CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-513

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	**21-513**
Brand Name:	**Enablex**
Generic Name:	**Darifenacin Hydrobromide**
Sponsor:	**Novartis Pharmaceuticals Corporation**
Relevant IND(s):	**45,457**
Date of Submission:	**December 03, 2002** **August 20, 2003 (BM)** **September 5, 2003 (BM)** **September 10, 2003 (BC)** **September 18, 2003 (BM)** **September 19, 2003 (BP)** **September 19, 2003 (C)**
Type of Submission:	**NME NDA**
Code:	**1S**
Formulation:	**Extended Release Tablet**
Strength:	**7.5 mg, 15 mg**
Indication:	**Treatment of Overactive Bladder**
Reviewer:	**Myong-Jin Kim, PharmD**
Team Leader:	**Ameeta Parekh, PhD**
OCPB Division:	**DPE-II**
OND Division:	**Reproductive & Urologic Drug Products**

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I. Executive Summary

Darifenacin, a selective muscarinic M_3 receptor antagonist, is proposed to be indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The sponsor seeks the approval of two ER tablet dosage strengths, 7.5 mg and 15 mg. The proposed starting dose of darifenacin is 7.5 mg once daily without regard to meals. For those patients requiring greater symptom relief, the dose may be increased to 15 mg once daily as early as two weeks after starting therapy. The sponsor's rationale of developing an extended release tablet was to reduce the incidence and severity of side effect of drug by minimizing the peak to trough ratio of darifenacin and to allow once daily dosing.

A. Recommendations

From the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics, Human Pharmacokinetics and Biopharmaceutics section of the NDA 21-513 is **acceptable**.

Final decision regarding the QT safety should be made in the context of these limitations:

- No prospectively planned, positive controlled QT study was conducted.
- There were lack of placebo controlled studies except in one study (Study 1015) with a limited number of subjects (n=10).
- Most of the ECG readings were from one measurement at screening, 4 hour post-dose at steady and at follow-up visits.
- No ketoconazole alone arm was studied.

B. Phase IV commitment

[ ]

C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics

Immediate Release/Extended Release Pharmacokinetics

Single Dose Pharmacokinetics

The AUC_∞ and C_{max} values of darifenacin after a single dosing with ER tablets were higher by 66

– 151 % and lower by 43 – 71%, respectively, than that with IR capsules at all doses. The mean T_{max} values were between 9.5 to 11.5 hours following a single dose administration of 7.5 – 20 mg ER tablets. The observed apparent $t_{1/2}$ of ER tablets was 11 to 13 hours while much shorter $t_{1/2}$ was observed with IR capsules (1.8 – 3.9 hrs). The CV% values of AUC for ER formulations were 46 – 89 %.

Multiple Dose Pharmacokinetics

Mean steady state total exposure to darifenacin in healthy male subjects was 27.9 ng*hr/mL from 7.5 mg ER once daily dosing and 79.6 ng*hr/mL from 15 mg ER once daily dosing. Mean peak concentrations at steady state were 1.92 ng/mL and 5.08 ng/mL, respectively. Assuming 98% protein binding, mean peak unbound darifenacin concentrations at steady state were estimated to be 0.04 ng/mL from 7.5 mg ER dosing and 0.10 ng/mL from 15 mg ER dosing. The steady state plasma concentration vs. time profile from ER tablet dosing was uniform across the dosing interval and peak to trough fluctuations were small across the proposed dose range (PTFR 0.7 – 0.9). The inter-subject variability was 47 – 69 % for steady state AUC. The T_{max} values were between 7.0 – 8.1 hours. The estimated $t_{1/2}$ from ER tablets was around 12.8 – 18.7 hours. Steady state was achieved by Day 6 of dosing for both the ER tablets 7.5 mg and 15 mg.

Darifenacin pharmacokinetics from ER tablets are both time- and dose-dependent. Darifenacin exposure from 15 mg ER tablets at steady state was 86% higher than after a single dose and doubling of the ER tablet dose increased steady state exposure by approximately 150 %. Time-dependency appears to be related to a reduction in the contribution of CYP2D6 metabolism to darifenacin oral clearance after repeated dosing. Dose-dependency may be related to increasing saturation of CYP3A4-mediated gut wall metabolism at higher doses, combined with a dose-dependent reduction in the contribution of CYP2D6-mediated metabolism at steady state.

Dose-Proportionality

Both C_{max} and AUC of darifenacin increased proportionally with dose after a single i.v. dose of 0.6 mg to 6 mg darifenacin (Study 219). However, the pharmacokinetics of oral darifenacin at steady state were not dose proportional for either the IR capsules or ER tablets.

Absorption

Absorption of darifenacin from the GI tract was rapid. Following administration of an oral solution in the fasting state, darifenacin rapidly appeared in the peripheral circulation and C_{max} occurred approximately 1 hour after dosing. The rate of absorption of darifenacin from ER tablets is limited by the rate of release of the drug from the tablet matrix. In a single ER dose pharmacokinetic study, C_{max} occurred at around 10 hr while pooled data from studies using repeated ER tablet dosing indicate that C_{max} from 7.5mg and 15 mg ER tablets at steady state is achieved approximately 7 hours after drug dosing. The mean absolute bioavailability of darifenacin from 30 mg ER tablets was estimated to be 37% at steady state in a mixed EM and PM population. Low oral bioavailability is mainly due to extensive first-pass metabolism.

Food Effect

Total darifenacin exposure following a single ER dose was not altered by the consumption of food while peak darifenacin exposure was 22% higher and T_{max} was 3.3 hours shorter in the presence of food. Once darifenacin plasma concentrations have reached steady state, ingestion of food had no effect on the pharmacokinetics of darifenacin from ER tablet dosing. Peak steady state darifenacin exposure and total exposure from dosing with 30 mg ER tablets was similar in both fed and fasted states. Therefore, darifenacin can be administered without regard to food intake.

Distribution
Darifenacin is a lipophilic base and is approximately 98% bound to plasma proteins (primarily to alpha-1-acid glycoprotein). Darifenacin protein binding is lower among subjects with reduced hepatic function. Mean f_u was 3.3 and 4.5 % in subjects with mild and moderate hepatic impairment, respectively, compared with 1.7 % in subjects with normal hepatic function. Protein binding is not altered by renal impairment. The steady state volume of distribution is about 276 L (range [ ] L) after i.v. administration. Based on free darifenacin concentrations in animal cerebrospinal fluid and plasma, darifenacin showed negligible penetration of the blood brain barrier.

Metabolism
Darifenacin is extensively metabolized by liver following oral dosing. Metabolism is mediated by CYP2D6 and CYP3A4 enzymes. Three major metabolic routes are (1) monohydroxylation in the dihydrobenzofuran ring, (2) dihydrobenzofuran ring opening and (3) N-dealkylation of the pyrrolidine nitrogen. The products of the hydroxylation and N-dealkylation pathways are major circulating metabolites but none contributes significantly to the overall clinical effect of darifenacin. The major circulating metabolites were UK-73,689 and UK-148,993 (~60 % and 7% of circulating radioactivity following a radiolabeled dose, respectively).

Elimination
Following administration of an oral dose of ^{14}C-darifenacin solution to healthy subjects, about 60% of the radioactivity was recovered in the urine and 40% in the feces. A small percentage (3%) of the total dose was excreted as unchanged. The mean clearance of darifenacin is about 36 L/hr (range [ ] L/hr) after i.v. administration.

Special Populations

Elderly
Darifenacin exposure from ER tablets is higher among elderly subjects. It is estimated that CL/F decrease with age by 6.2% per decade.

Sex
Darifenacin exposure is lower in males than in females. Darifenacin CL/F was 39% higher and steady state AUC was 28% lower in males than in females.

Race
The effects of race on darifenacin pharmacokinetics among subjects in Western studies have not been established because a small number of non-white subjects were enrolled. However, darifenacin exposure seems to be lower among Japanese subjects in studies conducted in Japan than subjects in Western studies.

CYP2D6 Genotype
Total exposure of darifenacin at steady state following administration of 7.5 mg ER tablets and 15 mg ER tablets was about 164% and 99 % higher in PM subjects compared to EM subjects, respectively. Corresponding values for mean peak exposures were 145% and 89%, respectively. Due to considerable inter-subject variability in darifenacin exposure in both EM and PM populations, AUC_{24} CV% across the dose range tested was 48-71% for EMs and 20-61% for PMs. Therefore, there was a high degree of overlap between ranges of individual exposures in EM and PM populations.

The sponsor submitted the subgroup analysis on the safety data based on CYP2D6 EM/PM status. Based on the submitted data, the sponsor proposed that no special dosing requirements are necessary for CYP2D6 PMs. The dosing recommendation based on CYP2D6 EM/PM status will be finalized at the time of labeling.

The sponsor claimed that there were no difference between CYP2D6 PMs and EMs with respect to the incidence and severity of adverse events or the nature and incidence of laboratory test abnormalities. However, discontinuations due to treatment related adverse events by CYP2D6 genotype and dose were higher in CYP2D6 PMs. In OAB fixed dose Phase 3 studies, the rates of discontinuation were 1.6 % (7.5mg), 4.8 % (15mg), and 15.0 % (30mg) in PM subjects whereas 0.4 % (7.5mg), 1.3 % (15mg), and 7.3 % (30mg) of EMs discontinued due to treatment related adverse events.

Renal Insufficiency
Regression analysis showed that there was no relationship between darifenacin clearance and renal function. In addition, plasma protein binding of darifenacin did not decrease in subjects with renal impairment. Hence, unbound darifenacin exposure will not be increased by diminished renal function.

Hepatic Insufficiency
Mild hepatic impairment (Child Pugh A) did not alter pharmacokinetics of darifenacin. While protein binding was lower in patients with mild hepatic impairment than subjects with normal hepatic function (mean f_u: 3.3 vs. 1.7 %) steady state unbound darifenacin exposure was similar between groups. Clearance of darifenacin was lower in subjects with moderate hepatic impairment (Child Pugh B) than subjects with normal hepatic function (steady state CL/F 56 mL/min vs. 149 mL/min). Steady state total darifenacin exposure was 168% higher among subjects with moderate hepatic impairment than subjects with normal hepatic function. Protein binding was also lower in subjects with moderate hepatic impairment (mean f_u: 4.5 vs. 1.7 %). After adjusting for plasma protein binding, steady state unbound darifenacin exposure was estimated to be 300 – 370 % higher in subjects with moderate hepatic impairment than subjects with normal hepatic function. Subjects with severe hepatic impairment (Child Pugh C) were not been studied. The sponsor proposed that the daily dose of darifenacin should not exceed 7.5 mg for patients with moderate hepatic impairment while patients with severe hepatic impairment should not take darifenacin. There are no special dosing requirements for patients with mild hepatic impairment.

Drug-Drug Interactions
Darifenacin is extensively metabolized via CYP2D6 and CYP3A4 enzyme pathways. *In vitro* metabolism studies and *in vivo* pharmacokinetic studies have shown that darifenacin inhibits CYP2D6.

Table 1. The Summary of Drug-Drug Interaction Studies (EM Subjects)

	Mean Ratio of AUC_{24}	Mean Ratio of C_{max}
Effect on Darifenacin		
Ketoconazole 400 mg QD	5.33 ↑ (7.5 mg) 11.6 ↑ (15 mg)* 10.6 ↑ (30 mg)	5.67 ↑ (7.5 mg) 10.0 ↑ (15 mg)* 9.5 ↑ (30 mg)
Erythromycin 500 mg BID	1.95 ↑ (30 mg)	2.28 ↑ (30 mg)
Fluconazole 200/100 mg QD	1.84 ↑ (30 mg)	1.88 ↑ (30 mg)

Paroxetine 20 mg QD	1.33 ↑ (30 mg)	1.36 ↑ (30 mg)
Cimetidine 800 mg BID	1.34 ↑ (30 mg)	1.42 ↑ (30 mg)
Effect of Darifenacin on		
Midazolam 7.5 mg oral	1.17 ↑ (30 mg)	No Change (30 mg)
COC (0.15/0.03 mg LNG/EE)	No Change (10 mg TID)	No Change (10 mg TID)
Digoxin 0.25 mg	1.16 ↑ (30 mg)	1.20 ↑ (30 mg)
Imipramine 25 mg TID	1.7 ↑ (30 mg)**	1.57 ↑ (30 mg)
Desipramine	2.63 ↑ (30 mg)**	2.56 ↑ (30 mg)

Effect of Darifenacin on	Darifenacin 7.5 mg	Darifenacin 15 mg	Darifenacin 30 mg
Debrisoquine MR	2.2 ↑	3.25 ↑	7.25 ↑

*n=3, **mean ratio of AUC_{72}

The main conclusions from the drug-drug interaction studies are as follows:

- Co-administration of potent CYP3A4 inhibitors with darifenacin caused a significant increase in darifenacin exposure but the magnitude of the effect varied across the darifenacin dose range. Mean steady state darifenacin exposure in EM subjects was about 5 and 12 folds higher when ketoconazole was co-administered with darifenacin 7.5 mg and 15 mg, respectively, than when darifenacin was administered alone. Co-administration of ketoconazole and darifenacin 30 mg showed about 11 fold increase in total exposure than when darifenacin 30 mg was administered alone. The sponsor proposed that the maximum daily dose of darifenacin should not exceed 7.5 mg when co-administered with potent CYP3A4 inhibitors.
- Co-administration of moderate CYP3A4 inhibitors, erythromycin and fluconazole, with darifenacin 30 mg increased mean steady state darifenacin exposure in EM subjects by about 2 folds. The effects of moderate CYP3A4 inhibitors on darifenacin exposure from 7.5 and 15 mg at steady state are predicted to be proportionately smaller than those seen with darifenacin 30 mg dosing.
- Co-administration of paroxetine, a CYP2D6 inhibitor, with darifenacin 30 mg increased mean steady state darifenacin exposure by 33% in EM subjects. At darifenacin doses of 7.5 mg and 15 mg at steady state, the effect of concomitant use of a CYP2D6 inhibitor with darifenacin in EMs is predicted to be similar to the difference between EM and PM subjects when dosed with darifenacin alone. The magnitude of this difference is consistent with the difference in darifenacin exposure between EM and PM subjects.
- Co-administration of a mixed CYP P450 inhibitor, cimetidine, with darifenacin 30 mg increased mean steady state darifenacin exposure by 34% in EM subjects.
- A 17% decrease in total midazolam exposure was observed when oral midazolam was co-administered with darifenacin compared with midazolam administered alone. There was no change in C_{max}.
- Co-administration of darifenacin inhibited the metabolism of CYP2D6 substrates in a dose-dependent manner. Among EMs, the debrisoquine metabolic ratio was increased 120 % following repeated dosing with 7.5 mg ER tablets, 225% with 15 mg ER tablets, and 625% with 30 mg ER tablets. Darifenacin dosing with either 7.5 mg or 15 mg doses does not cause complete phenocopying of EM subjects to a PM phenotype. However, caution should be taken when darifenacin is co-administered with drugs predominantly metabolized by CYP2D6 and which have a narrow therapeutic window.
- Darifenacin had no effect on the pharmacokinetics of the active components of the combined oral contraceptives (LNG, EE).

- Co-administration of darifenacin increased steady state digoxin peak exposure by 20% and total exposure by 16% than when digoxin was taken alone. Standard therapeutic drug monitoring for digoxin should be continued.
- Co-administration of darifenacin with a single dose warfarin did not alter the prothrombin time than when warfarin was administered alone. However, standard therapeutic prothrombin time monitoring for warfarin should be continued.

QT Analysis in Clinical Pharmacology Studies

No prospectively planned, positive controlled clinical study was conducted to evaluate the effect of darifenacin on QT interval. A pooled analysis of the effect of darifenacin on QTc interval was performed on the ECG data collected in 2 clinical pharmacology studies and 2 clinical studies. ECGs were recorded 4 to 9 hours post-dose at steady state following administration of doses ranged from 3.75 mg to 60 mg. ECGs were digitized and centrally read. Most of the ECG readings were from only one measurement at screening, 4 hour post-dose at steady state, and at follow-up visits. More frequent measurements were done in one study where QTc intervals were read at screening, 4, 8, and 24 hours post-dose following a single dose darifenacin 15 mg and at steady state (Hepatic Impairment Study). The supra-therapeutic plasma concentrations (~ 23 fold increase in C_{max} compared to C_{max} seen at 15 mg dose) were achieved with co-administration of darifenacin 30 mg and ketoconazole 400 mg for 6 days (Study 1007). 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). At supra-therapeutic concentrations of darifenacin, the mean change of 12 msec from baseline (range: - [ ] msec) in QTcF was observed. The sponsor recently submitted the QT data from a DDI study where darifenacin 7.5 mg or 15 mg were co-administered with ketoconazole 400 mg. This study showed a consistent mean increase of 10 – 12 msec in QTcF. The sponsor stated that the mean increases of 10-12 msec in QTcF are not a clinically meaningful signal citing that ketoconazole itself is known to increase QT interval. However, the sponsor did not conduct a study of ketoconazole arm alone to evaluate the effect of ketoconazole on QT interval. As a result, 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, these may not serve as a definitive study to address the issue of darifenacin's potential effect on QT prolongation.

