* |
| Protocol Violations | *2 (7.7)* | - |
| Other Reasons not Related to Study Treatment | *4 (15.4)* | *7 (58.3)* |

Source: Tables on pages 34 and 39 in Study A1371001 report / Tables on pages 36 and 40 in Study A1371002 report / Tables on pages 43 and 47 in Study A1371041 report / Tables on pages 41 and 46 in Study A1371047 report
Source: Table 3.1, Vol. 1.76, page 10-000138 and Table 3.2.2, Vol. 1.76, page 10-000141.
* With respect to number of treated subjects.
** With respect to number of all discontinuations.

Of the treated subjects, the mean age ranged from 55.1 to 60.3 years for all darifenacin doses and from 53.7 to 58.5 years for placebo. The majority of subjects are Caucasian (>90%) and female (85%) for all studies.

## 4.2 Sponsor's Efficacy Results and Conclusion

### *4.2.1 Frequency of Incontinence Episodes per Week*

Table 4.2 presents a summary of the average number of incontinent episodes per week at week 12 for all studies.

In Studies A1371002 and A1371041, a decrease in the average number of incontinent episodes per week at week 12 occurred in subjects treated with darifenacin 7.5 mg (-8.1 and -9 episodes, respectively) and 15 mg (-10.4 and -10.4 episodes, respectively) compared to placebo (-5.9 and -7.6 episodes, respectively) [all p<0.02].

In Study A1371047, a decrease in the average number of incontinent episodes per week at week 12 occurred in subjects starting at a dose of 7.5 mg and possibly upward dose adjusting to 15 mg after two weeks have (-8.2 episodes) compared to placebo (-6 episodes) [p=0.035]. Sixty percent (n=156) of subjects upward dose adjusted.

In Study A1371001, no significant decrease in the average number of incontinent episodes per week at week 12 occurred in subjects treated with darifenacin 15 mg (-11.4 episodes) compared to placebo (-9 episodes) [p>0.025].

**Table 4.2**
**Summary of the Average Number of Incontinent Episodes per Week at Week 12 for Studies A1371001, A1371002, A1371041, and A1371047**

| Average Number of Incontinent Episodes per Week Week 12 | Darifenacin 7.5 mg | Darifenacin 15 mg | Placebo |
|---|---|---|---|
| **Study A1371001 (U.S., Canada)** | | | |
| N | | 109 | 113 |
| Baseline Median (Median Change) | | 16.2 (-11.4) | 15.5 (-9.0) |
| Median Treatment Difference vs. Placebo (97.5% C.I.)[1] | | -2.4 (-5.2, -0.3) | |
| p-value for Treatment Difference[2] | | 0.049 | |
| **Study A1371002 (Europe, Israel)** | | | |
| N | 107 | 106 | 108 |
| Baseline Median (Median Change) | 14.0 (-8.1) | 17.3 (-10.4) | 16.1 (-5.9) |
| Median Treatment Difference vs. Placebo (95% C.I.)[1] | -2.8 (-4.8, -0.8) | -4.3 (-6.7, -2.2) | |
| p-value for Treatment Difference[2] | 0.007 | <0.001 | |
| **Study A1371041 (Europe, S. America, S. Africa, Israel)** | | | |
| N | 228 | 115 | 163 |
| Baseline Median (Median Change) | 16.3 (-9.0) | 17.0 (-10.4) | 16.6 (-7.6) |
| Median Treatment Difference vs. Placebo (95% C.I.)[1] | -1.5 (-3.0, -0.4) | -2.1 (-3.5, -0.3) | |
| p-value for Treatment Difference[2] | 0.010 | 0.017 | |
| | **Darifenacin 7.5 mg / 15 mg** | | |
| **Study A1371047 (U.S., Canada)** | | | |
| N | 261 | | 123 |
| Baseline Median (Median Change) | 16.0 (-8.2) | | 14.0 (-6.0) |
| Median Treatment Difference vs. Placebo (95% C.I.)[1] | -1.4 (-2.9, -0.0) | | |
| p-value for Treatment Difference[2] | 0.035 | | |

Source: Table on page 42 in Study 1001 report / Table on page 43 in Study 1002 report / Table on page 51 in Study 1041 report / Table on page 51 in Study 1047 report.
[1] Median treatment difference and confidence interval based on the Hodges-Lehmann estimate for treatment difference.
[2] p-value based on unstratified Wilcoxon rank-sum test for all studies except Studies A1371041 and A1371047, which used a stratified Wilcoxon rank-sum test adjusting for baseline disease severity.
* p-value statistically significant at the 0.05 significance level for Studies 1002 and 1041 and at the 0.025 significance level for Study 1001.

### *4.2.2 Frequency of Micturitions per Day*

Table 4.3 presents a summary of the average number of micturitions per day at week 12 for all studies.

In Studies A1371002 and A1371041, a decrease in the average number of micturitions per day at week 12 occurred in subjects treated with darifenacin 7.5 mg (-8.5 and –1.6 episodes, respectively) and 15 mg (-10.7 and –1.7 episodes, respectively) compared to placebo (-5.8 and –0.8 episodes, respectively) [all p<0.005].

In Study A1371047, a decrease in the average number of micturitions per day at week 12 occurred in subjects starting at a dose of 7.5 mg and possibly upward dose adjusting to 15 mg after two weeks have (-1.9 episodes) compared to placebo (-1 episodes) [p=0.001]. Sixty percent (n=156) of subjects upward dose adjusted.

In Study A1371001, no significant decrease in the average number of micturitions per day at week 12 occurred in subjects treated with darifenacin 15 mg (-1.9 episodes) compared to placebo (-1.2 episodes) [p=0.076].

**Table 4.3**
**Summary of the Average Number of Micturitions per Day at Week 12 for Studies A1371001, A1371002, A1371041, and A1371047**

| Average Number of Micturitions per Day Week 12 | Darifenacin 7.5 mg | Darifenacin 15 mg | Placebo |
|---|---|---|---|
| **Study A1371001 (U.S., Canada)** | | | |
| N | | 109 | 114 |
| Baseline Median (Median Change) | | 10.5 (-1.9) | 10.4 (-1.2) |
| Median Treatment Difference vs. Placebo (97.5% C.I.)[1] | | -0.5 (-1.1, 0.1) | |
| p-value for Treatment Difference[2] | | 0.076 | |
| **Study A1371002 (Europe, Israel)** | | | |
| N | 96 | 94 | 101 |
| Baseline Median (Median Change) | 14.0 (-8.5) | 17.8 (-10.7) | 15.6 (-5.8) |
| Median Treatment Difference vs. Placebo (95% C.I.)[1] | -3.0 (-5.1, -1.0) | -4.5 (-7.0, -2.4) | |
| p-value for Treatment Difference[2] | 0.004 | <0.001 | |
| **Study A1371041 (Europe, S. America, S. Africa, Israel)** | | | |
| N | 228 | 115 | 163 |
| Baseline Median (Median Change) | 10.1 (-1.6) | 10.1 (-1.7) | 10.1 (-0.8) |
| Median Treatment Difference vs. Placebo (95% C.I.)[1] | -0.8 (-1.2, -0.4) | -0.9 (-1.4, -0.4) | |
| p-value for Treatment Difference[2] | <0.001 | <0.001 | |
| | **Darifenacin 7.5 mg / 15 mg** | | |
| **Study A1371047 (U.S., Canada)** | | | |
| N | 261 | | 123 |
| Baseline Median (Median Change) | 9.9 (-1.9) | | 10.4 (-1.0) |
| Median Treatment Difference vs. Placebo (95% C.I.)[1] | -0.8 (-1.3, -0.3) | | |
| p-value for Treatment Difference[2] | 0.001 | | |

Source: Table on page 45 in Study 1001 report / Table on page 45 in Study 1002 report / Table on page 54 in Study 1041 report / Table on page 53 in Study 1047 report.
[1] Median treatment difference and confidence interval based on the Hodges-Lehmann estimate for treatment difference.
[2] p-value based on Wilcoxon rank-sum test for all studies except Studies A1371041 and A1371047, which used a stratified Wilcoxon rank-sum test adjusting for baseline disease severity.

### *4.2.3 Sponsor's Conclusion*

Studies A1371002 and A1371041 demonstrate statistically significant reductions in the average number of incontinent episodes per week and reductions in the average number of micturitions per day in subjects taking darifenacin 7.5 mg and 15 mg doses compared to subjects taking placebo (all p<0.01).

Study A1371047 demonstrate statistically significant reductions in the average number of incontinent episodes per week and in the average number of micturitions per day in subjects taking darifenacin 7.5 mg and possibly upward dose adjusting to 15 mg after two weeks compared to subjects taking placebo (all p=0.001).

Study A1371001 does not demonstrate statistically significant reductions in the average number of incontinent episodes per week and reductions in the average number of micturitions per day in subjects taking darifenacin 15 mg compared to subjects taking placebo.

## 4.3 Reviewer's Efficacy Analysis

Although the final statistical analysis plan for the primary and secondary efficacy variables in Studies A1371041 and A1371047 were not submitted to the Agency, the revised statistical analysis plans were approved and signed off by the sponsor before the data was unblinded (see Table 4.4). The original analyses called for a Wilcoxon rank-sum test to be used, the revised analyses called for a stratified Wilcoxon rank-sum test(van Elteren's test) with locally best weights and normal approximation to be used. The revised analyses are acceptable to this reviewer. Thus, I concur with the sponsor's analyses for all studies.