Exposure-Response Information

Darifenacin 7.5 mg and 15 mg were associated with a median reduction of 2.0 and 3.2 incontinence episodes per week from baseline to Week 12, respectively. Treatment effect was observed as early as at Week 2. Subjects treated with darifenacin 15 mg were associated with a higher median improvement in the number of incontinence episodes per week, compared to that of subjects treated with darifenacin 7.5 mg. Darifenacin 7.5 mg and 15 mg were also associated with the improvement in number of micturitions and in number of episodes of urgency. Treatment effect was about 0.8 episodes per day for both outcomes and did not appear to be dose dependent. Darifenacin 30 mg appeared to have the largest treatment effect with a median reduction between 4.2 and 6.3 incontinence episodes per week. However, Darifenacin 3.75 mg was not associated with a significant reduction in number of incontinence episodes per week (reduction of 0.7 per week).

Adverse events associated with darifenacin appear to be similar to that of other antimuscarinic agents. The majority of adverse events occurred in the first two weeks of the treatment and was dose-dependent. Darifenacin 7.5 mg was well tolerated. Dry mouth, constipation and dyspepsia were the most commonly reported events and they occurred in 20 %, 15 %, and 3 % of the

subjects treated with darifenacin 7.5 mg for 12 weeks, respectively. In subjects treated with darifenacin 15 mg, the corresponding adverse events occurred in 35%, 21%, and 8%, respectively.

Bioequivalence

Bioequivalence was established between the proposed commercial formulation 7.5 mg, 15 mg and 30 mg tablet strengths and the corresponding clinical research tablets at steady state. Bioequivalence was also established between the proposed commercial 30 mg tablet and the early research 30 mg tablet at steady state. In the absence of an established IVIVC model, bioequivalence was demonstrated between batches of proposed commercial 7.5 mg and 15 mg ER tablets produced at two proposed manufacturing sites. Bioequivalence studies were of a crossover design, but because the proposed commercial tablets are an extended release product and show both time- and dose-dependent pharmacokinetics, bioequivalence was assessed after repeated dosing.

In-Vitro Dissolution Specification

Test Time (hours)	Amount Dissolved (Q_i)		
	L_1 (Individuals)	L_2 (Mean)	L_2 (Individuals)
1		10 to 30%	
8		56 to 76%	
24		≥ 85%	

The sponsor's proposed in-vitro dissolution specification is acceptable.

II. Question-Based Review

A. General Attributes

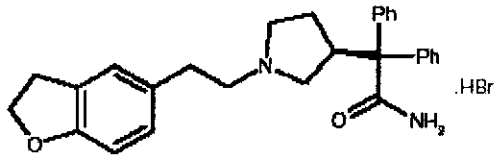
What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Darifenacin is moderately lipophilic and basic and is soluble in water.

Physico-chemical properties

Darifenacin hydrobromide drug substance is a white to almost white crystalline powder. It comprises of crystalline irregular shaped plates and prismatic particles.

- Structural formula:



- Molecular Weight: 507.5 (salt); 426.6 (free base)

- Molecular Formula: $C_{28}H_{30}N_2O_2 \cdot HBr$

- IUPAC name: (*S*)-2-{1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide hydrobromide

- pK_a: 9.20 ± 0.01 (measured in water with 10% methanol co-solvent at 25°C)

- log P:

	Species	log P
log $P_{neutral}$	darifenacin	3.64 ± 0.02
log P_{cation}	darifenacin. H^+	0.22 ± 0.06

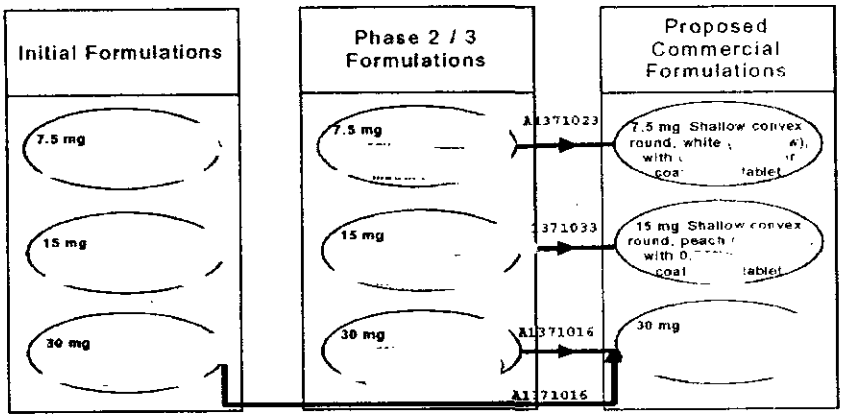
- Aqueous solubility at various pH levels (at 37°C)

Aqueous media	Solubility (mg/mL)	Solubility Classification
pH buffer		very slightly soluble
pH buffer		slightly soluble
pH buffer		slightly soluble
pH buffer		slightly soluble
pH buffer		slightly soluble
pH buffer		slightly soluble
pH buffer		slightly soluble
pH buffer		slightly soluble
		slightly soluble
		slightly soluble

Formulation

An extensive formulation development was undertaken with several formulations being explored, including an IR capsule and tablet dosage forms. Since it was apparent that three times a day dosing was required to maintain therapeutic plasma concentrations over an entire day with an IR formulation, an ER formulation was developed to provide once daily dosing regimen. In addition to the ER tablet formulations, a number of exploratory clinical studies were also undertaken using ER capsules and ER suspension formulations.

The TBM formulations of darifenacin 7.5 and 15 mg ER tablets are composed of darifenacin hydrobromide, dibasic calcium phosphate, hydroxypropyl methylcellulose and magnesium stearate. Following the ER tablets are film-coated with a colored coat and clear over-coat In addition to the TBM strengths of 7.5 mg and 15 mg, a 30 mg formulation was developed and used in clinical trials. The unit weight, tablet size and shape are the same for the 7.5 mg, 15 mg and 30 mg strengths. The excipient levels are the same for each formulation with the exception of dibasic calcium phosphate. To keep the unit weight constant, differences in tablet strengths are accommodated by adjusting the quantity of



N.B.: The 30 mg formulation is not being commercialised at this time.

The Early Clinical Research, Clinical Research and Proposed Commercial Formulations are the same except for the following:

Initial Formulations (Early Clinical Research Formulation)

- The tablet is different from the TBM formulation;

Phase 2/3 Formulations (Clinical Research Formulation)

- The tablet are different from the TBM formulation; the level is different;

Proposed Commercial Formulations (TBM)

- 8 mm round shallow convex shaped tablets are film-coated with a color coat and clear over-coat
- The unit weight, tablet size and shape are the same for the 7.5, 15, and 30 mg strengths
- The excipient levels are the same for each formulation with the exception of the , dibasic calcium phosphate
- The thickness of the film coat is increased from (Clinical Research Formulation) to (TBM); addition of a the core tablet and the matrix release system are not changed

Table 2. Composition of Darifenacin Hydrobromide MR Tablets, 7.5 mg and 15 mg[1]

Component	Grade	Function	7.5 mg Tablet[2] (mg/tablet)	15 mg Tablet[3] (mg/tablet)
Darifenacin Hydrobromide	Pharm	Active Ingredient		
Dibasic Calcium Phosphate	USP			
Hydroxypropyl Methylcellulose 2208	USP			
Magnesium Stearate	NF			
	Pharm	White Film-Coat Solid		------
	Pharm	Light Peach Film-Coat Solid	------	
	USP			
	Pharm			
	USP			
Total Weight			208.500	208.500

[1] All quantities are calculated to three decimal places.
[2] 8.0 mm round shallow convex, white film-coated tablets with clear over-coat, debossed with "Pfizer" on top and appropriate debossing on bottom.
[3] 8.0 mm round shallow convex, light peach film-coated tablets with clear over-coat, debossed with "Pfizer" on top and appropriate debossing on bottom.
[4] Equivalent to 7.5 mg of darifenacin based on a drug substance theoretical potency of
[5] Equivalent to 15 mg of darifenacin based on a drug substance theoretical potency of
[6] White ( ) contains Lactose Monohydrate (NF), Hydroxypropyl Methylcellulose Titanium Dioxide (USP), and Triacetin (USP).
[7] Orange ( ) contains Lactose Monohydrate (NF), Hydroxypropyl Methylcellulose Titanium Dioxide (USP), Triacetin (USP) and FD&C Yellow # 6 Aluminium Lake.
[8] Vehicle for film-coats. ( )
[9] Clear ( ) contains Hydroxypropyl Methylcellulose (USP) and Triacetin (USP).

What is the proposed mechanism of action?
Darifenacin is a selective, competitive muscarinic M_3-receptor antagonist. It inhibits muscarinic M_3-receptor mediated bladder and gastrointestinal smooth muscle contraction.

What is the proposed indication and dose?
Darifenacin is indicated for the treatment of overactive bladder. For all patients, the recommended starting dose is 7.5 mg daily. For those patients requiring greater symptom relief, the dose may be increased to 15 mg daily as early as 2 weeks after starting therapy.

B. General Clinical Pharmacology

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint of darifenacin was change in number of incontinence episodes per week from baseline to Week 12. The changes in number of micturitions and in number of episode of urgency from baseline to endpoint were defined as two of the secondary endpoints.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?
Yes.

What are the basic pharmacokinetic characteristics of Darifenacin?
The intrinsic PK properties of darifenacin have been evaluated from administration of single i.v. bolus doses over the range 0.6-6 mg. Independent of i.v. dose over the range studied, darifenacin had a Vd_{ss} well in excess of total body water (V_{ss} 168-276 L) while clearance was in the range 36-54 L/h, resulting in values of $t_{1/2}$ between 3.5 and 4.5 h. Dose proportionality analyses showed that both C_{max} and total darifenacin exposure increased proportionally with dose indicating that darifenacin i.v. PK are linear with dose. However, the pharmacokinetics of oral darifenacin at steady state were not dose proportional for either the IR capsules or ER tablets.

How does pharmacokinetics of ER formulation compare with IR formulation?
Estimates of $t_{1/2}$ from ER tablets (12.8 – 18.7 hrs) were considerably longer than corresponding values from IR capsule formulations (3 – 4 hrs) indicating that the extended release profile of the ER tablets causes absorption rate-limited elimination. The bioavailability was about 73% higher following the ER tablet formulation than corresponding IR capsule formulation at steady state. The inter-subject variability in darifenacin exposure was higher for both ER (CV % of 57%) and IR (CV % of 66%) formulations than for i.v. dosing (CV% of 21%). The C_{max} of the ER and IR formulations were similar but C_{avss} and C_{24} were both 70-79% higher from the ER tablets than the IR capsules. The ER tablet formulation showed smaller fluctuations in darifenacin plasma concentrations compared with IR capsule formulation (—).

Three studies were conducted to compare the pharmacokinetics of ER and IR formulations of darifenacin (Studies JP-95-501, 218, 222).

Single Dose Comparison (Study JP-95-501): A single-blind, two cohort, two step, four period, nine treatment, escalating dose design, placebo-controlled crossover study was conducted in 20 healthy Japanese male subjects aged 20-30 years to compare the PK of darifenacin following administration of a single IR capsule and ER tablet after a two-week washout period between the two formulations. During each period of the first step, subjects in the first cohort received an IR capsule 5 mg, ER tablet 5 mg, or placebo while subjects in the second cohort received an IR capsule 7.5 mg, ER tablet 7.5 mg or placebo. During each period of the second step, subjects in the first cohort received IR capsule 15 mg (2 x 7.5 mg), ER tablet 15 mg or placebo, while subjects in the second cohort received IR capsule 20 mg (4 x 5 mg), ER tablet 20 mg or placebo. Plasma (up to 72 hrs) and urinary (up to 96 hrs) concentrations of darifenacin were obtained at intervals after drug administration in each period. Log-transformed AUC_{72}, C_{max} and untransformed T_{max} were compared using ANOVA.

Figure 1. Mean Profiles for Plasma Concentrations of Darifenacin Following a Single Dose of ER Tablets and IR Capsules

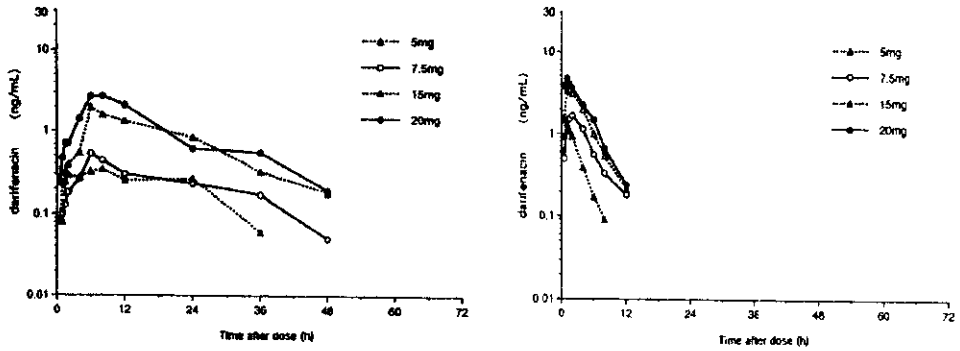


Table 3. The Pharmacokinetic Parameters of Darifenacin

Parameters of Darifenacin	CR tablet	IR capsule	Ratio of means (%)[c]	90% CI for ratio of means[c]
5mg				
$AUC_{0\infty}$[a] (ng·h/mL)	6.31	3.03	207.88	111.37, 388.0
C_{max}[a] (ng/mL)	0.39	1.35	28.95	16.92, 49.52
$MRT_{0\infty}$[a] (h)	14.68	2.19	670.17	547.10, 820.93
T_{max}[b] (h)	9.50	0.94	8.56[d]	411, 13.02
7.5mg				
$AUC_{0\infty}$[a] (ng·h/mL)	8.15	4.91	165.93	106.20, 259.27
C_{max}[a] (ng/mL)	0.41	1.10	37.27	22.75, 61.07
$MRT_{0\infty}$[a] (h)	18.20	3.75	484.88	378.27, 621.54
T_{max}[b] (h)	11.00	1.69	9.31[d]	4.11, 14.52
15mg				
$AUC_{0\infty}$[a] (ng·h/mL)	32.58	13.22	246.48	159.15, 381.74
C_{max}[a] (ng/mL)	1.94	3.39	57.37	42.64, 77.20
$MRT_{0\infty}$[a] (h)	16.60	3.82	434.84	312.91, 604.27
T_{max}[b] (h)	9.75	1.13	8.63[d]	4.17, 13.08
20mg				
$AUC_{0\infty}$[a] (ng·h/mL)	40.29	16.03	251.29	176.89, 356.99
C_{max}[a] (ng/mL)	2.18	3.81	57.33	41.91, 78.42
$MRT_{0\infty}$[a] (h)	17.11	3.83	446.70	327.98, 608.41
T_{max}[b] (h)	11.50	1.00	10.50[d]	3.69, 17.31

[a] Geometric mean. [b] Arithmetic mean. [c] Back transformed from the log scale. [d]difference between Arithmetic means (h). CI = confidence interval.

- The AUC_{72} and C_{max} values of darifenacin after dosing with ER tablets were higher by 66 – 151 % and lower by 43 – 71%, respectively, than that with IR capsules at all doses.
- The mean T_{max} values were between 9.5 to 11.5 hours after dosing with ER tablets and these values were higher than that of IR capsules (0.9 to 1.7 hrs) at all doses.
- The mean cumulative urinary excretion rates of darifenacin 96 hours following single dose oral administration were low for both ER (<0.3 %) and IR (<0.2 %) formulations. More than 60% of the darifenacin excreted in the urine up to 96 hours post-dose had been excreted by 24 hours post-dose, and 90% or more by 48 hours following administration of ER tablets.
- The observed apparent $t_{1/2}$ of ER tablets was 11 to 13 hours while much shorter $t_{1/2}$ was observed with IR capsules (1.8 – 3.9 hrs).
- The CV values for the AUC_{72} of ER and IR darifenacin administered were 46 – 89% and 70 – 118%, respectively.

Steady State Comparison: Study 218 An open, randomized, four-way crossover study without washout was conducted in healthy male subjects aged 21 to 40 years to evaluate the effect of dose on the PK of darifenacin after ER tablets (7.5, 15, and 30 mg once daily for 10 days) and IR oral capsules (2.5, 5, and 10 mg three times daily for 10 days) in fasting state, and to determine the time to reach steady state of darifenacin after administration of ER formulation. During three

periods, subjects were administered ER tablets at three dose levels (7.5, 15, 30 mg) once daily for 10 days per period without washout. For the remaining period, subjects received IR capsule at one of three possible doses (2.5, 5, 10 mg) three times daily. For debrisoquine phenotyping, subjects were given debrisoquine (10 mg tablet) to take immediately after emptying their bladders before bed on the day before the follow-up visit. All urine was then collected from the time of dosing until attending the clinic the next day at the follow-up. Baseline blood samples were taken pre-dose on the morning of the first day of the first treatment period. Subsequently, plasma concentrations of darifenacin were obtained pre-dose on Days 3, 5, 7, 9, and 10 and at intervals up to 24 hours on Day 10 of each treatment period (0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 14, 16, 16.5, 17, 17.5, 18, 18.5, 20, and 24 hours for IR; 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 24 hours for ER). Log-transformed and dose-normalized (to 15mg) AUC_{24}, C_{max}, and untransformed T_{max} were analyzed using ANOVA.