**Table 4.4**
**Dates of Final Statistical Analysis Plan Approval and Database Unblind for Studies A1371041 and A1371047**

| | Date |
|---|---|
| **Study A1371041 (U.S., Canada)** | |
| Final Statistical Analysis Plan Approved | August 29 – Sept. 5, 2002 |
| Database Unblinded | October 2, 2002 |
| **Study A1371047 (U.S., Canada)** | |
| Final Statistical Analysis Plan Approved | November 29, 2002 |
| Database Unblinded | February 5, 2003 |

Source: August 19 and August 21, 2003 submissions

I concur with the sponsor's conclusions for Studies A1371002, A1371041, and A1371047 but not with the conclusions for Study A1371001. For that study, the sponsor used two separate step down procedures for hypothesis testing, one to compare all darifenacin doses to placebo and one to compare all darifenacin doses to tolterodine, each at the 0.025 significance level. Since the sponsor does not seek claims involving tolterodine, I am inclined to view Study A1371001 as a placebo controlled only study. Thus, the significance level for the single step down procedure to compare all darifenacin doses to placebo should be viewed as having a significance level of 0.05. Given this view, a marginal decrease in the average number of incontinent episodes per week at week 12 occurs in subjects taking darifenacin 15 mg (-11.4 episodes) compared to subjects taking placebo (-9.0 episodes) [p=0.049]. This decrease is marginal because the p-value is close to the significance level of 0.05. On the other hand, no decrease in the average number of micturitions per day occurs in subjects taking darifenacin 15 mg compared to subjects taking placebo (p=0.076).

## 4.4 Conclusions

From a statistical standpoint, the sponsor has provided the following:

- Two foreign studies that are well controlled and adequate for demonstrating the effectiveness of darifenacin 7.5 mg and 15 mg in decreasing the number of incontinent episodes per week and number of micturitions per day.
- One U.S. study that is well controlled and adequate for demonstrating the effectiveness of darifenacin 15 mg in decreasing the number of incontinent episodes per week.
- One supportive U.S. study that is well controlled and adequate for demonstrating the effectiveness of taking darifenacin 7.5 mg and possibly upward dose adjusting to 15 mg after two weeks in decreasing the number of incontinent episodes per week and number of micturitions per day.

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/s/

Sonia Castillo
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Mike Welch
8/28/03 04:22:50 PM
BIOMETRICS
Concur with review.

S. Edward Nevius
9/4/03 01:47:12 PM
BIOMETRICS
Concur with review.

**Screening of New NDA for Statistical Filing**
**Division of Biometrics II**

**NDA #:** 21-513

**Applicant:** Pfizer Global Research and Development

**Trade/Generic Name:** ENABLEX (darifenacin hydrobromide) Extended Release Tablets

**Indication:** Treatment of overactive bladder

**Date of Submission:** December 3, 2002

**Filing Date:** January 17, 2003

**User Fee Goal Date:** October 3, 2003

**Project Manager:** King

**Medical Reviewer:** Li

**Comments:** This NDA is fileable from a statistical perspective.

| Checklist for Fileability | Remarks (NA if not applicable) |
|---|---|
| Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc. | OK |
| Original protocols & subsequent amendments submitted | OK |
| Study designs utilized appropriate for the indications requested | OK |
| Endpoints and methods of analysis spelled out in the protocols | OK |
| Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made | NA |
| Appropriate references included for novel statistical methodology (if present) | NA |
| Data and reports from primary studies submitted to EDR according to Guidances | EDR data present |
| Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated | OK |

Reviewer: S. Castillo

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/s/

Sonia Castillo
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| | |
|---|---|
| NDA: 21-513 | Submission Date: 06/23/2004 |
| | PDUFA Goal date: 12/23/2004 |
| Brand Name | Enablex® |
| Generic Name | Darifenacin |
| Reviewer | Sandhya Apparaju, Ph.D. |
| Team Leader | Ameeta Parekh, Ph.D. |
| OCPB Division | DPE II |
| Clinical division | Division of Reproductive & Urology Drug Products |
| Sponsor | Novartis Pharmaceuticals Corporation |
| Relevant IND(s) | 45,457 |
| Submission Type; Code | Complete response to AE letter; 1S |
| Formulation; Strength(s) | 7.5 mg & 15 mg Extended Release Tablets |
| Indication | Treatment of overactive bladder |

OCPB briefing: Optional inter-divisional briefing was held on 11/04/2004 from 11.30 AM to 12.30 PM in CDER PKLN 13B45 Conference Room; Attendees: Drs' Henry Malinowsky, John Hunt, Arzu Selen, Suresh Kaul, Mark Hirsch, Julie Beitz, Hae Yong Ahn, Dhruba Chatterjee, Stephan Ortiz, Leslie Kenna, Myong Jin Kim, Ameeta Parekh and Sandhya Apparaju.

**Background:** Study DAR328A 2302 was conducted by Novartis pharmaceutical corporation to evaluate the QT prolongation potential of darifenacin hydrobromide. Darifenacin (Enablex®) is a selective muscarinic M3 receptor antagonist indicated for the treatment of overactive bladder. The proposed starting doses are 7.5 mg oral once daily and 15 mg oral once daily without regard to food intake. The original NDA 21,513 received an approvable action from the division of reproductive and urology drug products on October 2nd, 2003. The absence of a definitive QT study was one of the deficiencies cited for the approvable action.

As per Dr. Myong-Jin Kim's CPB review of the original submission, in general there were no apparent QT signals at steady state following administration of darifenacin 3.75 mg – 60 mg (a pooled analysis of four controlled studies). Supra-therapeutic plasma concentrations (~ 23 fold increase in Cmax compared to Cmax at 15 mg dose) were achieved when 30 mg darifenacin was co-administered with 400 mg ketoconazole for 6 days (Study 1007). At these supra-therapeutic concentrations of darifenacin, a mean change of 12 msec from baseline QTcF (range: -[redacted] msec) was observed. The sponsor noted that the mean increase of 10-12 msec in QTcF is not clinically meaningful since ketoconazole itself has been known to prolong QT interval. Although sponsor's retrospective analysis of clinical trial database and dose-tolerability study showed no apparent QT signals, due to the absence of a positive control arm, adequate data on placebo group, and limited number of QT measurements, the NDA was judged to be deficient in sufficient information to address the issue of darifenacin's potential effect on QT prolongation. In their complete response (06/23/04) to the October 2nd action letter, the sponsor submitted the results of a completed thorough QT study employing multiple

doses of therapeutic (15 mg) and supratherapeutic (75 mg) doses of darifenacin. The study also included a subset of CYP2D6 poor metabolizers to achieve maximum exposure potential.

**QT study review (Study DAR328A 2302; NDA 21-513; Darifenacin hydrobromide)**

## METHODS

**Design and treatments:** DAR328A 2302 was a single center, double-blind, placebo and active controlled, randomized, parallel group, multiple dose trial. Subjects (n = 179; 44-45/group) were healthy male (44 %) and female (56 %) volunteers between ages 18-65 years. Approximately 43% of the study population was within the 45-65 years age range to represent the population with OAB. Subjects were enrolled according to their CYP2D6 metabolic status as follows: Poor metabolizers (18 %) and Extensive metabolizers (82 %). Subjects were randomly assigned to one of the following once daily (QD) treatments for 6 days (steady state):

| Group | Treatment |
|---|---|
| A | Darifenacin 15 mg qd |
| B | Darifenacin 75 mg qd |
| C | Avelox ®400 mg qd |
| D | Placebo qd |

While darifenacin 15 mg represents the therapeutic dose, the 75 mg dose was expected to attain plasma concentrations and exposure which are comparable to those observed in the CYP2D6 poor metabolizers (PMs) that received 15 mg darifenacin in combination with ketoconazole. Subjects also received one day of placebo dosing (day -1) to obtain baseline ECGs over 24 hours. Treatments were administered with water after at least 10 hours of overnight fasting. On days -1 and 6 subjects also fasted for 4 hours after dosing.

**Digital ECG evaluations:** Standard 12-lead ECGs were performed on Days –1 and 6 at pre dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 24 h post dose to measure cardiac conduction intervals. At a pre-specified ECG evaluation time-point, 3 ECGs (each ECG with a 3 beat reading) were extracted in 20 second windows (e.g., 0-20, 21-40 sec and 41-60 sec). Mean interval values are presented for each ECG evaluation time-point.

QT correction for RR dependency was primarily based on Fridericia's method although Bazette's and individual correction methods were also reported.

Fridericia's correction method: $QTcF = QT\,RR^{-1/3}$

Bazett's correction method: $QTcB = QT.\,RR^{-1/2}$,

Individual correction method: $QTcI = QT.\,RR^{b}$, where "b" is the estimated slope (or correction factor) of model: Log(QT) = a + b*Log (RR). The individual correction factors were derived using baseline QT-RR data from each subject.

**Pharmacokinetic evaluations:** A 5 mL blood sample was collected on Days 1-Day 5 for trough measurements to assess steady-state achievement for darifenacin. On Day 6 blood samples (5 mL) were collected at predose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 24 h post dose to match with ECG assessments. Tmax, Cmax and AUC (0-24) were derived for darifenacin and Avelox employing non-compartmental methods.

**Determination of CYP2D6 metabolic status**: The rationale for inclusion of CYP2D6 PMs was to ensure maximum darifenacin exposure. While 32 subjects were phenotypically identified as CYP2D6 poor metabolizers, only 18 of these were

genotypically confirmed. Amendment 2 (16-January-2004) to the protocol allowed for the inclusion of subjects based on CYP2D6 phenotype alone instead of phenotype and genotype, due to the low yield of genotypically identified CYP2D6 PMs. Therefore, a final criterion for CYP2D6 metabolic status was based on the metabolism of dextromethorphan.