Table 4. Summary of Steady State Darifenacin PK Parameters from IR Capsule and ER Tablet Dosing.

	IR capsules unadjusted mean			CR tablets unadjusted mean		
	2.5mg tid (N=9)	5mg tid (N=8)	10mg tid (N=8)	7.5mg od (N=25)	15mg od (N=26)	30mg od (N=25)
AUC_t (ng.h/ml)	15.3	40.1	167	30.8	75.1	188
C_{max} (ng/ml)	1.78	3.83	14.4	2.09	4.65	11.5
T_{max} (h)	1.7	1.9	1.4	7.0	7.5	8.1
C_{avss} (ng/ml)	0.637	1.67	6.96	1.28	3.13	7.82
C_{24} (ng/ml)	0.352	1.03	4.54	0.915	2.40	6.06
C_{max}/C_{24}	5.06	3.72	3.17	2.28	1.94	1.90
PTFR	2.18	1.65	1.35	0.798	0.627	0.632

Source: Study 137-218 Tables 5.1.1-5.1.7

Geometric mean for AUC_t, C_{max}, C_{24}, C_{avss}, C_{max}/C_{24} and PTFR. Arithmetic mean for T_{max}

- Absorption of darifenacin was rapid after IR dosing with mean T_{max} values of 1.4 – 1.9 hours. The T_{max} values were longer for the ER formulations (7.0 – 8.1 hrs).

Table 5. Comparison of Steady State Darifenacin PK Parameters from IR Capsule and ER Tablet Dosing (Dose Normalized).

	Ratio or difference between adjusted means (90% CI)		
	IR 2.5mg tid *vs* CR 7.5mg od	IR 5mg tid *vs* CR 15mg od	IR 10mg tid *vs* CR 30mg od
AUC_t (ng.h/ml)	1.61 (1.31, 1.98)	1.75 (1.41, 2.17)	1.50 (1.21, 1.86)
C_{max} (ng/ml)	0.96 (0.76, 1.20)	1.17 (0.92, 1.48)	1.03 (0.81, 1.30)
T_{max} (h)	4.6 (2.5, 6.7)	5.6 (3.5, 7.8)	7.0 (4.9, 9.2)
C_{avss} (ng/ml)	1.61 (1.31, 1.98)	1.75 (1.41, 2.17)	1.50 (1.21, 1.86)
C_{24} (ng/ml)	1.96 (1.47, 2.60)	2.20 (1.64, 2.95)	1.85 (1.37, 2.48)
C_{max}/C_{24}	0.49 (0.38, 0.63)	0.53 (0.41, 0.69)	0.56 (0.43, 0.72)
PTFR	0.39 (0.29, 0.52)	0.41 (0.30, 0.55)	0.42 (0.31, 0.57)

Source: Study 137-218 Table 5.4

Geometric mean for AUC_t, C_{max}, C_{avss}, C_{24}, C_{max}/C_{24} and PTFR. Arithmetic mean for T_{max}

- The AUC_{24} values for darifenacin were 50 – 75% higher after ER tablets than after IR capsules. The overall ratio between geometric means indicates that C_{max} for the ER tablet was 5% higher than for the IR capsule.
- The C_{24} values were about 100% higher after ER than after IR dosing.
- The PTFR for darifenacin was about 60% lower after administration of ER tablets than after IR capsules

Figure 2. Mean Plasma Concentrations of Darifenacin at Steady State on Day 10

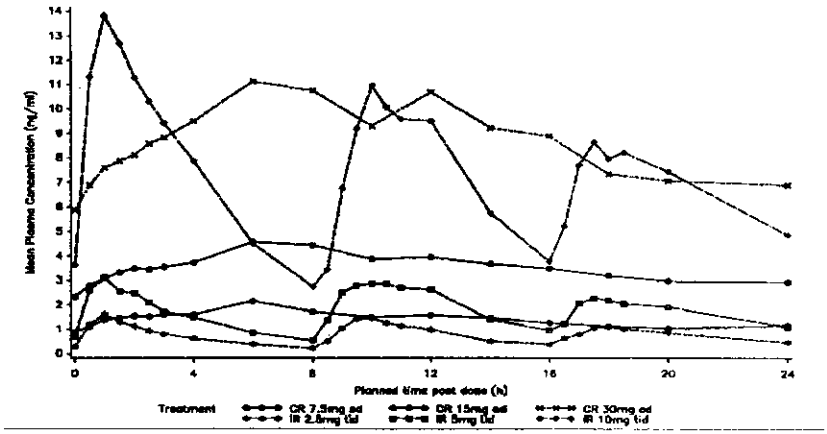
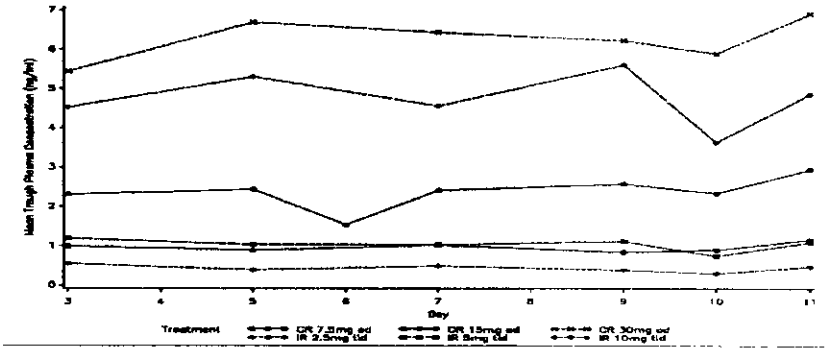


Figure 3. Mean Trough Plasma Concentrations of Darifenacin



Multiple Dose Comparison: Study 221

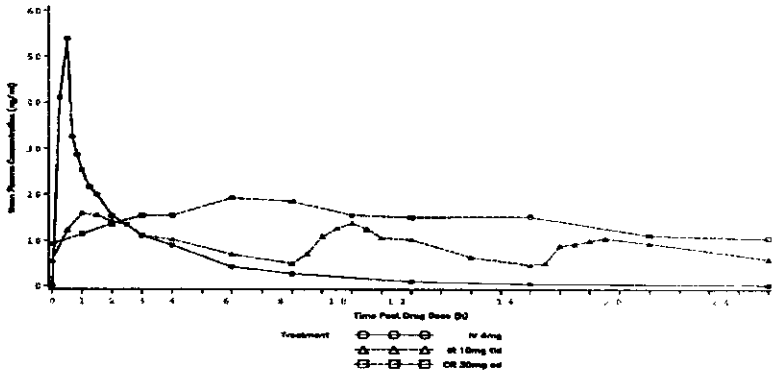
Table 6. Comparison of Steady State Darifenacin PK Parameters from IR Capsules 10 mg t.i.d. and ER Tablets 30 mg Once Daily Dosing

	Adjusted mean		Ratio or difference between adjusted means (90% CI)
	IR capsules 10mg tid (N=22)	CR tablets 30mg od (N=24)	
AUC_{24} (ng.h/ml)	178.2	301.7	1.73 (1.47, 2.03)
C_{max} (ng/ml)	17.65	19.91	-
C_{24} (ng/ml)	4.84	8.78	1.79 (1.52, 2.12)
C_{avss} (ng/ml)	7.42	12.6	1.70 (1.47, 1.97)
k_{el} (/h)	0.10	0.10	-0.001 (-0.014, 0.013)
PTFR	1.67	0.75	0.46 (0.35, 0.61)

Source: Study 137-221 Tables 5.1.4 and 5.1.5
Geometric mean for AUC_{24}, C_{max}, C_{24}, C_{avss} and PTFR. Arithmetic mean for k_{el}

- The inter-subject variability in darifenacin exposure was higher for both ER (CV % of 57%) and IR (CV % of 66%) formulations than for i.v. dosing (CV% of 21%).
- The ER tablet formulation showed smaller fluctuations in darifenacin plasma concentrations compared with IR capsule formulation (0.75 vs. 1.67).
- C_{max} of the ER and IR formulations were similar but C_{avss} and C_{24} were both 70-79% higher from the ER tablets than the IR capsules.

Figure 4. Mean Plasma Concentrations on Study Days 1 (i.v. infusion) and 10 at Steady State (ER tablet and IR capsule)



Is the dose selected for ER justified by pharmacokinetic comparison with IR formulation?

Pharmacokinetics (ADME)

Absorption

Absorption of darifenacin from the GI tract is rapid. Following administration of an oral solution in the fasting state, darifenacin rapidly appeared in the peripheral circulation and C_{max} occurred approximately 1 hour after dosing. The rate of absorption of darifenacin from ER tablets is limited by the rate of release of the drug from the tablet matrix. In a single ER dose pharmacokinetic study, C_{max} occurred at around 10 hr while pooled data from studies using repeated ER tablet dosing indicate that C_{max} from 7.5mg and 15 mg ER tablets at steady state is achieved approximately 7 hours after drug dosing. Estimates of the rate of absorption from the ER tablets were low. Low oral bioavailability is mainly due to extensive first-pass metabolism.

Absolute Bioavailability

The intrinsic pharmacokinetics properties of darifenacin were evaluated from administration of single i.v. bolus doses (0.6 – 6 mg) in two studies (Study 219, Study 221). A steady state Vd and clearance of darifenacin were 168 – 276 L and 36 – 54 L/hr, respectively, with a $t_{1/2}$ of 3.5 – 4.5 hrs. Darifenacin i.v. pharmacokinetics showed dose proportionality. The mean absolute bioavailability of darifenacin from 30 mg ER tablets was estimated to be 37% at steady state in a mixed EM and PM population.

Low bioavailability of darifenacin from oral dosing is mainly due to extensive first-pass metabolism since it is predominantly cleared by metabolism. In addition, darifenacin undergoes significant metabolism in the gut wall. The time- and dose-dependent bioavailability with oral darifenacin is proposed to be related to the metabolism of darifenacin. At steady state, there is a reduction in the relative contribution of CYP2D6 metabolism to darifenacin oral clearance with time which results an increase in bioavailability of darifenacin. In addition, it is proposed that dose-dependency reflects increasing saturation of CYP3A4-mediated gut wall metabolism at higher doses. While the reduction in CYP2D6 contribution at steady state is apparently related to dose and could contribute to the dose-dependency at steady state, darifenacin oral bioavailability also departs from linearity after a single oral dose. Therefore, the sponsor proposed that it is more likely that dose-dependency arises from concentrations of darifenacin in the gut wall

saturating CYP3A4-mediated gut wall metabolism. Incomplete absorption is unlikely since very little unchanged darifenacin is recovered from feces (<2% of a radiolabeled dose).

Study 219 (Dose proportionality, Single escalating dose): A double blind, randomized, placebo controlled, four-period, four-treatment, four-way crossover study was conducted in 8 healthy white male subjects (7 EM, 1 PM) aged 22 to 38 years to evaluate the PK of darifenacin after administration of a single i.v. dose of 0.6 mg, 2 mg, 6 mg, or placebo infused over 30 minutes after a 7-day washout period between treatments. Debrisoquine phenotyping (a single dose of 10 mg) was performed for all 8 subjects. Plasma concentrations of darifenacin were obtained pre-dose on Day 1 and at intervals up to 72 hours post-dose in each study period. Log-transformed AUC_t, AUC_∞, C_{max}, CL, and V_{ss} were analyzed using ANOVA. The values for AUC_t, AUC_∞, and C_{max} were dose normalized to 2 mg prior to analysis. The power law model was fitted for AUC_t, AUC_∞, and C_{max} to evaluate dose proportionality based on regression analysis.

Figure 5. Mean Plasma Concentrations of Darifenacin after a Single i.v. Dose (0.6 mg, 2 mg, and 6 mg)

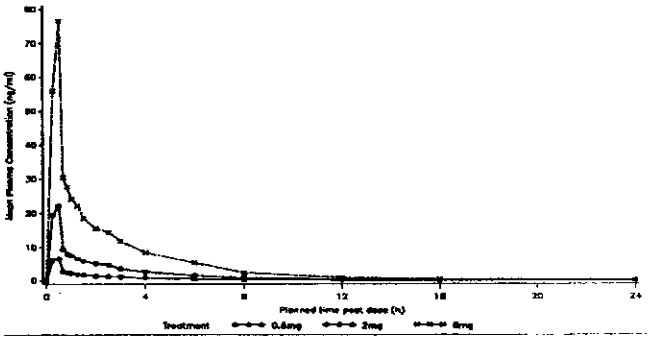


Table 7. Summary of Darifenacin PK Parameters from a Single i.v. Dose (0.6 mg, 2 mg, and 6 mg)

	Unadjusted mean			Dose proportionality constant (95% CI)	p value
	0.6mg (N=8)	2mg (N=8)	6mg (N=8)		
AUC (ng.h/ml)	11.6	37.3	119.8	1.02 (0.99, 1.06)	0.1199
AUC_t (ng.h/ml)	11.3	37.0	119.4	1.01 (0.98, 1.05)	0.4733
C_{max} (ng/ml)	6.58	23.30	73.14	1.05 (0.96, 1.13)	0.2644
T_{max} (h)	0.4	0.4	0.5	-	-
k_{el} (/h)	0.209	0.192	0.168	-	-
$t_{1/2}$ (h)	3.5	3.8	4.3	-	-
CL (L/h)	51.6	53.7	50.1	-	-
V_{ss} (L)	186	180	168	-	-

Source: Study 137-219 Tables 5.1.4 and 5.1.5

Geometric mean for AUC, AUC_t and C_{max}. Arithmetic mean for T_{max}, k_{el} and $t_{1/2}$

- The pharmacokinetics of darifenacin were dose proportional after i.v. doses of 0.6 mg to 6 mg darifenacin.
- CL (50 – 54 L/hr) and V_{ss} (168 to 186 L) were both independent of dose.
- The inter-subject variability was <25% for all PK parameters. Inter-subject variabilities of AUC and C_{max} were 7.0% and 18.8%, respectively.

Table 8. Comparison of Darifenacin Exposure from a Single i.v. Dose (0.6 mg, 2 mg, and 6 mg).

	Dose normalized mean			Ratio between dose normalized means (90% CI)		
	0.6mg	2mg	6mg	2mg vs 0.6mg	6mg vs 0.6mg	6mg vs 2mg
AUC (ng.h/ml)	38.8	37.3	39.9	0.96 (0.90, 1.02)	1.03 (0.97, 1.10)	1.07 (1.01, 1.14)
AUC_t (ng.h/ml)	37.6	37.0	39.8	0.98 (0.93, 1.04)	1.06 (1.00, 1.12)	1.08 (1.02, 1.14)
C_{max} (ng/ml)	21.94	23.30	24.38	1.06 (0.90, 1.25)	1.11 (0.94, 1.31)	1.05 (0.89, 1.24)

Source: Study 137-219 Table 5.1.4
Geometric mean for AUC, AUC_t and C_{max} dose normalized to 2mg darifenacin

CYP2D6 Phenotyping:

- The AUC_∞ and AUC_{72} at 6 mg darifenacin was higher (156 ng*hr/mL for both) in one PM subject than in 7 EM subjects (ranges, [redacted] ng*hr/mL and [redacted] ng*hr/mL). However, C_{max} values for 0.6 mg, 2 mg and 6 mg darifenacin for the PM were within the range of values obtained for the EMs.

Study 221 (MD, Phenotype): An open label, randomized, three-period, three-treatment, three-way crossover study was conducted in 26 healthy male subjects aged 20-45 years to evaluate the absolute and relative BA of darifenacin at steady state. Subjects were administered a single 4 mg i.v. dose (30 minute infusion) with washout period of 17 days, ER tablets 30 mg once daily for 10 days and IR capsules 10 mg (2 x 5 mg) t.i.d. for 10 days with washout period of 7 days in each study period. At the end of study period, subjects were instructed to take a 10 mg debrisoquine tablet after they emptied their bladders the evening before the follow-up visit and collect urine. Plasma concentrations of darifenacin were obtained at intervals on Day 1 for the i.v. regimen (up to 72 hours post-dose) and pre-dose on Days 1, 3, 5, 7, and 9 and at intervals on Day 10 for the oral regimens (up to 72 hours post-dose). Log-transformed AUC_{24} and C_{max} were analyzed by using ANOVA. Steady State was achieved by Day 6 for all formulations. Absolute bioavailability was assessed by comparing AUC_{24} for both the IR and ER formulations with AUC obtained for the IV dose. AUC was dose normalized to 30 mg. Relative bioavailability was assessed by comparing AUC_{24} on IR with AUC_{24} on ER.

Table 9. Summary of Darifenacin PK Parameters

	Unadjusted mean			Ratio or difference between dose normalized adjusted means (90% CI)*	
	iv 4mg (N=23)	IR caps 10mg tid (N=22)	CR tabs 30mg od (N=24)	IR capsules vs iv	CR tablets vs iv
AUC† (ng.h/ml)	113.0	178.2	291.3	0.22 (0.18, 0.25)	0.37 (0.32, 0.44)
C_{max} (ng/ml)	57.45	17.65	18.97	0.04 (0.04, 0.05)	0.05 (0.04, 0.06)
T_{max} (h)	0.5	1.4	9.7	-	-
k_{el} (/h)	0.152	0.098	0.098	-0.052 (-0.065, -0.038)	-0.052 (-0.066, -0.039)
$t_{1/2}$ (h)	4.5	7.1	7.1	-	-
F (%)	-	21.5	37.1	-	-
CL (L/h)	36.1	-	-	-	-
V_{ss} (L)	276	-	-	-	-

Source: Study 137-221 Tables 5.1.1, 5.1.2 and 5.1.4
Geometric mean for AUC and C_{max}. Arithmetic mean for T_{max} and k_{el}. Harmonic mean for $t_{1/2}$.
* AUC and C_{max} are dose normalized to 30mg. † AUC_{24} for CR and IR formulations, and AUC for iv dose.

- The Absolute bioavailability of darifenacin at steady state was estimated to be 37% for the 30 mg ER tablets and 22% for the IR capsules in a mixed EM and PM population.
- Mean CL of darifenacin was 36.1 L/hr (range [redacted] L/hr) and mean V_{ss} was 276 L (range . [redacted]) after the IV infusion.

2D6 PM

- Following IV administration, the AUC_{24} of darifenacin for the PM subjects (n=4) ranged from [redacted] ng*hr/mL which was within the range of values for the EMs ([redacted] ng*hr/mL).
- For the ER and IR formulations, AUC_{24} values of 203 to 284 ng*hr/mL and 115 to 204 ng*hr/mL, respectively, were within the range of values for the EMs ([redacted] ng*hr/mL and [redacted] ng*hr/mL, respectively).

Distribution

Darifenacin has a steady state V_d of 168-276 L indicating that darifenacin is extensively distributed into body tissues. Darifenacin is highly bound to plasma proteins. Equilibrium dialysis of human plasma samples mixed with darifenacin *in vitro* indicated that darifenacin is 98% bound corresponding to f_u of 2%. Plasma protein binding of darifenacin is lower among subjects with hepatic impairment but is not reduced by renal impairment. In vitro studies indicate that darifenacin is bound to α-1-acid glycoprotein.

Table 10. Estimated f_u from Subjects with Varying Degrees of Renal and Hepatic Impairments

		Renal or hepatic function category			
		Normal	Mild	Moderate	Severe
Renal impairment (A1371004)	N	1	2	4	2
	f_u (%)	2.0	2.3	1.2	1.1
	Range	-	1.7–2.8	0.9–1.5	0.9–1.5
Hepatic impairment (A1371005)	N	9	5	5	-
	f_u (%)	1.7	3.3	4.5	-
	Range	1.3–2.2	1.4–5.1	3.1–6.1	-

Source: Study A1371004 Table 5.1.9, Study A1371005 Tables 5.3.1 to 5.3.3

Metabolism and Excretion

Darifenacin is cleared almost exclusively by metabolism and has a high hepatic extraction ratio of 0.73. In vitro studies and clinical interaction data have demonstrated that CYP3A4 and CYP2D6 mediate the clearance of darifenacin in human.

The relative amounts of the metabolites recovered from urine and feces suggests that about 40% of the darifenacin dose is metabolized via the hydroxylation pathway, while 40% of the darifenacin dose is metabolized via the ring-opening pathway and 10% is N-dealkylated. Darifenacin is rapidly cleared from the peripheral circulation. Clearance of darifenacin was in the range 36-54 L/hr with $t_{1/2}$ between 3.5 and 4.5 hours following i.v. infusions of darifenacin solution. Clearance of darifenacin is primarily achieved through metabolism. Less than 2% of a dose is excreted unchanged in urine indicating that the renal contribution to total clearance is minimal.

Study 209: Study of the Absorption, Metabolism, and Excretion of a Single Oral Dose of [^{14}C] Darifenacin following Multiple Dosing with Darifenacin 5 mg three times daily.

An open study of the absorption, metabolism, and excretion of a single oral dose of [^{14}C] darifenacin following multiple dosing with darifenacin 5 mg three times daily was conducted in 6 healthy male subjects aged 18 to 45 years (1) to measure the cumulative amount of drug-related radiolabelled material excreted in the urine and feces following a single oral dose of 5 mg [^{14}C] darifenacin at steady state; (2) to determine the time course of elimination; (3) to characterize urinary and fecal radioactivity as unchanged darifenacin or metabolites; (4) to quantitate blood and plasma total radioactivity and unchanged drug concentrations during the 9 days immediately following dosing. Subjects were administered oral IR darifenacin 5 mg capsules three times daily for 5 days, then twice on Day 6. A single dose of 15μ Ci radiolabelled [^{14}C] darifenacin was

administered on Day 6. PK parameters were derived from plasma concentrations of darifenacin, UK-148,993, and total radioactivity obtained pre-dose on Day 6, and at fixed intervals post-dose up to Day 15. Urine and feces were collected to determine the route and rate of excretion, and identification of metabolites.

Table 11. The Mean PK Results of Darifenacin, UK-148,993 and Total Radioactivity.

	Poor metabolisers	Extensive metabolisers	All subjects
Darifenacin			
AUC_τ (ng.h/ml)[a]	20.6 (9.6)	15.0 (29.9)	17.6 (19.9)
C_{max} (ng/ml)[a]	5.48 (2.39)	4.62 (4.74)	5.03 (3.36)
T_{max} (h)[b]	0.7 (0.3)	1.3 (1.4)	1.0 (1.0)
UK-148,993			
AUC_τ (ng.h/ml)[a]	37.9 (11.7)	40.3 (27.5)	39.1 (19.2)
C_{max} (ng/ml)[a]	8.95 (1.95)	10.46 (5.38)	9.68 (3.85)
T_{max} (h)[b]	0.5 (0.0)	0.7 (0.3)	0.6 (0.2)
Total radioactivity			
AUC_τ (ng equivalents.h/ml)[a]	340 (54.1)	314 (10.3)	327 (38.2)
C_{max} (ng equivalents/ml)[a]	100 (19.1)	111 (30.3)	105 (23.6)
T_{max} (h)[b]	0.8 (0.3)	0.7 (0.3)	0.8 (0.3)
k_{el} (/h)[b]	0.0607 (0.0024)	0.0750 (0.0540)	0.0678 (0.0351)
$t_{1/2}$ (h)[c]	11.4 (0.5)	9.3 (6.3)	10.2 (4.0)

[a]Geometric mean. [b]Arithmetic mean. [c]Harmonic mean.

Table 12. The Cumulative Radioactive Excretion in Urine and Feces

	Mean cumulative excretion (sd)
Urine	58% (4%)
Faeces	43% (4%)
Total	101%

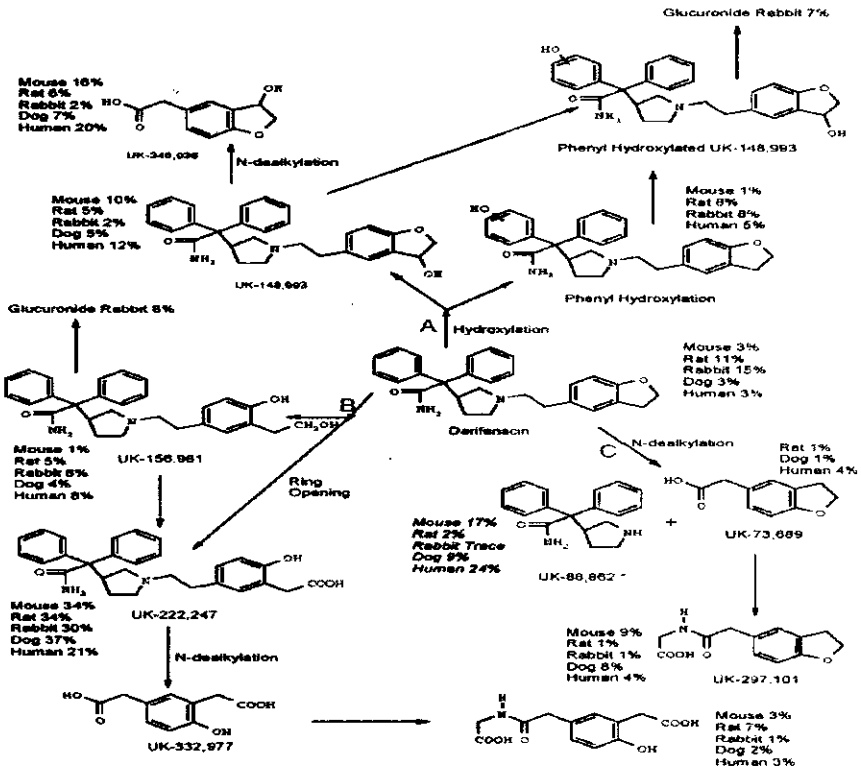
- An estimated 101% of the dose was excreted in the feces and urine combined.
- The cumulative radioactive excretion in urine and feces over 216 hours is expressed as a percentage of the administered dose.
- A high proportion of radioactivity (71%) was excreted during the first 48 hours of dosing. Mean cumulative radioactivity excretion reached a plateau by 144 hours for feces and by 120 hours for urine.
- The major circulating metabolite was the dihydrobenzfuran ring opened acid metabolite (UK-73,689) accounting for about 60% of the chromatogram. Another circulating metabolite was the dihydrobenzfuran ring hydroxylated metabolite (UK-148,993) accounting for 7 % of the chromatogram.
- The major urinary metabolites were UK-346,036 (N-dealkylation) representing 20 % of the excreted dose. UK-73,689 and UK-222,247 each represented 4% of the dose in urine. UK-88,862 represented a mean of 24% of the excreted dose in urine.
- In feces, UK-222,247 was one of the major metabolites with 17 % of the dose excreted in the feces. UK-148,993 was also present in the feces (7% of the dose).
- In EMs, a phenyl mono-hydroxylated version of darifenacin was excreted in the feces, representing 5% of the dose.
- Unchanged darifenacin was present in small amounts in both urine and feces (<2 %).

RBC penetration:

	Mean radioactivity (ng/ml)	
	Whole blood	Plasma
0.5 hours	61.0	98.0
1 hours	59.5	95.3
1.5 hours	47.2	77.8
2 hours	37.7	64.3
2.5 hours	31.5	53.3
3 hours	26.4	42.8
4 hours	23.0	32.7

- The concentration of radioactivity in whole blood was about 60% of that in plasma indicating poor penetration of darifenacin into RBC. The mean blood to plasma ratio was 0.68.

Figure 6. Schematic Representation of the Pathways for Darifenacin Metabolism in Humans.



In Vitro Metabolism

In vitro studies using microsomes to determine the enzyme pathways involved in metabolism of darifenacin demonstrated that darifenacin is metabolized via CYP2D6 and CYP3A4 pathways. Hydroxylation of darifenacin to form UK-148,993 was mediated by high affinity (K_m 4 μM) and low affinity (K_m 47 μM) components. Inhibition studies with quinidine and ketoconazole showed that the high affinity component was comprised of both CYP2D6 and CYP3A4 whereas the low affinity component was entirely CYP3A4. Similar studies on the N-dealkylation of darifenacin to UK-88,862 and UK-73-689 showed that this route of metabolism was mediated by CYP3A4 only (K_m 102 μM).

The primary metabolic route of darifenacin at steady state appeared to be the CYP3A4 route for both phenotypically EMs and PMs. In vitro testing against a standard probe CYP3A4 substrate, midazolam, ketoconazole exhibited an inhibitory K_i value of 0.1 μM while paroxetine had a value of 38 μM. Fluconazole was selected as a CYP3A4 inhibitor with in vitro K_i value of 11 μM.

Darifenacin is a competitive inhibitor of both CYP2D6 (IC_{50} 2-6 μM) and CYP3A4 (IC_{50} 5 μM vs. midazolam) *in vitro*. Its metabolite, UK-148,993 is a weaker inhibitor of both CYP2D6 (IC_{50} 16 μM) and CYP3A4 (IC_{50} > 45 μM) but may act as a mechanism-based inhibitor of CYP2D6 (IC_{50} 8 μM after pre-incubation). Neither UK-88,862 nor UK-73,689 inhibited CYP2D6 or CYP3A4.

Pharmacokinetics of Extended Release Tablets

Relative Bioavailability

ER Tablets vs. Solution: There were no studies which compared the bioavailability of the 18 hr release ER tablets (TBM, Early Clinical Research and Clinical Research formulations) with that of the oral solution. However, Study 214 compared darifenacin PK from a single 8 hr release ER tablet with those of an oral solution and a solution delivered to the ileocaecal region by intubation.

ER Tablets vs. IR Capsules: The bioavailability of darifenacin from ER tablets was compared with the IR capsule formulations after a single dose (Study JP-95-501) and at steady state (Study 218, Study 221). The bioavailability of darifenacin from ER tablets was consistently higher than that from corresponding IR capsules. Total darifenacin exposure after a single ER tablet dose was 166-251 % higher than after an equivalent IR capsule dose. Similar results were seen at steady state. The relative bioavailability from the ER tablet 30 mg once daily regimen compared with IR capsules 10 mg t.i.d. in Study 221 was 173%, while the total exposure from 7.5 mg, 15 mg, and 30 mg ER tablets was 50-75% higher than from the IR capsule dosing in Study 218. The sponsor postulated that the differences in bioavailability between ER and IR formulations arise from regional differences in gut wall CYP3A4 expression. Darifenacin delivered to the distal regions of the intestine from ER tablets is potentially subject to lower gut wall first-pass extraction compared with a dose delivered to the top of the GI tract from IR capsules.

ER Tablets vs. Solution (Study 214): An open label, randomized, four-period, four-treatment, four-way crossover study was conducted in 9 healthy white male subjects aged 23 to 41 years to evaluate the effect of site of drug delivery and formulation of the PK of darifenacin. Subjects were administered a single dose of one of four treatments in a fasting state with two weeks washout between doses: (1) an oral solution of 15 mg, (2) a solution of 15 mg delivered to the ileocaecal region of the gastrointestinal tract by intubation, (3) an 8 hr release ER tablet of 20 mg, (4) an 8 hr release ER capsule of 20 mg. Plasma concentrations of darifenacin were obtained pre-dose and at fixed intervals up to 96 hours post-dose. Log-transformed AUC_t, C_{max} and AUC_∞ and untransformed T_{max} were analyzed using ANOVA. The PK parameters for the ER tablet and ER capsule groups were dose normalized prior to analysis (multiplying by 0.75).

Table 13. Summary of Darifenacin PK Parameters

	Unadjusted mean			Ratio or difference between dose normalized adjusted means (90% CI)*	
	Oral solution (15mg) (N=8)	Ileocaecal solution (15mg) (N=8)	8h release CR tablet (20mg) (N=8)	Ileocaecal solution vs oral solution	8h release CR tablet vs oral solution
AUC (ng.h/ml)	30.7	46.5	68.5	1.52 (1.14, 2.02)	1.67 (1.26, 2.23)
AUC_t (ng.h/ml)	30.3	45.8	66.9	1.48 (1.12, 1.96)	1.47 (1.11, 1.94)
C_{max} (ng/ml)	10.92	14.93	4.52	1.37 (0.998, 1.87)	0.31 (0.23, 0.43)
T_{max} (h)	0.5	1.3	7.1	0.8 (-0.8, 2.4)	6.6 (5.0, 8.2)
k_{el} (/h)	0.220	0.158	0.073	-0.062 (-0.094, -0.031)	-0.147 (-0.178, -0.115)
$t_{1/2}$ (h)	3.2	4.4	9.5	-	-

Source: Study 137-214 Tables 5.1.1–5.1.3 and Table 5.2
Geometric mean for AUC, AUC_t and C_{max}. Arithmetic mean for T_{max}, k_{el} and $t_{1/2}$
* AUC, AUC_t and C_{max} dose-normalized to 15mg.

- Darifenacin BA was higher (67%) when the drug was administered as an 8 hr release ER tablet than when given as an oral solution indicating that delivery of the drug as an 8 hr release ER tablet reduced the extent of first pass metabolism.
- Delivery of the drug from ER tablets slowed that appearance of darifenacin in the peripheral circulation compared with oral solution (a lower C_{max} and increased T_{max}) and caused absorption rate-limited elimination (a longer $t_{1/2}$ of 9.5 hr) relative to administration by intubation (4.4 hours) or as the oral solution (3.2 hours).
- Delivery of darifenacin as a solution by intubation directly to the ileocaecal region of the GI tract resulted in a 52% increase in systematic availability of darifenacin compared with that obtained from the oral solution, with a similar rate of absorption.