**Phenotyping**: Determination of CYP2D6 phenotype was based on the metabolic ratio (MR) of dextromethorphan / dextrorphan in plasma. Subjects received a single 60 mg dose of dextromethorphan ( [redacted] ) and plasma samples were collected 2 hrs post ingestion for analysis of dextromethorphan and dextrorphan concentrations. If the dextromethorphan 2 hour post-dose MR was greater than 0.30 subjects were considered to have a deficiency in CYP2D6 expression i.e. poor metabolizers (PM). If the MR was less than 0.30 subjects were categorized as extensive metabolizers (EM). During this visit, blood samples were also collected for CYP2D6 genotype determinations.

**Genotyping**: Individuals possessing two non-functional alleles (*3, *4, *5) were characterized as poor metabolizers (PMs). Individuals with at least one wild-type *(wt)* allele were labeled as extensive metabolizers (EMs). Individuals with at least one *10 or *17 alleles (reduced function) were characterized as intermediate metabolizers. However, for the final analysis all IMs were categorized as EMs.

**Reviewer's comments:**

- Patients who were genotypically identified as PMs or EMs were also confirmed by phenotype.
- 14 patients (13 of these were African-Americans) who could not be confirmed as PMs by genotype were included in the final analysis as PMs based on phenotype alone. Darifenacin exposures were comparable among those patients identified by both genotype as well as phenotype and those identified by phenotype alone.

## RESULTS

**Darifenacin pharmacokinetics:** Darifenacin is metabolized by CYP3A4 and CYP2D6. Therefore supra-therapeutic exposure potential exists when these pathways of metabolism are hindered. In the October 2003 approvable action letter, the sponsor was advised to conduct a thorough QT study employing a dose of darifenacin that is sufficient to produce plasma concentrations that meet or exceed plasma concentrations that might be attained when a CYP2D6 poor metabolizer (PM) is administered darifenacin 15 mg and CYP3A4 inhibitor, ketoconazole (worst-case scenario). To accomplish this objective, the sponsor employed in addition to the highest therapeutic dose (15 mg), a supra-therapeutic dose of 75 mg that resulted in the desired supra-therapeutic exposure as shown below in Table 1 and Figure 1. The range of darifenacin systemic exposures achieved in the QT study following daily dosing with 15 mg and 75 mg doses encompassed the therapeutic as well as supra-therapeutic concentrations described above and understanding the QT prolongation potential in the presence of these clinically relevant exposures will be a valuable means to assess the cardiac risk potential of darifenacin. In addition, it appears that the Cmax and AUC values for the 15 mg therapeutic dose in the PMs and EMs were comparable between the original NDA study (1035) and the QT study (2302), suggesting that the CYP2D6 classification was comparable in both cases although the original studies limited genotyping to *3 and *4 alleles, while the QT study genotyping included *5, *10 and *17 alleles also.

Table 1: Systemic exposure parameters (Cmax and AUC) of darifenacin among CYP2D6 EMs and PMs following administration of various doses (7.5 – 75 mg) in the presence and absence of potent CYP3A4 inhibitor ketoconazole (400 mg). The shaded areas represent the targeted and the observed supra-therapeutic darifenacin exposures, respectively. The results of the QT study are shown in bold and encompass clinically possible therapeutic and supratherapeutic exposures of darifenacin.

| | Cmax (ng/ml) | | AUC (ng.h/ml) | |
|---|---|---|---|---|
| Dose (n = EMs/PMs) | EMs | PMs | EMs | PMs |
| 7.5 mg (n = 9/1) | 1.91 | 5.85 | 25.8 | 79.9 |
| 7.5 mg +ketoconazole (n = 9/1) | 11.2 | 55.4 | 143 | 939 |
| 15 mg (n = 3/1) | 6.77 | 6.17 | 95.7 | 87.7 |
| [redacted] | | | | |
| 30 mg (n = 185/40) | 13.73 | 20.59 | 207.2 | 327.6 |
| 45 mg (n = 22/1) | 25.25 | 26.2 | 386.6 | 449.6 |
| 60 mg (n = 30/5) | 47.52 | 64.54 | 775.3 | 964.3 |
| **15 mg QT study (n=39/7)** | **5.6** | **10.5** | **92.3** | **157.3** |
| [redacted] | | | | |

*Sources: Study 2302 (Thorough QT study) & Dr. Kim's CPB review of the original submission (pages 44 & 48-50; includes results from Study 1035 (the effects of ketoconazole on the PK of darifenacin at steady state) & pooled PK data from various studies)*

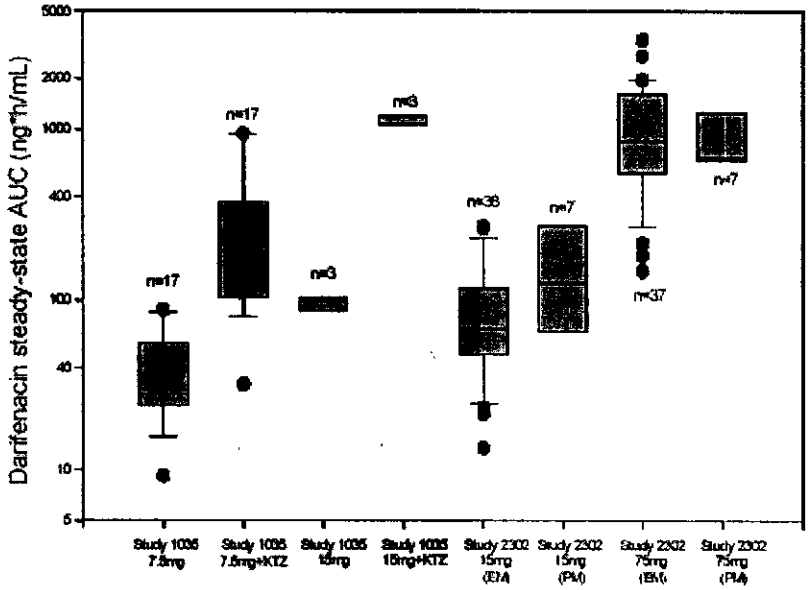


Figure 1: Darifenacin systemic exposure following the administration of 7.5 mg and 15 mg doses with ketoconazole in Study 1035 and 15 mg & 75 mg doses in Study 2302 (QT study). The exposure achieved with 75 mg darifenacin dose in study 2302 (QT study) was comparable to the highest exposure observed following administration of 15 mg darifenacin with ketoconazole.

Steady-state darifenacin concentrations were achieved during the 6-day treatment with 15 mg and 75 mg darifenacin. Trough values were consistently higher in the PMs compared to EMs in both the treatment arms. For the 15 mg dose group, the mean trough values ranged from 2.45 to 3.16 ng/mL for EMs and 4.25 to 5.88 ng/mL for PMs. For the 75-mg dose group, the trough concentrations appeared to have reached a plateau after Day 3 and the trough concentrations ranged from 25.2 to 30.58 ng/mL for EMs and 30.9 to 45.1 ng/mL for PMs, respectively.

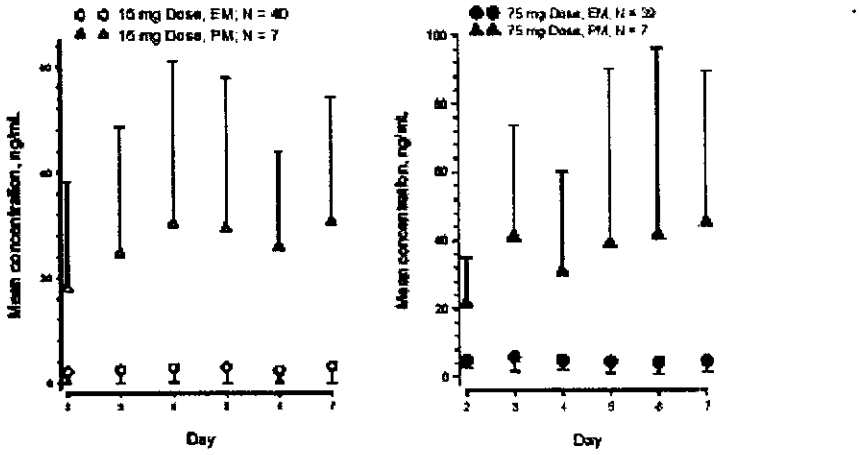


Figure 2: Mean trough concentrations of darifenacin following administration of 15 mg and 75 mg of darifenacin in fasted healthy subjects for extensive metabolizer (EM) and poor metabolizer (PM).

Table 2: The day 6 (steady-state) pharmacokinetic parameters following administration of 15 mg and 75 mg darifenacin ER tablets.

| | 15 mg | | | | 75 mg | | | |
|---|---|---|---|---|---|---|---|---|
| | EM (N=38) | | PM (N=7) | | EM (N=37) | | PM (N=7) | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Cmax, ng/mL | 5.6 | 3.8 | 10.5 | 6.5 | 65.0 | 47.0 | 68.5 | 65.7 |
| Tmax, h* | 8 | 0-24 | 7 | 5-12 | 7 | 3-14 | 6 | 4-24 |
| AUC(0-24) ng-h/mL | 92.3 | 68.9 | 157.3 | 104.4 | 1069.2 | 737.6 | 1219.3 | 1245.7 |

* Expressed as median and range

**Effect of CYP2D6 metabolic status on darifenacin PK:** The impact of CYP2D6 metabolic status on darifenacin exposure was evident from the PK parameters. The CYP2D6 poor metabolizer subgroup exhibited high exposure with respect to both Cmax and AUC. The darifenacin AUC ratio (PM:EM) was 1.7 and 1.14 for 15 mg and 75 mg doses and the Cmax ratio (PM:EM) was 1.87 and 1.05 for 15 mg and 75 mg doses, respectively. The contribution of CYP2D6 to darifenacin metabolism appears to have reduced at higher doses as apparent from the diminished influence of CYP2D6 metabolic status on the AUC & Cmax at 75 mg dose. This pattern was also noted in several studies reviewed by Dr. Kim in the original submission.

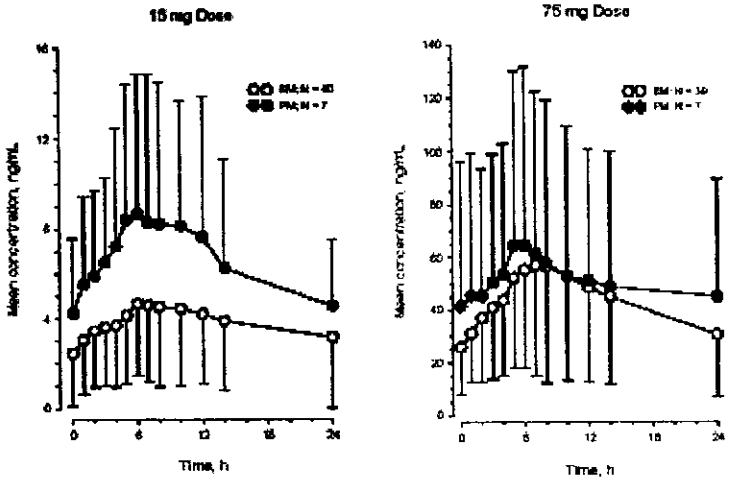


Figure 3: Mean darifenacin plasma concentration-time profiles following administration of 15 mg and 75 mg darifenacin in male and female healthy subjects who are extensive (EM) or poor metabolizers (PM).

**Effect of gender on darifenacin PK:** Females demonstrated consistently higher darifenacin exposure compared to males and the differences in exposure were apparent following both doses of darifenacin (15 mg and 75 mg). Both genders showed greater mean values for Cmax and AUC in the PM group than in the EM group. The variability in darifenacin PK was high, especially in the PM subgroup (small number of subjects), but nevertheless the influence of gender on darifenacin pharmacokinetics was obvious at both doses of darifenacin. Following treatment with 15 mg darifenacin, extensive metabolizer (EM) females had 98 % higher Cmax and 110 % higher AUC compared to males. Following treatment with 75 mg darifenacin, EM females had ~ 75 % higher Cmax and AUC compared to males. On average (both PMs and EMs), female subjects in the thorough QT study had approximately 57-79 % higher Cmax values and 61-73 % higher AUCs compared to male subjects.

Table 3: Darifenacin pharmacokinetics in males and females.

| | 15 mg Darifenacin | | | |
|---|---|---|---|---|
| | Male (n = 20) | Female (n = 20) | Male (n = 2) | Female (n = 5) |
| Cmax PM:EM | N/A | N/A | 2.19 | 1.53 |
| AUC PM:EM | N/A | N/A | 2.11 | 1.37 |
| | 75 mg Darifenacin | | | |
| | Male (n = 15) | Female (n = 24) | Male (n = 3) | Female (n = 4) |
| Cmax PM:EM | N/A | N/A | 1.10 | 1.11 |
| AUC PM:EM | N/A | N/A | 1.21 | 1.19 |

**Effect of age on darifenacin PK:** The study consisted of subjects classified into two different age groups: Young; 18-44 years and elderly; 45-65 years. Following darifenacin 15 mg dosing, the Cmax and AUC in the young (3.55 ng/ml and 54.28 ng.h/ml) were comparable to the Cmax and AUC values observed in the elderly subpopulation (3.99 ng/ml and 64.55 ng.h/ml, respectively). Following darifenacin 75 mg dosing, the observed Cmax and AUC values in the young subpopulation (41.64 ng/ml and 727.7 ng.h/ml, respectively) were comparable to the observed values in the elderly subgroup (Cmax and AUC of 43.29 ng/ml and 703.2 ng.h/ml, respectively). The influence of age on darifenacin pharmacokinetics was not evident within the age groups studied.

**QT correction**

The need for QT correction for RR (or heart rate, HR) dependency is evident from the observed trend for increasing QT values with increasing RR (Figure 4). This relationship is normal physiological association between QT and RR. The Bazette's method resulted in over correction particularly for QT with lower RR values or higher HR, due to high proportion of subjects with higher HR relative to 60 bpm in this study. As shown in figures 5 and 6, both QTcF and QTcI provided adequate correction, i.e., the change in QTcF or QTcI are independent of RR or HR. The sponsor employs Fridericia's as the primary correction method in this analysis. When mean heart rate changes over baseline values were computed over a 24 hour period on day 6, the 15mg and 75 mg doses of darifenacin resulted in mean increases of 8.4 ± 2.9 and 6.6 ± 2.8 bpm, while placebo and Avelox demonstrated heart rate changes of 5.3 ± 2.4 and 3.3 ± 1.0 bpm respectively, on day 6.

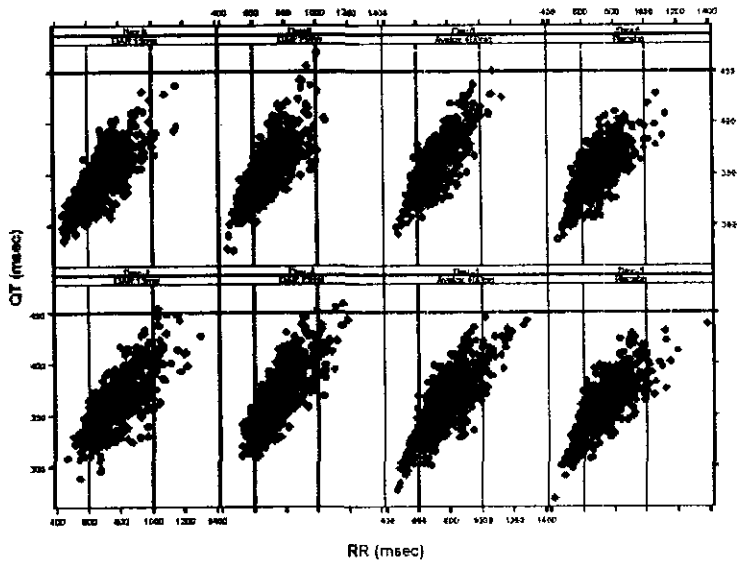


Figure 4: RR versus uncorrected QT intervals in all four treatment groups (from left to right: DAR 15mg, DAR 75 mg, Avelox 400 mg and Placebo) on day -1 (bottom plots) and day 6 (top plots).

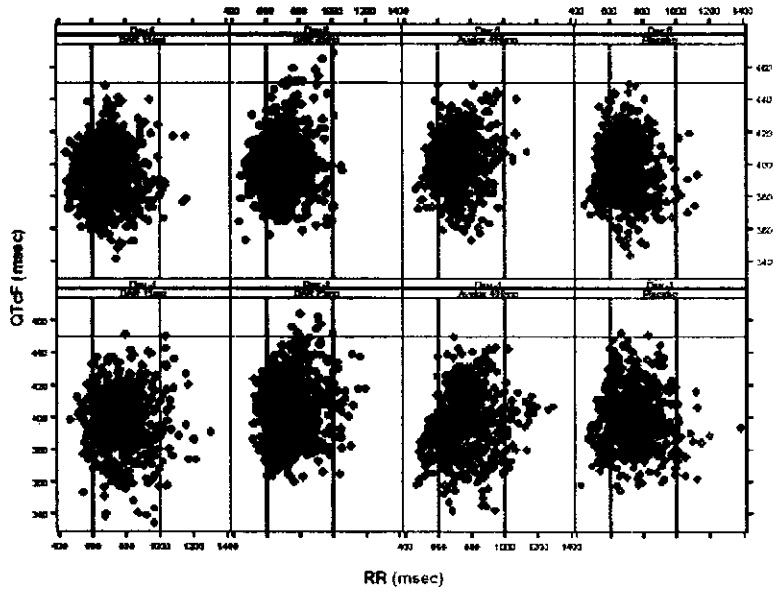


Figure 5: RR versus QTcF (Fridericia's correction) relationship for all four treatments (from left to right: DAR 15mg, DAR 75 mg, Avelox 400 mg and Placebo) at baseline (day -1; bottom panels) and steady-state (day 6; top panels).

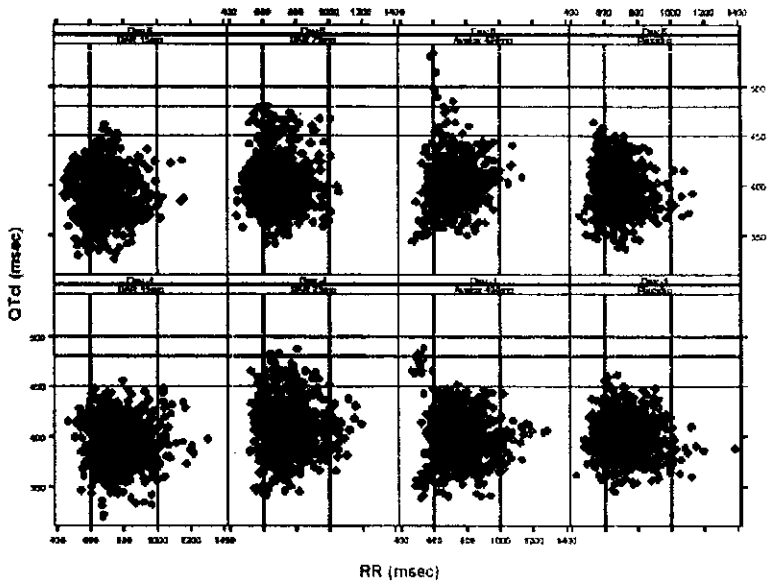


Figure 6: RR versus QTcI (individual correction) relationship for all four treatment groups (from left to right: DAR 15mg, DAR 75 mg, Avelox 400 mg and Placebo) at baseline (day -1) and steady-state (day 6).