ER Tablets vs. IR Capsules: Single dose comparison (Study JP-95-501): A single-blind, two cohort, two step, four period, nine treatment, escalating dose design, placebo-controlled crossover study was conducted in 20 healthy Japanese male subjects aged 20-30 years to compare the PK of darifenacin following administration of a single IR capsule and ER tablet. During each period of the first step, subjects in the first cohort received an IR capsule 5 mg, ER tablet 5 mg, or placebo while subjects in the second cohort received an IR capsule 7.5 mg, ER tablet 7.5 mg or placebo. During each period of the second step, subjects in the first cohort received IR capsule 15 mg, ER tablet 15 mg or placebo, while subjects in the second cohort received IR capsule 20 mg, ER tablet 20 mg or placebo. Plasma and urinary concentrations of darifenacin and UK-148,993 were obtained at intervals after drug administration in each period.

Figure 7. Mean Profiles for Plasma Concentrations of Darifenacin (ER Tablets)

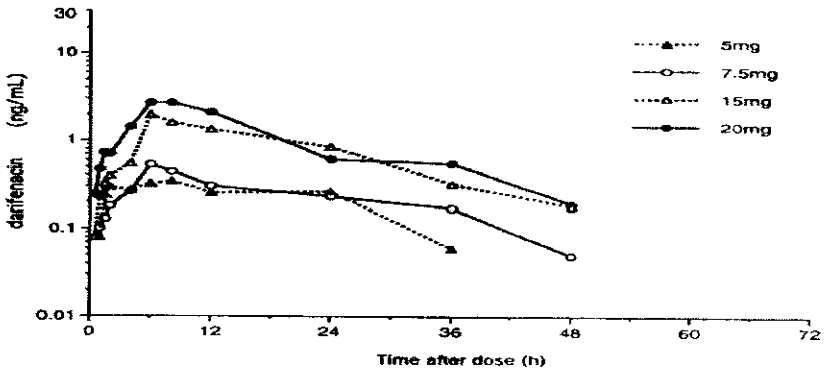


Table 14. Summary of Single Dose Darifenacin PK Parameters from IR Capsules and ER Tablets.

	IR capsule unadjusted mean				CR tablet unadjusted mean			
	5mg (N=8)	7.5mg (N=8)	15mg (N=8)	20mg (N=8)	5mg (N=8)	7.5mg (N=8)	15mg (N=8)	20mg (N=8)
AUC_t (ng.h/ml)	3.0	4.9	13.2	16.0	6.3	8.2	32.6	40.3
C_{max} (ng/ml)	1.35	1.10	3.39	3.81	0.39	0.41	1.94	2.18
T_{max} (h)	0.9	1.7	1.1	1.0	9.5	11.0	9.8	11.5
MRT (h)	2.2	3.8	3.8	3.8	14.7	18.2	16.6	17.1

Source: Study JP-95-501 Tables 5.2.1, 5.2.2, 5.2.3 and 5.2.4
Geometric mean for AUC_t, C_{max}, and MRT. Arithmetic mean for T_{max}

- AUC_t of darifenacin after dosing with ER darifenacin were higher by between 66 and 151 % than that with IR darifenacin at all doses.
- C_{max} values of after administration of ER darifenacin were lower by between 43 and 71% than that with IR darifenacin at all doses.
- T_{max} values were between 9.5 and 11 hours after dosing with ER darifenacin and these values were higher than that of IR darifenacin (0.9 to 1.7 hours) at all doses.
- The mean cumulative urinary excretion rates of darifenacin 96 hours following single dose oral administration were low for both ER darifenacin (0.22 - 0.26%) and for IR darifenacin (0.09 - 0.19%). More than 60% of the darifenacin excreted in the urine up to 96 hours post-dose had been excreted by 24 hours post-dose, and 90% or more had been excreted by 48 hours post-dose.

Table 15. Comparison of Single Dose Darifenacin PK Parameters from IR Capsule and ER Tablet Dosing.

	Ratio between adjusted means (90% CI)			
	IR capsule 5mg vs CR tablet 5mg	IR capsules 7.5mg vs CR tablet 7.5mg	IR capsules 15mg vs CR tablet 15mg	IR capsules 20mg vs CR tablet 20mg
AUC_t (ng.h/ml)	2.08 (1.11, 3.88)	1.66 (1.06, 2.59)	2.46 (1.59, 3.82)	2.51 (1.77, 3.57)
C_{max} (ng/ml)	0.29 (0.17, 0.50)	0.37 (0.23, 0.61)	0.57 (0.43, 0.77)	0.57 (0.42, 0.78)
MRT (h)	6.70 (5.47, 8.21)	4.85 (3.78, 6.22)	4.35 (3.13, 6.04)	4.47 (3.28, 6.09)

Source: Study JP-95-501 Table 5.2
Geometric mean for AUC_t, C_{max}, and MRT.

- AUC_t was 1.66 – 2.51 fold higher from the ER tablets across the dose range tested. However, C_{max} was 43-71% lower from the ER tablets than the IR capsules.
- The CV% values for darifenacin AUC_t of ER (CV% 46 – 89%) and IR (CV% 70-118%) darifenacin indicated moderate variability among the subjects.

ER Tablets vs. IR Capsules: Study 221: (Refer to Absolute BA section for study design, 30 mg)

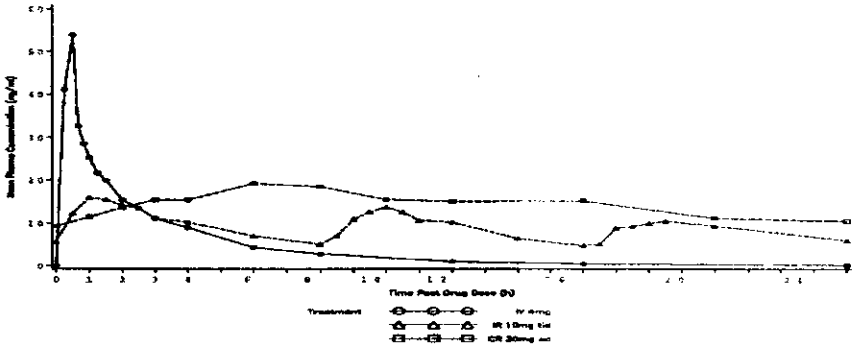
Table 16. Summary of the Statistical Analysis of Steady State Darifenacin PK Parameters Comparisng the IR and ER Formulations.

Parameter	Mean		Ratio (%) / Difference [90% CI]
	IR 10mg tid	CR 30mg od	
AUC_{24} (ng.h/ml) [a,c]	178	302	172.9 [147.3, 203.0]
C_{max} (ng/ml) [a]	7.42	12.6	170.1 [147.0, 196.9]
C_{24} (ng/ml) [a]	4.84	8.78	179.0 [151.5, 211.5]
PTF (ratio) [a]	1.67	0.75	46.1 [35.1, 60.6]
k_{el} (/h) [b]	0.10	0.10	-0.001 [-0.014, 0.013]

Source: Table 5.1.5. [a]Adjusted geometric mean; [b]Adjusted arithmetic mean; [c]CR vs IR gives F_{rel}.

- The F_{rel} of darifenacin for the ER tablet compared with the IR capsule was 173%. (90% CI 147.3, 203.0)
- The PTF for darifenacin at steady state was lower for the ER formulation compared with the IR formulation (0.75 vs. 1.67).
- The C_{max} of darifenacin was similar for the ER and IR formulations (17.7 – 19.9 ng/mL), and $t_{1/2}$ values were the same for both formulations ($t_{1/2}$ of 7.1 hr).

Figure 8. Mean Plasma Concentrations of Darifenacin on Study Days 1 (i.v. infusion) and 10 (ER Tablet and IR Capsule).



Study 218: (Refer to ER/IR PK Comparison section for study design)

Table 17. Ratios of the Dose Normalized (to 15 mg) Means for AUC_{24} and C_{max} (ER tablets 7.5 mg, 15 mg, and 30 mg once daily for 10 days and IR capsules 2.5 mg, 5 mg, and 10 mg t.i.d for 10 days)

	AUC_t		C_{max}	
Comparison:	Ratio Between Geometric Means (%)	90% Confidence Interval	Ratio Between Geometric Means (%)	90% Confidence Interval
7.5mg od/2.5mg tid	161	131, 198	95.6	76.0, 120
15mg od/5mg tid	175	141, 217	117	92.1, 148
30mg od/10mg tid	150	121, 186	103	80.7, 130
overall od/overall tid	162	145, 181	105	92.3, 119

- The total exposure from 7.5 mg, 15 mg, and 30 mg ER tablets was 50-75% higher than from the IR capsule dosing

Dose Proportionality

Dose proportionality analyses showed that both C_{max} and AUC of darifenacin increased proportionally with dose indicating that darifenacin i.v. pharmacokinetics linear with dose (Study 219). However, the pharmacokinetics of darifenacin at steady state were not dose proportional for either the IR capsules (2.5 mg, 5 mg and 10 mg t.i.d. for 10 days) or ER tablets (7.5 mg, 15 mg, and 30 mg once daily for 10 days). Doubling the darifenacin dose resulted in a 151% increase in AUC_t for the ER tablets (dose proportionality constant 1.33, 95% CI 1.21, 1.45) and 160% for the IR capsules (dose proportionality constant 1.38, 95% CI 1.14, 1.62) and there were similar trends in C_{max}, C_{avss}, and C_{24} parameters (Study 218). Doubling the darifenacin dose resulted in a 138% increase in C_{max} for the ER tablets.

Table 18. Analysis of Darifenacin Dose Proportionality for ER Tablets (7.5 mg, 15 mg and 30 mg once daily for 10 days) and IR Capsules (2.5 mg, 5 mg and 10 mg t.i.d. for 10 days)

Slopes of the Regression of log(parameter) against log(dose)			
Darifenacin	***Slope***	***95% Confidence Interval***	***p-value***
AUC_t IR AUC_t CR	1.38 1.33	1.14, 1.62 1.21, 1.45	0.0022 <0.0001
C_{max} IR C_{max} CR	1.20 1.25	0.938, 1.47 1.12, 1.39	0.1321 0.0004
C_{24} IR C_{24} CR	1.44 1.40	1.11, 1.76 1.23, 1.56	0.0090 <0.0001

- Both IR and ER formulations did not exhibit dose-proportionality for AUC_t, C_{max} and C_{24}

Variability in Pharmacokinetics

Darifenacin exhibits time-dependent, non-linear pharmacokinetics as a function of a reduction in the extraction ratio upon repeated dosing and it appears to be related to a reduction in the relative contribution of CYP2D6-mediated metabolism.

Estimates of inter-subject variability in steady state darifenacin exposure from ER tablets in individual Western studies ranged between 33 and 91%, and the CV% for estimates of mean steady state darifenacin AUC_{24} derived from pooling of data from all relevant Phase 1 studies was 47-69% across the dose range tested. The variability in oral BA of darifenacin is likely to be caused by a combination of factors including dose, formulation, CYP2D6 genotype, co-administration of CYP3A4 inhibitors, race, gender, age and hepatic function. In addition, first-pass extraction may be another source of inter-subject variability in darifenacin PK. Inter-subject variability was higher following oral dosing than i.v. administration (AUC CV% 57% for ER tablets 30 mg vs. 21% for single i.v. dose, Study 221) but was similar between oral formulations (AUC_{24} CV% 57% for ER tablets 30 mg vs. 66% for IR capsules 10 mg t.i.d., Study 221). This indicates that the passage of darifenacin from the GI tract into the systemic circulation adds to the PK variability.

Single Dose Pharmacokinetics

Darifenacin exposure at steady state was higher than predicted from single dose data. Darifenacin exposure from 15 mg ER tablets at steady state was 86% higher than after a single dose and doubling of the ER tablet dose increased steady state exposure by approximately 150%. The AUC_∞ and C_{max} values of darifenacin after a single dosing with ER tablets were higher by 66 – 151 % and lower by 43 – 71%, respectively, than that with IR capsules at all doses. The mean T_{max} values were between 9.5 to 11.5 hours following a single dose administration of 7.5 – 20 mg ER tablets. The observed apparent $t_{1/2}$ of ER tablets was 11 to 13 hours while much shorter $t_{1/2}$ was observed with IR capsules (1.8 – 3.9 hrs). The CV% values of AUC for ER formulations following a single dose administration were 46 – 89 %.

Multiple dose Pharmacokinetics

Mean steady state total exposure to darifenacin in healthy male subjects was 27.9 ng*hr/mL from 7.5 mg ER once daily dosing and 79.6 ng*hr/mL from 15 mg ER once daily dosing. Mean peak concentrations at steady state were 1.92 ng/mL and 5.08 ng/mL, respectively. Assuming 98% protein binding, mean peak unbound darifenacin concentrations at steady state were estimated to be 0.04 ng/mL from 7.5 mg ER dosing and 0.10 ng/mL from 15 mg ER dosing. The steady state plasma concentration vs. time profile from ER tablet dosing was uniform across the dosing interval and peak to trough fluctuations were small across the proposed dose range (PFTR 0.7 – 0.9). The inter-subject variability was 47 – 69 % for steady state AUC. The T_{max} values were

between 7.0 – 8.1 hours. The estimated $t_{1/2}$ from ER tablets was around 12.8 – 18.7 hours. Steady state was achieved by Day 6 of dosing for both the ER tablets 7.5 mg and 15 mg.

Darifenacin pharmacokinetics from ER tablets are both time- and dose-dependent. Darifenacin exposure from 15 mg ER tablets at steady state was 86% higher than after a single dose and doubling of the ER tablet dose increased steady state exposure by approximately 150 %. Time-dependency appears to be related to a reduction in the contribution of CYP2D6 metabolism to darifenacin oral clearance after repeated dosing. Dose-dependency may be related to increasing saturation of CYP3A4-mediated gut wall metabolism at higher doses, combined with a dose-dependent reduction in the contribution of CYP2D6-mediated metabolism at steady state.

Study 218: An open label, randomized, four period, six treatment, four-way crossover study was conducted in 26 healthy male subjects to assess the effect of dose on the steady state PK of darifenacin.

Table 19. The Summary of PK of Darifenacin using IR and ER Formulations at Steady State.

Parameter	CR tablets			IR capsules		
	7.5mg od	15mg od	30mg od	2.5mg tid	5mg tid	10mg tid
Plasma AUC_τ (ng.h/ml)	30.8	75.1	187.6	15.3	40.1	166.8
Blood AUC_τ (ng.h/ml)	21.0	51.1	127.6	10.4	27.3	113.5
Oral Clearance (ml/min/kg)	85	70	56	172	131	63
Extraction Ratio	0.76	0.72	0.67	0.85	0.83	0.71
Relative Systemic Availability (%)	22	26	30	12	16	28

- The relative systemic availability increased with increasing dose. The relative systemic availability values for the ER tablets were higher than those for the IR capsules.

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

Efficacy

The primary efficacy endpoint of darifenacin was change in number of incontinence episodes per week from baseline to Week 12. The changes in number of micturitions and in number of episode of urgency from baseline to endpoint were defined as two of the secondary endpoints. In general, darifenacin 7.5 and 15 mg showed a statistically significant improvement in the number of incontinence episode per week over the placebo in a 12-week period. The darifenacin 15 mg treatment group experienced a statistically significant median reduction of 10.4 in the number of incontinence episodes per week from baseline compared to that of 5.9 to 7.6 in the placebo group. The darifenacin 7.5 mg treatment group experienced a statistically significant median reduction of 8.1 and 9.0 in the number of incontinence episodes per week from baseline compared to that of 5.9 to 7.6 in the placebo group. However, subjects treated with darifenacin 15 mg were associated with a higher median improvement in the number of incontinence episodes per week, compared to that of subjects treated with darifenacin 7.5 mg (an improvement of 3.2 vs. 2.0 episodes per week, respectively). The changes in the number of micturitions per week and the number of episodes of urgency from baseline to Week 12 showed the following: Darifenacin 7.5 mg and 15 mg showed a statistically significant improvement in both micturition and urgency outcomes over placebo in a 12-week period. The effects of darifenacin on the number of micturations and number of episodes of urgency were similar for the 7.5 mg and 15 mg groups (an improvement of about 0.8 – 0.9 episodes per day for both outcomes across the two treatment

groups. Improvement in incontinence outcome did not seem to be affected by the incontinence severity at baseline for the darifenacin 7.5 mg group while it seemed to be associated with severity of incontinence at baseline for the darifenacin 15 mg group. The earliest time point to observe the treatment effect was at Week 2 for both darifenacin 7.5 mg and 15 mg groups.