## Effect on QT prolongation: central tendency analyses

**Change in QT/QTc at pharmacokinetic Tmax:**

- Avelox 400 mg (positive control) treatment resulted in a significant QTcF prolongation of 10.3 ms ($p < 0.001$) from baseline at the pharmacokinetic Tmax, thus confirming the study sensitivity.

- At peak darifenacin exposure (i.e. at Tmax) following 15 mg or 75 mg daily dosing for 6 days, there was no evidence of QT/QTc prolongation. Post-dose (day 6) QTc intervals in darifenacin treatment groups were in fact lower compared to baseline QTc intervals. The sponsor attributes this behavior in the darifenacin and placebo groups to a "regression towards mean" effect.
- Lack of evidence of QT prolongation with darifenacin was observed with absolute values (uncorrected QT) as well as corrected intervals (QTcB, QTcF or QTcI).

Table 4: Summary of QT/QTc changes at PK_Tmax (day 6). Baseline values used for comparison are time-averaged intervals over 24 hours on day -1 (placebo).

| PD Endpoint | Conduct interval (ms) | Treatment | Baseline N | Baseline Mean(ms) | Baseline STD | Change from baseline N | Change from baseline Mean(ms) | Change from baseline STD | Change from baseline p-value | 90% CI for Mean |
|---|---|---|---|---|---|---|---|---|---|---|
| E_tmax | QT | DAR328 15mg | 46 | 362.3 | 19.5 | 46 | -15.6 | 18.0 | <0.001 | ( -21, -10) |
| | | DAR328 75mg | 43 | 367.8 | 23.6 | 43 | -21.8 | 25.2 | <0.001 | ( -30, -14) |
| | | Avelox 400mg | 46 | 360.3 | 25.8 | 46 | 10.2 | 22.6 | 0.004 | ( 3.5, 16.9) |
| | | Placebo | 44 | 360.5 | 19.4 | 44 | -10.3 | 15.2 | <0.001 | ( -15, -5.7) |
| | QTcF | DAR328 15mg | 46 | 397.5 | 16.8 | 46 | -2.6 | 12.3 | 0.160 | (-6.3, 1.1) |
| | | DAR328 75mg | 43 | 405.2 | 17.6 | 43 | -6.3 | 15.7 | 0.012 | ( -11, -1.5) |
| | | Avelox 400mg | 46 | 396.0 | 17.1 | 46 | 10.3 | 15.1 | <0.001 | ( 5.8, 14.8) |
| | | Placebo | 44 | 399.8 | 15.3 | 44 | -2.6 | 9.2 | 0.065 | (-5.4, 0.2) |
| | QTcB | DAR328 15mg | 46 | 416.9 | 20.7 | 46 | -5.1 | 13.3 | 0.012 | ( 1.2, 9.1) |
| | | DAR328 75mg | 43 | 425.8 | 19.2 | 43 | 2.8 | 15.4 | 0.233 | (-1.9, 7.6) |
| | | Avelox 400mg | 46 | 415.8 | 18.0 | 46 | 10.2 | 17.2 | <0.001 | ( 5.1, 15.3) |
| | | Placebo | 44 | 421.6 | 19.4 | 44 | 1.9 | 10.5 | 0.271 | (-1.4, 5.0) |
| | QTcI | DAR328 15mg | 46 | 395.9 | 22.5 | 46 | -3.6 | 12.7 | 0.064 | (-7.3, 0.2) |
| | | DAR328 75mg | 43 | 407.1 | 26.2 | 43 | -6.6 | 16.2 | 0.011 | ( -12, -1.6) |
| | | Avelox 400mg | 46 | 398.2 | 24.4 | 46 | 8.2 | 14.5 | <0.001 | ( 3.9, 12.5) |
| | | Placebo | 44 | 400.3 | 19.8 | 44 | -2.7 | 10.1 | 0.080 | (-5.8, 0.3) |

- After subtracting the placebo response, the changes in QTcF from time-averaged baseline were -0.4 msec (90 %CI: -4.1, 3.2) and -2.2 msec (90 %CI: -6.6, 3.2) for 15 mg and 75 mg doses of darifenacin and 11.6 msec (90 %CI: 7.6, 15.5) for Avelox 400mg.
- A more pronounced decrease in QTc from baseline with darifenacin supra-therapeutic (75 mg) dose (ΔQTcF -6.3 msec) compared to placebo or darifenacin 15 mg (ΔQTcF -2.6 msec) could be due to the higher pre-dose baseline values (405.2 msec) in this group compared to other three treatment arms as shown below:

Table 5: Comparison of absolute QTcF intervals at baseline (day -1) and steady-state (day 6).

| | QTcF (msec) Mean ± SD (95 % CI) | |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| **DAR 15 mg** | 397.5 ± 16.8 (393, 402) | 394.9 ± 12.3 (390, 400) |
| [redacted] | [redacted] | [redacted] |
| **Placebo** | 399.8 ± 17.1 (395, 404) | 397.2 ± 15.1 (393, 402) |
| [redacted] | [redacted] | [redacted] |

- Non-baseline subtracted QTcF intervals at steady state were comparable among the placebo and the two darifenacin treatment groups, suggesting that the effect of darifenacin on QT interval was not different from that of placebo.
- The differences in baseline QTcF intervals can be seen in the graph below on the left side. DAR 75 mg (◊) had a higher baseline compared to the other treatment groups. At steady state (right panel), only Avelox (Δ) shows markedly higher QTcF intervals compared to baseline, while placebo and the two darifenacin treatments result in QTcF intervals that are slightly lower than at baseline.

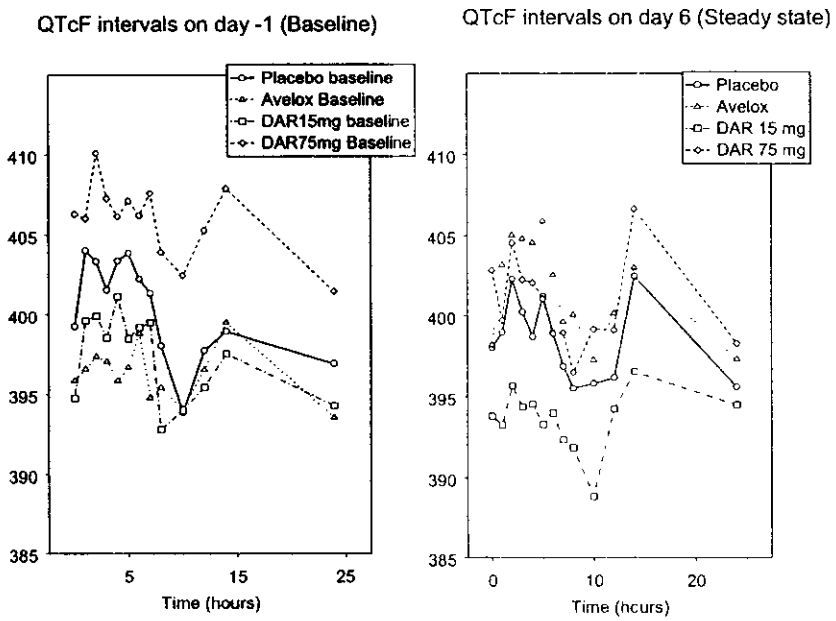


Figure 7: QTcF intervals at baseline (left) and at steady state (right) following treatment with placebo (o), darifenacin 15 mg ( ), darifenacin 75 mg ( ◊) and Avelox 400 mg (Δ).

- Additionally, the sponsor submitted analysis comparing the QTc intervals at PK_Tmax on day 6, with the corresponding time-matched baseline QTc intervals. As seen in table 6 below, this additional analysis yielded results very similar to the previous comparison of E_Tmax to time-averaged baseline data. The conclusion derived essentially remains unchanged i.e. at the highest exposure (i.e. at Tmax) darifenacin treatments did not result in QTc prolongation relative to either time-matched or time-averaged baseline values.

Table 6: **Summary of QT/QTc changes at PK_Tmax** (day 6). Baseline values used for comparison are the corresponding time-matched intervals on day -1.