As indicated earlier, the median reduction in number of incontinence episodes per week was 2.0 and 3.2 for darifenacin 7.5 mg and 15 mg, respectively. Darifenacin 30 mg appeared to have the largest treatment effect with a median reduction between 4.2 and 6.3 episodes per week. Darifenacin 3.75 mg was not associated with a significant reduction in number of incontinence episodes per week (reduction of 0.7 per week).

Safety

Adverse events associated with darifenacin appear to be similar to that of other antimuscarinic agents. The majority of adverse events occurred in the first two weeks of the treatment and was dose-dependent. Darifenacin 7.5 mg was well tolerated. Dry mouth, constipation and dyspepsia were the most commonly reported events and they occurred in 20%, 15%, and 3% of the subjects treated with darifenacin 7.5 mg for 12 weeks, respectively. In subjects with darifenacin 15 mg, the corresponding adverse events occurred in 35%, 21%, and 8%, respectively.

CYP2D6 Genotype

Table 20. Discontinuations due to Treatment Related Adverse Events by CYP2D6 Genotype and Dose (OAB Fixed Dose Phase 3 Studies)

	Subjects discontinued – n (%)	
	Poor metabolizers	**Extensive metabolizers**
Darifenacin:		
7.5mg (N = 64 PM, 236 EM)	1(1.6%)	1 (0.4%)
15mg (N = 42 PM, 230 EM)	2 (4.8%)	3 (1.3%)
30mg (N = 20 PM, 233 EM)	3 (15.0%)	17 (7.3%)
7.5mg/15mg (N = 106 PM, 466 EM)	3 (2.8%)	4 (0.9%)
Tolterodine: (N = 14 PM, 167 EM)	0	2 (1.2%)
Placebo: (N = 20 PM, 103 EM)	0	2 (1.9%)

Source: Table 30.5

- Discontinuations due to treatment related adverse events by CYP2D6 genotype and dose were higher in CYP2D6 PMs than in EMs. In OAB fixed dose Phase 3 studies, the rates of discontinuation were 1.6 % (7.5mg), 4.8 % (15mg), and 15.0 % (30mg) in PM subjects whereas 0.4 % (7.5mg), 1.3 % (15mg), and 7.3 % (30mg) of EMs discontinued due to treatment related adverse events.

QT effects of darifenacin

Six Phase 1 and Phase 3 studies were evaluated to assess the QT effects of darifenacin. These studies included a wide range of darifenacin exposures including 60 mg ER (mean C_{max} 8-fold higher than the proposed highest 15 mg dose). 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). There were no apparent mean differences from placebo for heart rate and QTc, overall or in any of the sub-groups analyses based on age and sex. No heart rate effects were demonstrated. However, the mean change of 12 msec from baseline (range: [ ] msec) in QTcF was observed at supra-therapeutic concentrations (mean C_{max} 23 fold higher than the proposed highest 15 mg dose) of darifenacin.

General Comments:

- The concentration-response relationship for QTc prolongation was characterized with exploration of concentrations that were higher than those achieved following the anticipated therapeutic doses of 7.5 mg and 15 mg (Study 1007, darifenacin + ketoconazole drug interaction study).
- The duration of darifenacin dosing was sufficient to ensure that steady-state concentrations were achieved.
- An attempt was made to assess the peak effect of darifenacin on the QTc interval by performing ECG recordings at time point around the C_{max}.
- There was absence of a concurrent placebo-placebo control group in Studies 1005 and 1007.
- There was a lack of a concurrent positive control group to establish assay sensitivity in all five studies.

ECGs were recorded 4 to 9 hours post-dose at steady state following administration of doses ranged from 3.75 mg to 60 mg. ECGs were digitized and centrally read. The supra-therapeutic plasma concentrations were achieved with co-administration of darifenacin 30 mg and ketoconazole 400 mg for 6 days (Study 1007). Three studies (Studies 1005, 1007, and 1015) submitted under Section 6 of the NDA were reviewed to assess the QT effects of darifenacin. Two Phase 3 studies (Studies 1002 and 137-684) and a pooled analysis of 4 controlled studies (Studies 1002, 1007, 1015, and 137-684) were reviewed by the Medical Officer (refer to MO review). The following summarizes the QTc safety results from the pooled analysis (administration of darifenacin 3.75 mg – 60 mg):

- In general, there were no apparent QT signals with darifenacin (ΔQTcF from baseline: darifenacin 2.2 msec vs. placebo 1.9 msec).
- The percentage of subjects with an individual increase in QTcF from baseline of 30 – 60 msec was 7.2 % for darifenacin-treated group (vs. 5.7% for placebo group).
- The percentage of subjects with a maximum individual increase in QTcF from baseline of ≥ 60 msec was the same for both darifenacin (0.4%) and placebo (0.4%) treated groups (all showed QTcF < 500 msec).
- There were no additional risks of QT prolongation in females and in elderly populations (≥ 65 years and < 65 years).
- No female subjects exhibited a maximum on-treatment QTcF values of > 470msec.
- In male subjects, both the mean changes from baseline (4.6 msec vs. 0.6 msec) and the percent of subjects with QTcF change from baseline > 30 msec (7.6 % vs. 5.5%) were slightly higher in darifenacin-treated group compared to placebo treated group. Four male subjects exhibited a maximum on-treatment QTcF of more than 450msec.

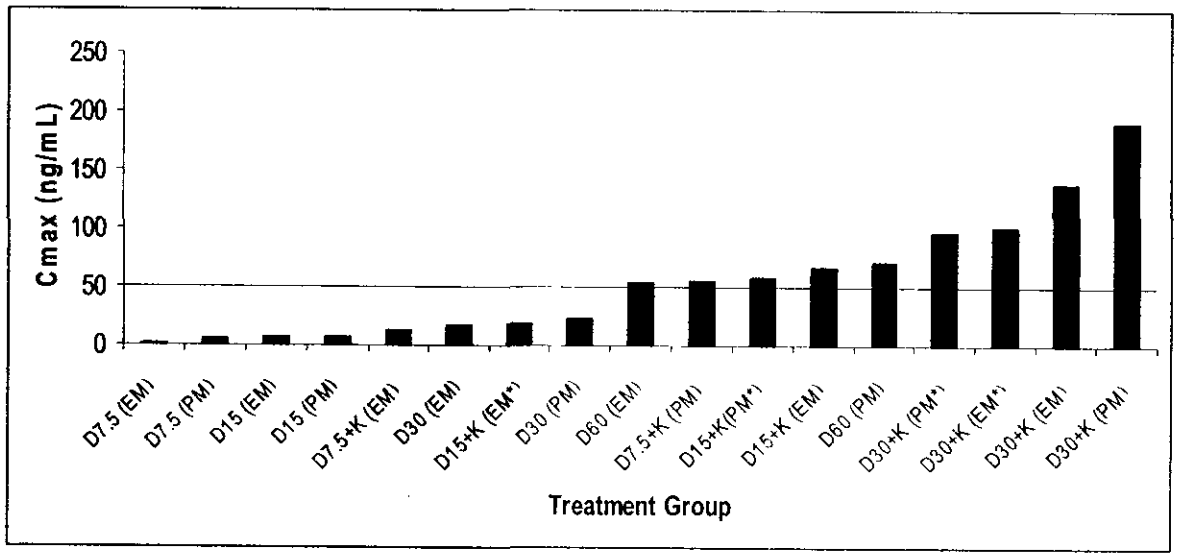
At the supra-therapeutic concentrations of darifenacin, the mean change of 12 msec from baseline (range: - — msec) in QTcF was observed when darifenacin 30 mg was co-administered with ketoconazole 400 mg once daily for 6 days (Study 1007). The mean corresponding plasma concentration of darifenacin at the time of ECG measurements was 103.7 ng/mL, with a range of — ng/mL (4 hour post-dose on Day 6). The sponsor stated that the mean increase of 12 msec in QTcF is not a clinically meaningful signal citing that ketoconazole itself is known to increase QT.

The mean change of QTcF from baseline was -0.51 msec (range: - — msec) when darifenacin 30 mg was co-administered with placebo once daily for 6 days. The mean corresponding mean plasma concentration was 11.8 ng/mL (range of — ng/mL).

Darifenacin 30 mg alone does not appear to result significant changes in QTc prolongation. However, no placebo-placebo control group was evaluated in the study.

The worst case scenario of PMs administered ketoconazole and darifenacin was not fully explored by the sponsor. However, the limited data indicate that effect of ketoconazole on darifenacin peak exposure in a PM who received 7.5 mg dose of darifenacin was similar to the effect of ketoconazole in EMs who received higher doses of darifenacin (15 mg, 30 mg).

Figure 9. The Mean Peak Exposure of Darifenacin in EM and PM Subjects (Studies 1035, 1007, 1015)



(Source: Studies 1035, 1007, and 1015): QTc reading at 4 hour post-dose on Day 6 (D 30 + K), and on Day 14 (D 60)
Note. No QTc data are available for Study 1035 (DDI study of Darifenacin 7.5 or 15 mg plus ketoconazole 400 mg)
*Dose titration due to AES (Darifenacin 15 mg group: Darifenacin 15 mg + Ketoconazole 400 or Placebo on Days 1-3, then Darifenacin 7.5 mg + Ketoconazole 400 mg or Placebo on Days 4-6), (Darifenacin 30 mg group Darifenacin 30 mg + Ketoconazole on Days 1-3, then Darifenacin 15 mg + Ketoconazole 400 mg on Days 4-6)

Table 21. The Peak Exposure of Darifenacin in EM and PM Subjects (Studies 1035, 1007, and 1015)

	C_{max}								
	D 7.5 + P	D 15 + P	D 7.5 + Keto	D 30 + P	D 60	D 15 + Keto (Days 1-3), D 7.5 + Keto (Days 4-6)	D 15 + Keto	D 30 + Keto (Days 1-3), D 15 + Keto (Days 4-6)	D 30 + Keto
EM	Study 1035 (n=9)	Studies 1035 & 1007 (n=5)	Study 1035 (n=10)	Study 1015 (n=8) Study 1007 (n=9)	Study 1015 (n=30)	Study 1035 (n=5)	Study 1035 (n=3)	Study 1007 (n=3)	Study 1007 (n=9)
	2.1 (0.6-4.0)	6.8 (5.5 -7.5)	13 (3.2-30.5)	19 ± 11 15.3 (7.8 – 28.5)	53.6 ± 25.3	18 (8.3 - 33.4)	67.6 (65.5 - 70.9)	102.0 (26.9 - 150)	139.0 (42.5 – 177)
PM	Study 1035 (n=1)	Studies 1035 & 1007 (n=2)	Study 1035 (n=1)	Studies 1015 & 1007 (n=4)	Study 1015 (n=5)	Study 1035 (n=1)	NA	Study 1007 (n=2)	Study 1007 (n=2)
	5.9	6.9 (6.2, 7.6)	55.4	23 (37.4, 9.82, 21.3, 23.3)	71.9 ± 35.7	58.9	NA	97.5 (79, 115)	191.5 (143, 240)

Table 22. The Plasma C_{max} Data for Phase 1 Subjects in Multiple-Dose Studies using the ER Formulation (EM Subjects)

	Darifenacin 7.5mg CR	Darifenacin 15mg CR	Darifenacin 30mg CR	Darifenacin 60mg CR	Darifenacin 30mg CR + ketoconazole 400mg
N	101	114	225	35	9
	ng/ml (nM)	ng/ml (nM)	ng/ml (nM)	ng/ml (nM)	ng/ml (nM)
Geometric mean	1.92 (4.50)	5.08 (11.91)	14.76 (34.60)	49.64 (116.36)	129.49 (303.54)
Arithmetic mean	2.23 (5.23)	6.26 (14.67)	17.23 (40.39)	56.21 (131.76)	139.03 (325.90)
Maximum	[redacted]				[redacted]

Source: Module 2.7.2, Summary Table A.2.2.2 and Study A1371007 Summary Table 5.1.2. Note: nM values calculated by dividing ng/ml values by 0.4266, based on the molar weight of darifenacin free base of 426.6 Daltons.

Study 1007 (see **DDI section** for study design): Sixteen subjects (12 EM, 4 PM) received darifenacin 30 mg once daily on Days 1 to 6 and either ketoconazole 400 mg or placebo once daily on Days 1 to 6 after a minimum washout period of 7 days between two treatments. A 12-lead ECG was performed within 3 weeks before the start of the study, 4 hours post-dose on Day 6, and at follow-up visit 14 days after the final dose. The baseline QTc reading was the mean of the screening and follow-up QTc measurements.

- The mean change of 12.05 ± 14.35 msec from baseline (range: - [redacted] msec) in QTcF was observed when darifenacin 30 mg was co-administered with ketoconazole 400 mg once daily for 6 days. The mean corresponding plasma concentration of darifenacin at the time of ECG measurements was 103.7 ng/mL, with a range of [redacted] ng/mL (4 hour post-dose on Day 6).
- The mean change of QTcF from baseline was -0.51 ± 11.82 msec (range: - [redacted] msec) when darifenacin 30 mg was co-administered with placebo once daily for 6 days. The mean corresponding mean plasma concentration was 11.8 ng/mL (range of [redacted] ng/mL).
- The highest darifenacin C_{max} [redacted] ng/mL) was observed in a CYP2D6 PM subject following co-administration of darifenacin 30 mg and ketoconazole 400 mg. An increase of 24.5 msec in QTcF from baseline of 361.5 msec was observed in this subject.
- The highest increase in QTcF from baseline was 45.5 msec following co-administration of darifenacin 30 mg and ketoconazole 400 mg. This male subject was a CYP2D6 PM who had his darifenacin dose reduced at Day 4 to darifenacin 15 mg due to antimuscarinic AEs (baseline QTcF 368.5 msec, C_{max}=C_4=[redacted] ng/mL).

Table 23. Individual Mean Changes in QTc from Baseline by Treatment

		Baseline* QTc (Bazetts) Interval (msec)	Change from OTC Bazetts Baseline (msec)	Baseline* (Fridericias) Interval (msec)	Change from Fridericias Baseline (msec)
Darifenacin+Ketoconazole	n	16	16	16	16
	Mean	354.58	6.79	353.64	12.05
	Std. Dev.	18.70	16.70	17.41	14.35
	Minimum	[			]
	Maximum	[			]
Darifenacin+Placebo	n	16	16	16	16
	Mean	354.58	-4.30	353.64	-0.51
	Std. Dev.	18.70	11.59	17.41	11.82
	Minimum	[			]
	Maximum	[			]

Figure 10. Individual Mean Changes in QTcF from Baseline by Treatment

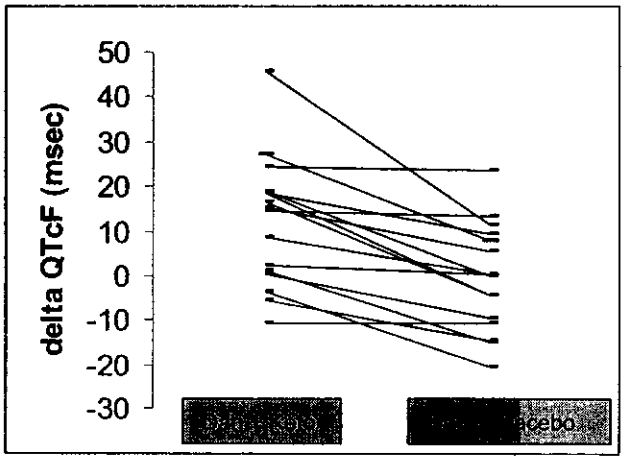
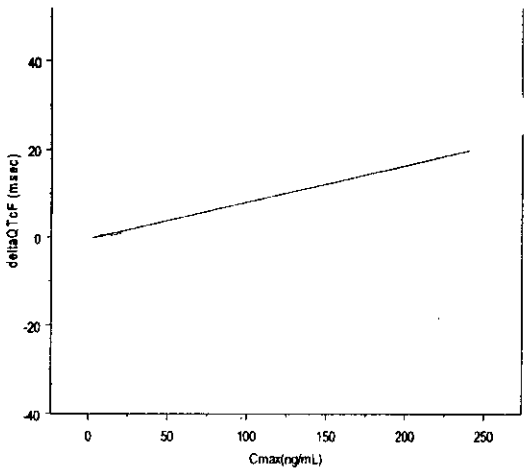


Figure 11. The Effects of Darifenacin Peak Exposure on QTcF Intervals

(a) C_{max} vs. Δ QTcF



(b) C_4 vs. Δ QTcF

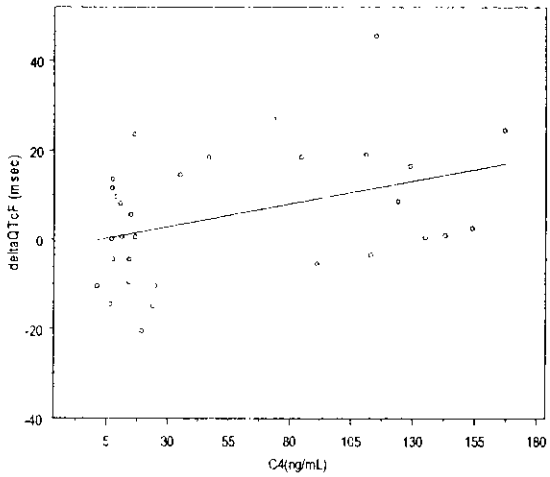
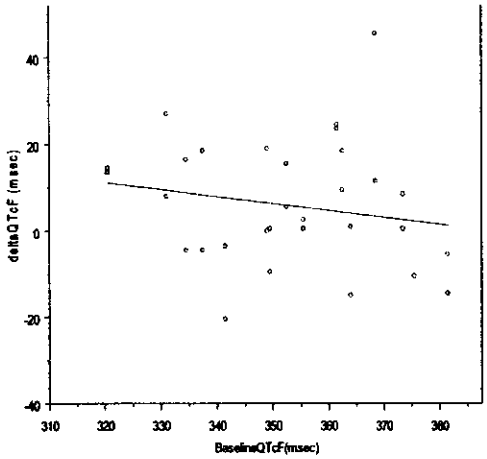


Figure 12. The Relationship between Baseline QTcF and Mean Change in QTcF

(a) Baseline QTcF vs. Δ QTcF



(b) Baseline QTcF vs. QTcF at 4 hour post-dose on Day 6

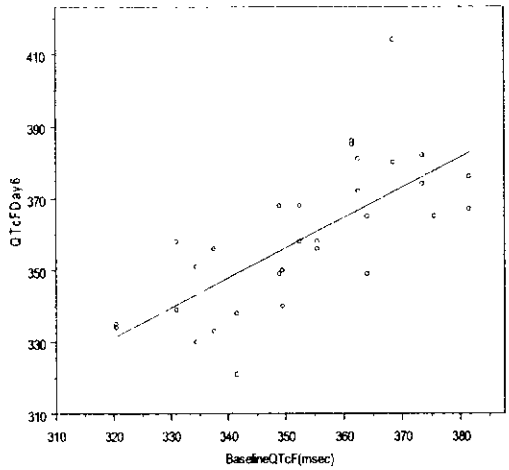


Table 24. Individual QTc Reading with Corresponding Darifenacin Concentrations at 4 Hour Post-Dose on Day 6

(a) Darifenacin 30 mg + Ketoconazole 400 mg Treatment Group

Darifenacin 30 mg + Ketoconazole 400 mg								
Subject	T_{max} hr	C_{max} ng/mL	$C_{at\ t=4\ hr}$ ng/mL	Screening QT_cF msec	Baseline QT_cF msec	QTcF @ 4 hr Day 6 msec	Δ QT_cF (Screening) msec	Δ QT_cF (Baseline) msec
001								
002								
003*								
004								
005								
006								
007*								
008*								
009								
010								
011								
012								
013* (PM)								
014* (PM)								
015 (PM)								
016 (PM)								
Mean	**7.3**	**133.4**	**103.7**	**354**	**353.7**	**365.7**	**11.69**	**12.03**

*Subjects 003, 007, 008, 013, and 014 were dose down titrated (Darifenacin 30 mg + Ketoconazole 400 mg on Days 1-3, Darifenacin 15 mg + Ketoconazole 400 mg on Days 4-6)

(b) Darifenacin 30 mg + Placebo Treatment Group

Subject	T_{max} hr	C_{max} ng/mL	$C_{at\ t=4\ hr}$ ng/mL	Screening QT_cF msec	Baseline QT_cF msec	QTcF @ 4 hr Day 6 msec	ΔQT_cF (Screening) msec	ΔQT_cF (Baseline) msec
001								
002								
003*								
004								
005								
006								
007*								
008								
009								
010								
011								
012								
013* (PM)								
014 (PM)								
015 (PM)								
016 (PM)								
Mean	**6**	**14.2**	**11.8**	**354**	**353.7**	**351.3**	**-0.75**	**-0.406**

*Subjects 003, 007, and 013 were administered darifenacin 15 mg + placebo on Days 1-6.

Study 1035 (see **DDI section** for study design): A randomized, placebo controlled, two-period crossover study was conducted in healthy male subjects to determine the effects of ketoconazole on the pharmacokinetics of two doses of darifenacin (7.5mg and 15mg). Subjects were administered with either darifenacin 7.5 mg or 15 mg for 6 days and ketoconazole 400 mg once daily for 8 days after a minimum washout period of 7 days between two treatments. A 12-lead ECG was recorded pre-dose and at 4 hr post-dose on Day 6.

Table 25. Mean Changes from Baseline by Treatment Group (Darifenacin 7.5 mg Group)

Measurements	Darifenacin 7.5 mg and ketoconazole	Darifenacin 7.5 mg and Placebo
Subject (N)	8	7
Fredericia's correction (QTcF)		
Mean Baseline* and SD (ms)	390 (16.8)	380 (23.4)
Mean change from baseline (ms)	12	2
Standard Deviation for the change	17.8	15.7
Min and max change (ms)		
Bazett's correction (QTcB)		
Mean Baseline* (ms)	383 (20.3)	378 (28.7)
Mean change from baseline (ms)	7	1
Standard Deviation for the change	19.2	16.3
Min and max change (ms)		

Source: Table 3.1 and Table 4 of report on preliminary analysis for QT data from study A1371035

Table 26. Mean Changes from Baseline by Treatment Group (Darifenacin 15 mg Group)

Measurements	Darifenacine 15 mg and ketoconazole	Darifenacine 15 mg and Palcebo
Subject (N)	6	6
Fredericia's correction (QTcF)		
Mean Baseline* and SD (ms)	388 (11.2)	376 (10.6)
Mean change from baseline (ms)	10	-3
Standard Deviation for the change	13.6	13.9
Min and max change (ms)		
Bazett's correction (QTcB)		
Mean Baseline* and SD (ms)	386 (15.5)	377 (14.7)
Mean change from baseline (ms)	1	-8
Standard Deviation for the change	20.4	18.9
Min and max change (ms)		

Source: Table 3.1 and Table 4 of report on preliminary analysis for QT data from study A1371035

- This study showed a consistent mean increase of 10 – 12 msec in QTcF from baseline when darifenacin 7.5 mg or 15 mg was co-administered with ketoconazole 400 mg.

Study 1015: A randomized, double blind, parallel group, placebo controlled study was conducted in 62 healthy male and female subjects (56 EM, 6 PM) aged 50 years or over to evaluate PK, safety and toleration of multiple oral doses of darifenacin 60 mg. Subjects were administered with either darifenacin 60 mg (n=42), darifenacin 30 mg (n=10), or placebo (n=10) for 14 days. Plasma concentrations of darifenacin were obtained pre-dose on Days 1 to 14 and at 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours post-dose on Day 14. ECGs were measured on the morning of Day 1 prior to darifenacin administration, at 4 hour post dose on Day 14 and at follow-up visits.

- The mean difference between QTcF change from baseline following administration of darifenacin 60 mg when placebo corrected was an increase of 2.74 msec. The placebo corrected mean change in QTcF following darifenacin 30 mg was 1 msec.
- The largest mean changes in QTcF observed in the darifenacin 60 mg and 30 mg groups were a decrease of 7.6 msec and of 9.4 msec, respectively.
- A 10.4 msec decrease was the largest mean change in QTcF observed from baseline in the placebo group.
- The highest darifenacin peak exposure following administration of darifenacin 60 mg was 126 ng/mL. The mean C_{max} values of EM and PM subjects following darifenacin 60 mg were 53.6 ± 25.3 ng/mL (n=30) and 71.9 ± 35.7 ng/mL (n=5), respectively. The estimated mean concentrations of darifenacin at 4 hour post-dose on Day 14 were about 43 ng/mL and 58 ng/mL in EMs and PMs, respectively.

Table 27. Individual Mean Changes in QTc from Baseline by Treatment

		QTc (Bazzetts) (msec)			QTc (Fridericias) (msec)		
		Baseline	Change from baseline		Baseline	Change from baseline	
		Day 1 pre-dose	Day 14 pre-dose	Day 14 4h post dose	Day 1 pre-dose	Day 14 pre-dose	Day 14 4h post dose
Darifenacin 60mg	N	38	39	34	38	39	34
	Mean	407.987	-1.961	-4.034	408.101	-2.625	-7.628
	Std. Dev.	18.5959	17.2921	19.7032	15.9266	13.3041	15.4918
	Minimum						
	Maximum						
Darifenacin 60mg -> 30mg	N	2	2	2	2	2	2
	Mean	404.560	-0.570	3.090	399.565	2.605	1.125
	Std. Dev.	9.6308	9.0934	7.3539	10.7258	8.8983	7.4458
	Minimum						
	Maximum						
Darifenacin 60mg -> Placebo	N	2	2	2	2	2	2
	Mean	401.720	3.660	6.315	406.930	-1.090	-4.550
	Std. Dev.	22.4719	34.1815	32.9724	23.6457	36.4301	24.0699
	Minimum						
	Maximum						

		QTc (Bazzetts) (msec)			QTc (Fridericias) (msec)		
		Baseline	Change from baseline		Baseline	Change from baseline	
		Day 1 pre-dose	Day 14 pre-dose	Day 14 4h post dose	Day 1 pre-dose	Day 14 pre-dose	Day 14 4h post dose
Darifenacin 30mg	N	9	9	9	9	9	9
	Mean	416.786	-4.069	-6.747	414.852	-2.994	-9.424
	Std. Dev.	26.4915	13.5929	16.4372	19.0863	15.0286	14.9085
	Minimum	[					]
	Maximum						
Darifenacin 30mg -> Placebo	N	1	1	1	1	1	1
	Mean	370.430	5.550	0.160	374.430	6.710	-1.950
	Std. Dev.						
	Minimum	[					]
	Maximum						
Double Blind Placebo	N	10	11	9	10	11	9
	Mean	407.394	-2.698	-6.786	407.145	-3.389	-10.369
	Std. Dev.	20.2761	19.7476	19.2563	21.2643	17.2030	15.0213
	Minimum	[					]
	Maximum						

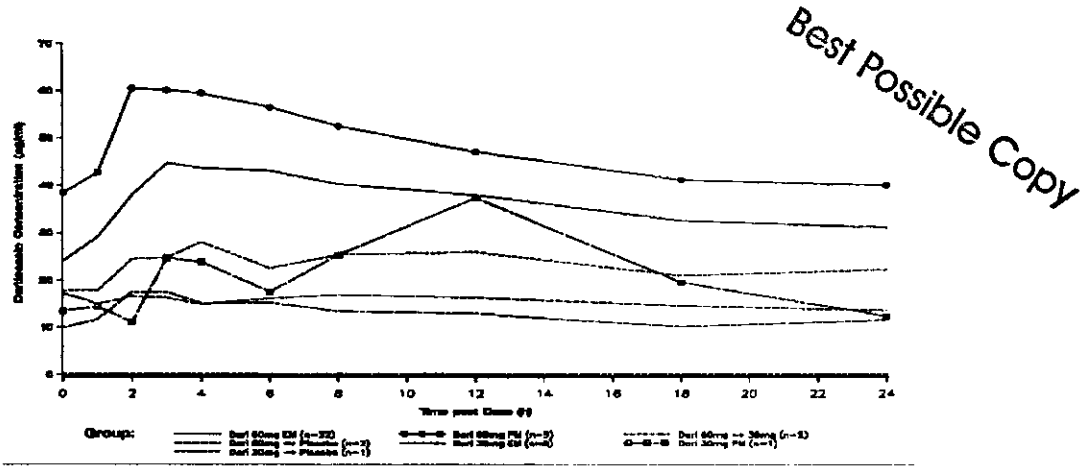
Table 28. The Day 14 Darifenacin Pharmacokinetic Parameters for EM and PM Subjects

	Darifenacin 60mg		Darifenacin 60mg→ 30mg	Darifenacin 60mg→ Placebo	Darifenacin 30mg	
	EM (N=30)	PM (N=5)	EM (N=2)	EM (N=1)	EM (N=8)	PM (N=1)
AUC_{24} (ng.h/ml)	775	964	538	740	254	544
C_{max} (ng/ml)	47.5	64.5	28.3	34.3	17.0	37.4
T_{max} (h)*	5.4	3.8	7.0	0.0	4.0	12.0
C_{av} (ng/ml)	32.3	40.2	22.4	30.8	10.6	22.7
C_{min} (ng/ml)	17.9	19.4	15.9	27.0	5.47	11.1
PTF (scalar)	0.86	0.91	0.55	0.24	1.03	1.16
$t_{1/2}$ (h)*	18.8[a]	14.0[b]	34.6[c]	N/D	6.7[d]	7.5
k_d (1/h)**	0.037[a]	0.050[b]	0.020[c]	N/D	0.103[d]	0.092
CL/F (ml/min)	77.4	62.2	111	81.1	118	55.1

Source: Tables 5.1.1 to 5.1.9

*Arithmetic mean, ** harmonic mean, all other means are geometric. [a] N=17; [b] N=3; [c] N=1; [d] N=3

Figure 13. Mean Plasma Concentrations of Darifenacin



Study 1005: An open, two-period, parallel, group study in three groups of subjects (healthy, subjects with mild [Child Pugh A] or moderate [Child Pugh B] hepatic impairment) was conducted to evaluate the PK of darifenacin between healthy subjects and subjects with hepatic impairment. Subjects received oral darifenacin single dose of 15 mg in Period 1 followed by multiple 15 mg oral doses for 6 days in Period 2. Plasma darifenacin concentrations were obtained: pre-dose on Day 1 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, and 48 hours post-dose (Period 1) and pre-dose on Days 1 to 6 and on Day 6 at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours post-dose (Period 2).

- The result of this study was not included in the pooled analysis since this was not a placebo controlled study.
- The QT analyses were conducted by two independent consultants. The analysis of QTcF change at 4 hour post-dose from baseline was done by [ ] The analysis of maximum post-dose QTcF change from baseline was done by [ ]
- The mean change of -0.9 to 6.7 msec in QTcF at 4 hour post-dose from baseline and the mean maximum post-dose change of 4.7 to 11.9 msec in QTcF from baseline were observed following single dose or multiple dose administration of darifenacin 15 mg in healthy subjects or patients with mild to moderate hepatic impairment.
- No subject experienced a maximum individual increase in QTcF from baseline of ≥ 60 msec in any group or in either dosing period.

Table 29. Mean Values for QTcF in Healthy Subjects and Subjects with Mild or Moderate Hepatic Impairment.

		Darifenacin Single Dose	Darifenacin Multiple Dose
Healthy	Number evaluable	12	12
QTcF (msec)	Mean Baseline	407.7	408.9
	Mean Change from baseline	10.8	11.9
Child Pugh A	Number evaluable	14	15
QTcF (msec)	Mean Baseline	405.9	406.7
	Mean Change from baseline	9.9	4.7
Child Pugh B	Number evaluable	12	12
QTcF (msec)	Mean Baseline	427.2	428.7
	Mean Change from baseline	7.1	9.3

Source: QT Appendix Table 7

Table 30. Maximum Individual Increase in QTcF

		Darifenacin Single Dose	Darifenacin Multiple Dose
Healthy	**Number evaluable**	**12**	**12**
		Number (%)	Number (%)
Change in QTcF from baseline	**0 - <30msec**	**11 (91.7)**	9 (75.0)
	30 - <60msec	**0 (0)**	1 (8.3)
	≥60msec	**0 (0)**	0 (0)
Child Pugh A	**Number evaluable**	**14**	**15**
		Number (%)	Number (%)
Change in QTcF from baseline	**0 - <30msec**	**9 (64.3)**	8 (53.3)
	30 - <60msec	**2 (14.3)**	1 (6.7)
	≥60msec	**0 (0)**	0 (0)
Child Pugh B	**Number evaluable**	**12**	**12**
		Number (%)	Number (%)
Change in QTcF from baseline	**0 - <30msec**	**9 (75.0)**	10 (83.3)
	30 - <60msec	**0 (0)**	0 (0)
	≥60msec	**0 (0)**	0 (0)

Source. QT Appendix Table 8

How does the systemic exposure change with various intrinsic and extrinsic factors? Is there a need for dosage adjustment or contraindication/caution with these factors?
The effects of age, gender, race, hepatic and renal impairment, and CYP2D6 genotype status on the systemic exposure of darifenacin were evaluated. No dosage adjustment is warranted. In patients with moderate hepatic impairment, darifenacin dosage should not exceed 7.5 mg while darifenacin should be contraindicated in patients with severe hepatic impairment. There are no special dosing requirements for patients with mild hepatic impairment. The maximum daily dose of darifenacin should not exceed 7.5 mg when co-administered with potent CYP3A4 inhibitors. Therefore, use of potent CYP3A4 inhibitors with darifenacin 15 mg should be contraindicated. Caution should be taken when darifenacin is co-administered with drugs predominantly metabolized by CYP2D6 and which have a narrow therapeutic window. Standard therapeutic drug monitoring for digoxin and warfarin should be continued when these drugs are co-administered with darifenacin.