**Table 1.1 Summary of change from baseline for PD endpoints of cardiac conduct intervals**
**Use time-matched baseline**

| PD Endpoint | Conduct interval (ms) | Treatment | Baseline N | Baseline Mean(ms) | Baseline STD | Change from baseline N | Change from baseline Mean(ms) | Change from baseline STD | Change from baseline p-value | 90% CI for Change |
|---|---|---|---|---|---|---|---|---|---|---|
| E_tmax | QT | DAR328 15mg | 46 | 358.6 | 25.6 | 46 | -11.9 | 21.6 | <0.001 | ( -18, -5.5) |
| | | DAR328 75mg | 43 | 363.2 | 24.8 | 43 | -17.1 | 26.1 | <0.001 | ( -25, -9.1) |
| | | Avelox 400mg | 46 | 371.8 | 32.1 | 46 | -1.3 | 28.4 | 0.759 | ( -9.7, 7.1) |
| | | Placebo | 44 | 360.5 | 19.4 | 44 | -10.3 | 15.2 | <0.001 | ( -15, 5.7) |
| | QTcF | DAR328 15mg | 46 | 397.4 | 17.9 | 46 | -2.5 | 14.9 | 0.260 | (-6.5, 1.5) |
| | | DAR328 75mg | 43 | 404.3 | 17.6 | 43 | -9.4 | 16.4 | 0.035 | ( -18, -0.4) |
| | | Avelox 400mg | 46 | 397.3 | 18.0 | 46 | 9.0 | 15.9 | <0.001 | ( 4.3, 13.7) |
| | | Placebo | 44 | 399.8 | 15.3 | 44 | -2.6 | 9.2 | 0.065 | (-5.4, 0.2) |
| | QTcB | DAR328 15mg | 46 | 418.8 | 22.2 | 46 | 3.2 | 16.2 | 0.193 | (-1.8, 8.0) |
| | | DAR328 75mg | 43 | 427.1 | 20.7 | 43 | 1.5 | 17.9 | 0.577 | (-4.0, 7.0) |
| | | Avelox 400mg | 46 | 411.3 | 19.9 | 46 | 14.6 | 19.4 | <0.001 | ( 8.9, 20.4) |
| | | Placebo | 44 | 421.6 | 19.4 | 44 | 1.8 | 10.5 | 0.271 | (-1.4, 5.0) |
| | QTcI | DAR328 15mg | 46 | 395.1 | 24.1 | 46 | -2.7 | 15.1 | 0.235 | (-7.2, 1.8) |
| | | DAR328 75mg | 43 | 406.9 | 25.8 | 43 | -6.4 | 16.3 | 0.014 | ( -11, -1.4) |
| | | Avelox 400mg | 46 | 399.6 | 24.8 | 46 | 6.8 | 14.9 | 0.003 | ( 2.4, 11.3) |
| | | Placebo | 44 | 400.3 | 19.9 | 44 | -2.7 | 10.1 | 0.080 | (-5.8, 0.3) |

- After subtracting the placebo response, the changes in QTcF from time-matched baseline values were -0.6 msec (90 %CI: -4.6, 3.5) and -1.5 msec (90 %CI: -6.0, 3.0) for 15 and 75 mg darifenacin and 10.7 msec (90 %CI: 6.7, 14.7) for Avelox.

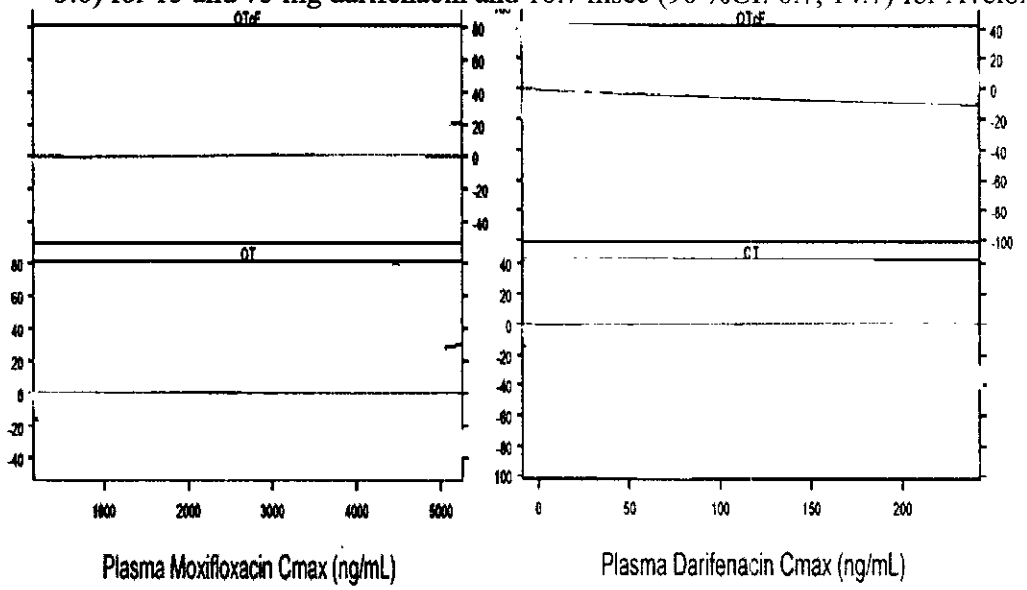


Figure 8: **Trend profiles for plasma moxifloxacin &** darifenacin Cmax values versus QT/QTcF changes from baseline.

- The absence of QT interval prolongation by darifenacin treatments is also evident in the above exposure-response trend profile (Figure 7) that documents the change in QTcF interval from baseline with plasma darifenacin $C_{max}$ (slope = -0.03 and p = 0.38 for Cmax vs QTcF changes). An increase in plasma darifenacin exposure (Cmax) did not lead to any increase in QTc change from baseline over observed Cmax range from [ ] ng/mL following 6 days QD dosing of darifenacin (15mg or 75mg).
- In contrast, Avelox 400mg (moxifloxacin) showed a tendency to increase QT/QTc intervals from baseline values as seen in the trend profile (slope = +0.004 and p = 0.058 for Cmax vs QTcF). Increase in plasma moxifloxacin exposure (Cmax) resulted in an increase in QTc change from baseline over

observed Cmax range from [ ] ng/mL following 6 days QD dosing of Avelox 400mg.

- In conclusion, peak darifenacin exposure (i.e. at PK_Tmax) following therapeutic (15 mg) and supra-therapeutic (75 mg) doses was not associated with QT/QTc prolongation.

**Mean change in QT/QTc from baseline mean:**

- When the mean QT/QTc intervals over the 24-hour collection period on day 6 (steady-state) were compared to the time-averaged baseline (day -1) intervals, there was no evidence of QTc prolongation with darifenacin treatments.

Table 7: Summary of mean changes in QT/QTc intervals from baseline values. Time-averaged baseline intervals were used for comparison.

| PD Endpoint | Conduct interval [ms] | Treatment | Baseline | | | Change from baseline | | | | 90% CI for Mean |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | Mean(ms) | STD | N | Mean(ms) | STD | p-value | |
| E_mean | QT | DAR328 15mg | 46 | 362.3 | 19.5 | 46 | -14.8 | 9.3 | <0.001 | [ -18, -12] |
| | | DAR328 75mg | 43 | 367.8 | 23.6 | 43 | -13.5 | 18.0 | <0.001 | [ -19, -7.9] |
| | | Avelox 400mg | 46 | 360.3 | 25.8 | 46 | -1.8 | 18.0 | 0.722 | [-6.3, 4.4] |
| | | Placebo | 44 | 360.5 | 19.4 | 44 | -10.3 | 15.2 | <0.001 | [ -15, -5.7] |
| | QTcF | DAR328 15mg | 46 | 397.5 | 16.8 | 46 | -3.8 | 6.2 | <0.001 | [-5.7, -2.0] |
| | | DAR328 75mg | 43 | 405.2 | 17.6 | 43 | -5.1 | 10.9 | 0.004 | [-8.5, -1.7] |
| | | Avelox 400mg | 46 | 396.0 | 17.1 | 46 | 5.5 | 11.6 | 0.002 | [ 2.1, 8.9] |
| | | Placebo | 44 | 395.8 | 15.3 | 44 | -2.6 | 9.2 | 0.065 | [-5.4, 0.2] |
| | QTcB | DAR328 15mg | 46 | 415.9 | 20.7 | 46 | 2.7 | 7.0 | 0.013 | [ 0.6, 4.7] |
| | | DAR328 75mg | 43 | 425.8 | 19.2 | 43 | -0.2 | 10.1 | 0.917 | [-3.3, 2.9] |
| | | Avelox 400mg | 46 | 415.8 | 18.8 | 46 | 9.1 | 11.4 | <0.001 | [ 5.7, 12.5] |
| | | Placebo | 44 | 421.6 | 19.4 | 44 | 1.8 | 10.5 | 0.271 | [-1.4, 5.0] |
| | QTcI | DAR328 15mg | 46 | 395.9 | 22.5 | 46 | -4.6 | 6.5 | <0.001 | [-6.6, -2.7] |
| | | DAR328 75mg | 43 | 407.1 | 26.2 | 43 | -5.2 | 11.0 | 0.003 | [-8.6, -1.9] |
| | | Avelox 400mg | 46 | 398.2 | 24.4 | 46 | 4.3 | 10.8 | 0.010 | [ 1.1, 7.5] |
| | | Placebo | 44 | 400.3 | 19.8 | 44 | -2.7 | 10.1 | 0.090 | [-5.8, 0.3] |

- After subtracting the placebo response, the changes in mean QTcF from time-averaged baseline values were -1.6 msec (90 %CI: -4.2, 1.0) and -1.2 msec (90 %CI: -4.6, 2.2) for 15 mg and 75 mg doses of darifenacin and 6.9 msec (90 %CI: 3.7, 10.1) for Avelox 400mg.
- The placebo and baseline corrected mean change from baseline QTcF induced by Avelox was estimated as 6.9 msec ($p < 0.001$), smaller than the 10.7 msec QTcF prolongation observed at Tmax. Due to exposure-PD relationship the estimate at Tmax is expected to be larger than that based on mean change from baseline data.
- The mean QTcF changes from baseline at each time point over the 24 hour collection period are shown in table 8 and figure 8 below for all four treatment groups. While Avelox consistently resulted in a positive change from baseline at all time points on day 6, both doses of darifenacin demonstrated a mean negative change over baseline at all time points. The response with darifenacin treatments was very similar to that of placebo.

Table 8: QTcF changes from baseline (mean ± SD) at all ECG collection time points over 24 hours on day 6.

| Time (hours) | Placebo | Avelox 400mg | DAR 15mg | DAR 75mg |
|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 1 | -5.1 ± 15.1 | 7.1 ± 17.8 | -6.3 ± 13.3 | -6.6 ± 19.3 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 3 | -1.3 ± 16.8 | 8.1 ± 16.4 | -4.2 ± 13.9 | -5.2 ± 20.1 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 5 | -2.6 ± 18.2 | 9.5 ± 18.6 | -5.2 ± 15.8 | -6.2 ± 18.6 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 7 | -5.5 ± 17.6 | 4.9 ± 16.7 | -7.1 ± 16.7 | -8.1 ± 23.0 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 10 | 0.1 ± 14.7 | 2.8 ± 16.3 | -5.1 ± 13.7 | -3.6 ± 18.6 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 14 | 3.5 ± 20.7 | 3.6 ± 17.9 | -1.0 ± 14.8 | -1.7 ± 18.5 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

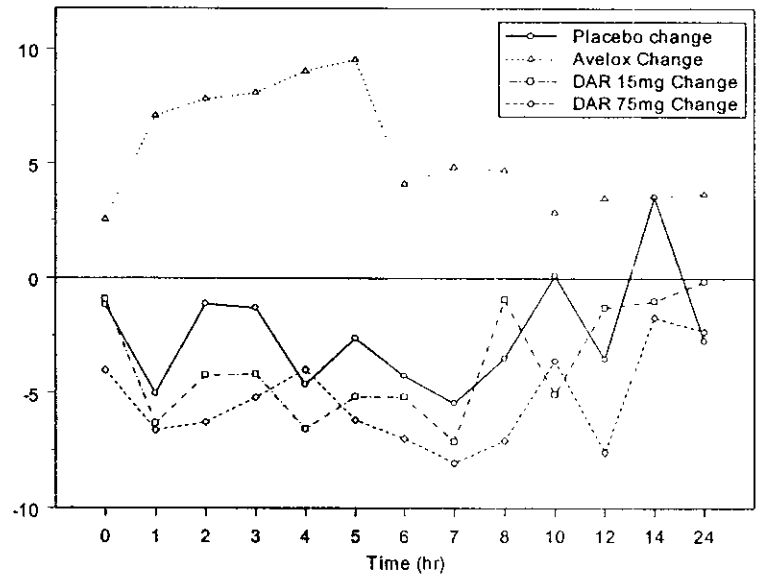


Figure 9: QTcF changes from baseline over 24 hours in all four treatment groups.

- The figure below is a scatter plot depicting the QTcF changes in individual subjects at each time point on day 6 (steady state).

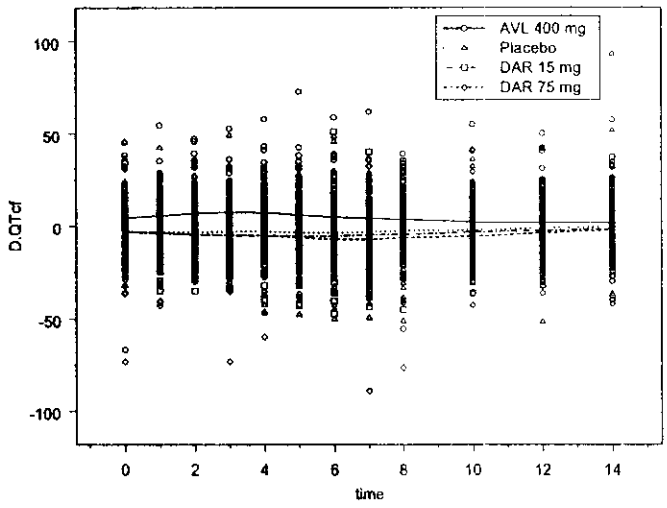


**Figure 10:** Scatter plot of individual QTcF changes at each time point over 14 hours on day 6 of the study. While placebo and darifenacin treatments result in a mean profile that essentially remains flat through out the time period, moxifloxacin shows a markedly different profile with QTcFmax of ~ 10 msec occurring at approximately 5 hours post-dose.

- In conclusion, multiple dose treatment with darifenacin 15 mg and 75 mg did not result in prolongation of mean QT/QTc intervals from baseline means.

**Mean maximum change in QT/QTc from baseline:**

- Time matched baseline QT/QTc values were employed for study endpoint E_max.
- The maximum observed QT/QTc changes induced by the two darifenacin treatments were not different from each other.
- When maximum changes induced by the active treatments were compared to placebo, a statistically significant difference was observed only with moxifloxacin (6.2 msec; 90 % CI (1.3, 11.2); $p < 0.05$). Maximum changes in QT/QTc by darifenacin doses were not different from that of placebo ($p>0.1$).

Table 9: Summary of mean maximal change in QT/QTc compared to baseline. Time-matched baseline QT/QTc values were employed.

| PD Endpoint | Conduct interval (ms) | Treatment | Baseline N | Baseline Mean(ms) | Baseline STD | Change from baseline N | Change from baseline Mean(ms) | Change from baseline STD | Change from baseline p-value | 90% CI for Mean |
|---|---|---|---|---|---|---|---|---|---|---|
| E_max | QT | DAR328 15mg | 46 | 390.8 | 23.7 | 46 | 22.7 | 14.4 | <0.001 | (18.4, 26.9) |
| | | DAR328 75mg | 43 | 398.7 | 30.1 | 43 | 24.1 | 21.2 | <0.001 | (17.6, 30.7) |
| | | Avelox 400mg | 46 | 391.4 | 31.0 | 46 | 34.6 | 21.7 | <0.001 | (28.1, 41.1) |
| | | Placebo | 44 | 390.3 | 25.2 | 44 | 24.4 | 18.0 | <0.001 | (19.0, 29.9) |
| | QTcF | DAR328 15mg | 46 | 413.1 | 18.3 | 46 | 13.7 | 10.7 | <0.001 | (10.6, 21.9) |
| | | DAR328 75mg | 42 | 421.0 | 19.9 | 42 | 13.6 | 11.2 | <0.001 | (10.1, 22.1) |
| | | Avelox 400mg | 46 | 412.2 | 19.2 | 46 | 29.4 | 15.0 | <0.001 | (25.0, 33.8) |
| | | Placebo | 44 | 418.4 | 17.8 | 44 | 22.3 | 13.1 | <0.001 | (18.3, 26.2) |
| | QTcB | DAR328 15mg | 46 | 436.2 | 20.1 | 46 | 23.7 | 11.2 | <0.001 | (20.4, 33.0) |
| | | DAR328 75mg | 43 | 445.2 | 20.8 | 43 | 25.2 | 11.2 | <0.001 | (22.7, 29.6) |
| | | Avelox 400mg | 46 | 437.5 | 19.8 | 46 | 37.2 | 16.2 | <0.001 | (32.4, 42.1) |
| | | Placebo | 44 | 443.2 | 19.4 | 44 | 32.3 | 16.0 | <0.001 | (27.4, 37.2) |
| | QTcI | DAR328 15mg | 46 | 410.9 | 23.9 | 46 | 17.7 | 10.5 | <0.001 | (14.6, 20.8) |
| | | DAR328 75mg | 43 | 422.3 | 27.8 | 43 | 17.8 | 11.3 | <0.001 | (13.5, 20.5) |
| | | Avelox 400mg | 46 | 414.3 | 26.8 | 46 | 28.8 | 15.1 | <0.001 | (24.3, 33.3) |
| | | Placebo | 44 | 417.8 | 22.2 | 44 | 22.8 | 14.1 | <0.001 | (17.7, 26.3) |

- In conclusion, the effect of darifenacin treatments on the maximum change from baseline was not significantly different from that of placebo.

## Effect on QT prolongation: categorical analyses

In addition to the central tendency analyses discussed above, categorical analyses of the QT/QTc interval data was also provided to understand the frequency and percentage of subjects whose absolute QTc values and changes from baseline QTc intervals fell above a predefined upper limit value:

Table 11: Categorical analyses: Number and % frequency of individuals with QTcF intervals and changes above an upper limit.

| Day | Cardiac interval (ms) | Treatment | N | Category | Count (% of N) |
|---|---|---|---|---|---|
| 6 | QTcF | DAR328 15mg | 46 | >450 | 0 ( 0) |
| | | | | >480 | 0 ( 0) |
| | | | | >500 | 0 ( 0) |
| | | DAR328 75mg | 43 | >450 | 2 ( 5) |
| | | | | >480 | 0 ( 0) |
| | | | | >500 | 0 ( 0) |
| | | Avelox 400mg | 46 | >450 | 0 ( 0) |
| | | | | >480 | 0 ( 0) |
| | | | | >500 | 0 ( 0) |
| | | Placebo | 44 | >450 | 0 ( 0) |
| | | | | >480 | 0 ( 0) |
| | | | | >500 | 0 ( 0) |

| | | | | |
|---|---|---|---|---|
| QTcF | DAR328 15mg | 46 | >30 | 8 (17) |
| | | | >60 | 0 ( 0) |
| | DAR328 75mg | 43 | >30 | 8 (19) |
| | | | >60 | 0 ( 0) |
| | Avelox 400mg | 46 | >30 | 18 (39) |
| | | | >60 | 2 ( 4) |
| | Placebo | 44 | >30 | 9 (20) |
| | | | >60 | 0 ( 0) |

- No subject within any treatment group experienced QTcF interval > 480msec.
- While no individual exhibited QTcF > 450 msec in the lower dose darifenacin, placebo or Avelox groups, two subjects (5 %) in the high dose (75 mg) darifenacin group presented with intervals > 450 msec. This however, could be a reflection of the higher baseline QT intervals (occasional baseline QTcF values ≥ 450 msec) in this group compared to other treatment groups. (The QT study only excludes males/females with baseline QTcF intervals > 450/470 msec).
- Moxifloxacin (Avelox 400 mg) group had the highest frequency of QTcF change > 30 msec (n=18; 39 %) and > 60 sec (n = 2; 4 %).
- QTcF changes > 30 msec occurred at a similar frequency (17-20 %) in the placebo and darifenacin treatment groups, suggesting that the effect of darifenacin on the QTc change from baseline was not different from that of placebo.
- There were no QTcF increases > 60 msec with the darifenacin or placebo treatments.
- None of the individuals in any treatment group experienced a change in the RR interval > 25 % that is reflective of heart rate change less than 50 bpm (bradycardia) or greater than 100 bpm (tachycardia).
- In conclusion, treatment with therapeutic and supra-therapeutic doses of darifenacin did not result in a greater frequency of individuals with absolute QTcF and interval changes above pre-determined upper limits when compared to placebo.

**Cardiac intervals in subgroups:** Due to lack of statistical power for sub-group analysis (not primary objective), the change from baseline values were provided by treatment but no further analyses to compare with placebo were made by the sponsor.

Table 12: QTcF changes in various subgroups (CYP2D6 status, age and gender):

| Subgroup | QTcF /ΔQtcF | DAR 15 mg | DAR 75 mg | Avelox 400 mg | Placebo |
|---|---|---|---|---|---|
| [redacted] | | | | | |
| | E_Tmax | -3.5 (-19, 11.7) | -5 (-15, 5.1) | 7.1 (-0.9, 15.1) | -6 (-12, -0.2) |
| | Placebo-corrected E_Tmax | 2.5 | 1.0 | 13.1 | - |
| | E_mean | -3.5 (-12, -4.7) | -1.6 (-11, 8.1) | 2.3 (-4.6, 9.3) | -6 (-12, -0.2) |
| | Placebo-corrected E_mean | 2.5 | 4.4 | 8.3 | - |
| | E_max | 13.9 (6.5, 21.3) | 20.5 (8.0, 33.1) | 21.2 (13.4, 29.1) | 23.7 (12.5, 34.8) |
| [redacted] | | | | | |
| | E_Tmax | -2.4 (-6.2, 1.4) | -6.6 (-12, -0.9) | 11.1 (5.8, 16.4) | -1.9 (-5.1, 1.3) |
| | Placebo-corrected E_Tmax | -0.5 | -4.7 | 13 | |
| | E_mean | -3.9 (-5.7, -2.0) | -5.8 (-9.5, -2.1) | 6.3 (2.3, 10.3) | -1.9 (-5.1, 1.3) |
| | Placebo-corrected E_mean | -2.0 | -3.9 | 8.2 | - |
| | E_max | 19.6 (16.1, 23.2) | 17.7 (13.9, 21.4) | 31.4 (26.3, 36.5) | 22.0 (17.5, 26.4) |
| [redacted] | | | | | |
| | E_Tmax | -2.7 (-9.1, 3.8) | -11.7 (-18, -5.8) | 9.1 (2.9, 15.3) | -3.9 (-8.3, 0.5) |
| | Placebo-corrected E_Tmax | 1.2 | -7.8 | 13 | - |
| | E_mean | -2.9 (-6.0, 0.2) | -7.6 (-13, -2.3) | 4.5 (-0.1, 9.0) | -3.9 (-8.3, 0.5) |
| | Placebo-corrected E_mean | 1 | -3.7 | 8.4 | - |
| | E_max | 20.2 (15.2, 25.1) | 15.5 (9.9, 21.0) | 28.4 (21.6, 35.3) | 20.6 (14.7, 26.5) |
| [redacted] | | | | | |
| | E_Tmax | -2.5 (-6.3, 1.2) | -1.6 (-8.9, 5.7) | 11.6 (4.6, 18.6) | -1.6 (-5.4, 2.3) |
| | Placebo-corrected E_Tmax | -0.9 | 0 | 13.2 | - |
| | E_mean | -4.8 (-6.9, -2.7) | -2.9 (-7.3, 1.5) | 6.6 (1.1, 12.2) | -1.6 (-5.4, 2.3) |
| | Placebo-corrected E_mean | -3.2 | -1.3 | 8.2 | - |

| | | | | | |
|---|---|---|---|---|---|
| | E_max | 17.2 (13, 21.4) | 20.4 (15.8, 25.1) | 30.5 (24.3, 36.6) | 23.7 (18, 29.4) |
| [redacted] | | | | | |
| | E_Tmax | -3.8 (-9.3, 1.7) | -8.2 (-15, -1.6) | 8.4 (1.0, 15.8) | -1.1 (-5.2,3.0) |
| | Placebo-corrected E_Tmax | -2.7 | -7.1 | 9.5 | - |
| | E_mean | -4.9 (-7.3, -2.4) | -5.9 (-11, -0.9) | 5.0 (-0.7, 10.6) | -1.1 (-5.2, 3.0) |
| | Placebo-corrected E_mean | -3.8 | -4.8 | 6.1 | - |
| | E_max | 18.7 (13.9, 23.6) | 19.8 (14.9, 24.6) | 30.1 (23.6, 36.7) | 23.7 (18.4, 29.0) |
| [redacted] | | | | | |
| | E_Tmax | -1.2 (-6.3, 4.0) | -3.3 (-11, 4.1) | 12.4 (7.1, 17.7) | -4.5 (-8.4, -0.6) |
| | Placebo-corrected E_Tmax | 3.3 | 1.2 | 16.9 | - |
| | E_mean | -2.6 (-5.5, 0.4) | -3.8 (-8.2, 0.5) | 6.1 (1.9, 10.3) | -4.5 (-8.4, -0.6) |
| | Placebo-corrected E_mean | 1.9 | 0.7 | 10.6 | - |
| | E_max | 18.7 (14.4, 23.1) | 16.8 (11.3, 22.2) | 28.6 (22.1, 35.1) | 20.6 (14.1, 27.0) |

**Effect of gender on changes in QTcF:**

- Females had a higher darifenacin exposure compared to males. Females also had a higher baseline mean QTcF interval compared to males in all treatment groups. Individuals in the darifenacin 75 mg group had higher mean baseline QTcF compared to darifenacin 15 mg.
- Greater darifenacin concentrations in females were not associated with significant changes in the primary and secondary ECG endpoints, compared to males.
- The mean changes from baseline namely E_Tmax, E_mean and E_max were more negative in females compared to males and were also more negative in darifenacin 75 mg than in darifenacin 15 mg. This can be attributed to the higher baseline mean values in these subgroups. Although the placebo corrected QTcF interval changes (E_Tmax and E_mean) demonstrated small positive values in males, these increases were less than 5 msec and considerably smaller compared to moxifloxacin response.
- A two-sample t-test of the changes documented for the various ECG endpoints revealed that there were no statistically significant differences ($p > 0.2$) between males and females in either of the darifenacin treatments.

**Effect of CYP2D6 phenotype on changes in QTcF:**

- Darifenacin exposure was higher in CYP2D6 poor metabolizers (PMs) compared to extensive metabolizers (EMs), especially at the lower dose.

- The effect of darifenacin treatments on QT/QTc interval was not significantly different from that of placebo in EMs or PMs.
- Although PMs exhibited small positive changes in QTcF (placebo & baseline corrected), these increases were less than 5 msec. Moreover due to the small number of subjects in the PM subgroup, the validity of this observation cannot be determined.
- There were no significant differences ($p > 0.2$) between QTcF changes in PMs vs. EMs, suggesting that supra-therapeutic exposures of darifenacin achieved in this study were not associated with QTc interval prolongation.

**Effect of age on QTcF changes**

- There were no significant differences in QTcF changes in young versus elderly subjects.
- In conclusion, the effect of darifenacin on QTc did not differ among individuals belonging to various subgroups such as gender, CYP2D6 metabolic status or age.

**Safety conclusions:** All test drugs were well tolerated in healthy volunteers when administered for 6 days. There were no subject discontinuations. No serious adverse events were reported. Eighty-three subjects (44%) reported a total of 213 adverse events during the study (Day -1 run-in to end of study evaluations). The most frequently reported events were headache (19.7%), dry mouth (17%) and indigestion (7.5%), irrespective of treatment.

Table 13: Summary of adverse events by body system and treatment

| | | | | |
|---|---|---|---|---|
| Eye (irritation, blurred vision) | 0 | 4 (8.7) | 0 | 0 |
| General disorders (chest pain, flu-like illness, pain) | 0 | 2 (4.3) | 1 (2.1) | 1 (2.1) |
| CNS (headache, dizziness, somnolence) | 6 (12.8) | 9 (19.6) | 13 (27.1) | 5 (10.6) |
| Renal & urinary | 0 | 3 (6.5) | (2.1) | 1(2.1) |
| Skin (dry skin, pruritis, rash) | 2 (4.3) | 1 (2.2) | 1 (2.1) | 0 |

**Overall study conclusion**: Multiple dose treatment (for 6 days) with therapeutic (15 mg) or supra-therapeutic (75 mg) doses of darifenacin was not associated with QT/QTc interval prolongation.

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/s/

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12/13/04 10:31:10 AM
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12/20/04 11:35:02 AM
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I concur