C. Intrinsic Factors

Population Pharmacokinetics

Effect of Age
Darifenacin exposure from ER tablets is higher among elderly subjects. It is estimated that CL/F decrease with age by 6.2% per decade. However, based on no consistent difference in the efficacy of darifenacin treatment in patients < 65 and ≥ 65 years of age and age had little apparent impact on safety or toleration (see MO review), no dose adjustment is required.

Effect of Sex
Darifenacin exposure is lower in males than in females. Darifenacin CL/F was 39% higher and steady state AUC was 28% lower in males than in females.

Effect of Race
The effects of race on darifenacin pharmacokinetics among subjects in Western studies have not been established because a small number of non-white subjects were enrolled. However, darifenacin exposure seems to be lower among Japanese subjects in studies conducted in Japan than subjects in Western studies. The difference in darifenacin exposure may be related to extrinsic factors (e.g., diet). Hence, data from Japanese studies cannot be extrapolated to patients

in Western countries. Given the differences in exposure between subjects in Japanese and Western studies, the sponsor recommends that for Japanese OAB patients in Japan should be primarily based on the comparison of efficacy and safety data between Japanese and Western Phase 3 studies.

Renal Impairment

Darifenacin is mainly cleared by metabolism and about 3% of total dose is present in the urine and feces as unchanged. Therefore, changes in renal function are not likely to have a direct effect on darifenacin clearance. However, renal disease may alter other factors which may affect plasma concentrations or protein binding.

Study 1004: An open, parallel group study was conducted in 24 subjects (18 M, 6 F) aged 23 to 65 years with varying degrees of renal function to evaluate the effects of impaired renal function on the PK of darifenacin. Subjects were assigned to one of the following groups based on their serum creatinine clearance (CL_{CR}) at screening and Day 0, estimated using the Cockcroft and Gault equation:
(1) normal (CL_{CR}> 80 mL/min), (2) mild (CL_{CR} 51 – 80 mL/min), (3) moderate (CL_{CR} 30 - 50 mL/min), (4) severe (CL_{CR} < 30 mL/min).

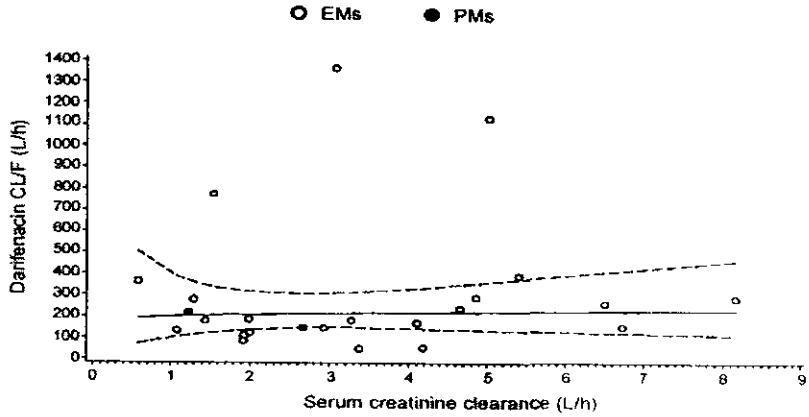
Six subjects were assigned to each group. Subjects were administered 15 mg ER darifenacin once daily for 6 days. Plasma concentrations of darifenacin were obtained pre-dose on Days 1 to 6 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours post-dose on Day 6. Urine concentrations of darifenacin were obtained from urine samples taken 0-6, 6-12, 12-18, and 18-24 hours post-dose on Day 6. An additional blood sample was taken at 6 hours post-dose on Day 6 to determine plasma protein binding of darifenacin. The genders, ages and weights of subjects in all four groups were similar. All subjects were EM except one subject in the severe renal impairment group was a PM (excluded from the analyses). The primary analysis was a regression analysis based on regressing CL/F and CL_R for darifenacin against Day 6 CL_{CR}. As a secondary analysis, log transformed AUC_{24}, C_{max}, CL/F and CL_R were analyzed using a one-way ANOVA with renal impairment group as the factor in the model.

Table 31. A Regression Analysis Based on Regressing CL/F and CL_R for Darifenacin

Parameter	n	Intercept (95% CI)	Slope (95% CI)	R^2
$\ln CL/F$ vs. $\ln CL_{CR}$	23	5.29 (4.59, 5.99)	0.067 (-0.501, 0.634)	0.003
$\ln CL_R$ vs. $\ln CL_{CR}$	20	-0.637 (-1.40, 0.129)	1.50 (0.888, 2.10)	0.598

- There was no association between darifenacin clearance and the severity of renal impairment (CL_{CR} of 10 to 136 mL/min).
- There was a weak association between renal clearance and the severity of renal impairment.
- Renal impairment had no apparent effect on plasma protein binding of darifenacin (mean f_u: normal 2.0%, mild 2.3%, moderate 1.2%, severe 1.1%).

Figure 14. A Regression Analysis of CL/F versus Serum Creatinine Clearance on Day 6 for Darifenacin



- There is no relationship between darifenacin clearance and renal function.

Figure 15. A Regression Analysis of CL_R versus Serum Creatinine Clearance on Day 6 for Darifeinacin

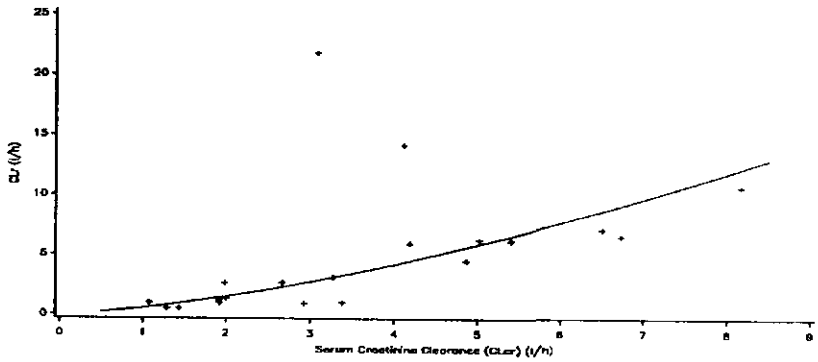


Table 32. Raw Mean Pharmacokinetic Parameters of Darifenacin on Day 6

Parameter	Normal renal function (n=6)	Mild renal impairment (n=6*)	Moderate renal impairment (n=6)	Severe renal impairment (n=5†)
Darifenacin				
AUC_{24} (ng.h/ml)	44.5	86.1	116	52.9
C_{max} (ng/ml)	3.03	5.21	8.35	5.46
CL/F (l/h)	337	174	129	284
CL_R (l/h)	6.66	5.65	1.46	0.65
T_{max} (h)	6.3	6.7	5.2	5.4
UK-148,903				
AUC_{24} (ng.h/ml)	49.8	79.6	114	54.0
C_{max} (ng/ml)	3.34	4.95	7.90	4.98
T_{max} (h)	5.0	4.7	4.8	4.2

Means presented are geometric for AUC_{24}, C_{max}, CL/F and CL_R, and arithmetic for T_{max}.
* n=5 for CL_R † n = 3 for CL_R

- The analysis of the log transformed PK parameters AUC_{24}, C_{max}, CL/F and CL_R between the renal function groups indicated no clear relationship with the severity of renal impairment.
- In general, AUC_{24} and C_{max} were higher and CL/F and CL_R were lower in subjects with renal impairment than in subjects with normal renal function.

- There were statistically significant differences in darifenacin exposure and clearance between subjects with normal renal function and those with moderate renal impairment, while no differences between normal and mild or severe groups were seen.

Figure 16. Mean Trough Plasma Concentrations of Darifenacin

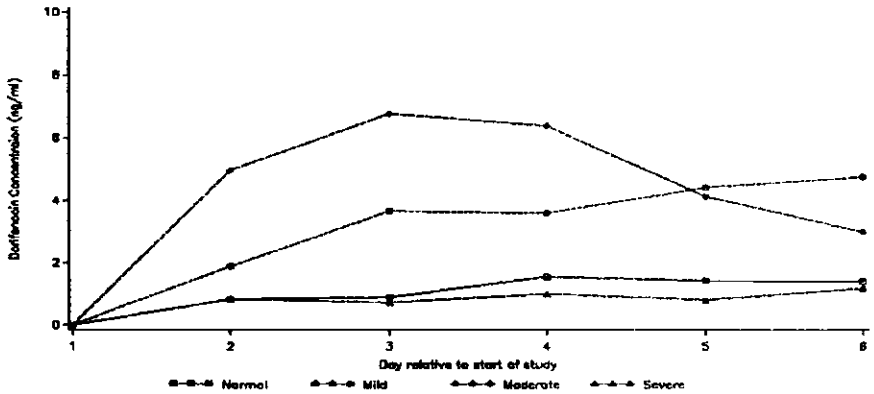
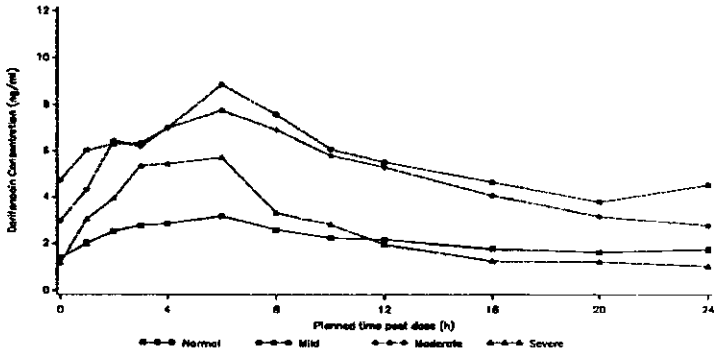


Figure 17. Mean Plasma Concentrations of Darifenacin on Day 6



Hepatic impairment

Study 1005: An open, two-period, parallel group study in 3 groups of subjects (12 healthy subjects, 15 subjects with mild [Child Pugh A, score 5-6], 12 subjects with moderate [Child Pugh B, score 7-9] hepatic impairment) was conducted to compare the single and multiple dose pharmacokinetics of darifenacin between healthy subjects and subjects with hepatic impairment. White subjects aged 45 to 65 years (28 M, 13 F) were administered oral darifenacin single dose of 15 mg in Period 1, followed by multiple 15 mg oral doses for 6 days in Period 2. Plasma drug concentrations were taken at pre-dose on Day 1 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, and 48 hours post-dose in Period 1, and pre-dose on Days 1 to 6 and on Day 6 only at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours post-dose in Period 2. Additional samples were taken at 6 hours post-dose on Day 1 of Period 1 and Day 6 of Period 2 for determination of plasma protein binding of darifenacin. Twelve-lead ECG measurements were taken at screening, on admission the day before dosing (both periods), at 4, 8, and 24 hours post-dose on Day 1 (Period 1), and pre-dose Day 3, at 4, 8, and 24 hours post-dose on Day 6 (Period 2), and at follow-up. For EM subjects only, AUC_{48} and C_{max} of Day 1 single dose and AUC_{24}, C_{max}, unbound AUC_{24} and unbound C_{max} of Day 6 multiple dose were log transformed prior to ANOVA. T_{max} and f_u

(fraction of darifenacin unbound/free fraction (%)) was analyzed as untransformed parameters (T_{max}: Day 1 and Day 6, f_u: Day 6). The age, weights and sexes of the subjects in all three groups were matched.

Table 33. The Effect of Hepatic Impairment on Steady State Pharmacokinetic Parameters of Darifenacin in EM Subjects

	Hepatic function category, unadjusted means			Ratio or difference between adjusted means (95% CI)	
	Normal (N=12)	Mild (N=13)	Moderate (N=11)	Mild vs Normal	Moderate vs Normal
AUC_{24} (ng.h/ml)	101	65.4	269	0.65 (0.40, 1.06)	2.68 (1.60, 4.48)*
C_{max} (ng/ml)	6.00	3.95	14.2	0.66 (0.41, 1.06)	2.36 (1.44, 3.88)*
T_{max} (h)	10.0	9.3	11.3	-0.7 (-5.09, 3.70)	1.3 (-3.31, 5.86)
C_{min} (ng/ml)	2.19	1.38	6.80	-	-
C_{avg} (ng/ml)	4.19	2.72	11.2	-	-
CL/F (ml/min)	149	229	55.7	-	-
PTFR	0.87	0.88	0.58	-	-
f_u (%)	1.7†	3.3‡	4.5‡	1.7 (0.3, 3.0)*	2.8 (1.4, 4.2)*

Source: Study A1371005 Tables 5.3.1 to 5.3.3 and 5.4
Geometric mean for AUC_{24}, C_{max}, C_{min}, C_{avg} and CL/F. Arithmetic mean for T_{max} and f_u
* $p<0.05$. † N=9. ‡ N=5

- There was an increase in AUC_{48} (168%) and C_{max} (136%) for Child Pugh B subjects compared with healthy subjects at steady state on Day 6.
- Clearance of total darifenacin was lower among subjects with moderate hepatic impairment than subjects with normal hepatic function (steady state CL/F 56 mL/min vs. 149 mL/min).
- There was no difference between Child Pugh A subjects and healthy subjects.
- After multiple dosing with darifenacin, there was an apparent correlation between fraction of unbound darifenacin and extent of hepatic impairment. There was an increase in f_u between Child Pugh B and Child Pugh A subjects compared with healthy subjects.

Table 34. The Results of the Statistical Analysis of Single Dose Darifenacin Pharmacokinetic Parameters for EM Subjects

Parameter	Comparison	Raw means[a]	Ratio/ difference of geometric means[b,c]	95% CI
AUC_{48} (ng.h/ml)	Child Pugh B - Healthy	162 – 54.0	301%	(152%, 596%)
	Child Pugh A - Healthy	46.1 – 54.0	85.3%	(43.0%, 169%)
C_{max} (ng/ml)	Child Pugh B - Healthy	5.86 – 2.41	244%	(135%, 441%)
	Child Pugh A - Healthy	2.38 – 2.41	99.1%	(54.8%, 179%)
T_{max} (h)	Child Pugh B - Healthy	17.8 – 11.7	6.1	(-0.73, 12.9)
	Child Pugh A - Healthy	14.3 – 11.7	2.6	(-4.23, 9.39)

[a] means are geometric (AUC_{48} and C_{max}) and arithmetic (T_{max}); [b] the ratios (expressed as percentages) and corresponding confidence intervals (CI), are back-transformed from the log scale for AUC_{48} and C_{max}; [c] difference between means (T_{max})

- There was an increase in AUC_{48} (301%) and C_{max} (244%) for Child Pugh B subjects compared with healthy subjects for Day 1 single dose.
- There was no difference between Child Pugh A subjects and healthy subjects.

Figure 18. Mean Plasma Concentrations of Darienacin at Steady State on Day 6 in EM Subjects

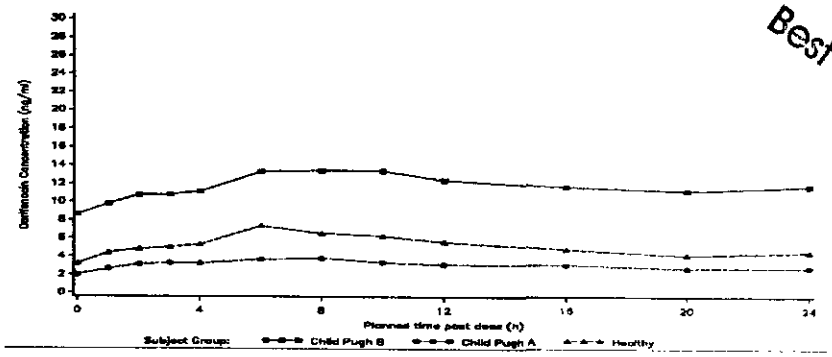


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Table 35. The Effect of Hepatic Impairment on Steady State **Unbound Darifenacin** PK Parameters (EMs only)

	Hepatic function category, unadjusted means			Ratio or difference between adjusted means (95% CI)	
	Normal (N=9)	Mild (N=5)	Moderate (N=5)	Mild vs Normal	Moderate vs Normal
Unbound AUC_{24} (ng.h/ml)	2.12	2.24	10.0	1.06 (0.54, 2.07)	4.69 (2.39, 9.21)*
Unbound C_{max} (ng/ml)	0.128	0.136	0.509	1.06 (0.56, 2.03)	3.97 (2.08, 7.59)*
Unbound CL/F (ml/min)	7066	6700	1507	-	-

Source: Study A1371005 Tables 5.3.1 to 5.3.3 and 5.4
Geometric mean for unbound AUC_{24}, unbound C_{max} and unbound CL/F.
* $p<0.05$

- After multiple dosing with darifenacin, the fraction of darifenacin unbound was higher for Child Pugh B and Child Pugh A subjects compared with healthy subjects (difference between means: 2.79% and 1.65%, respectively).
- There was an increase in unbound AUC_{24} and unbound C_{max} for Child Pugh B subjects compared with healthy subjects on Day 6 but no difference between Child Pugh A subjects and healthy subjects.
- Unbound darifenacin exposure from use of 15 mg and 7.5 mg darifenacin in subjects with moderate hepatic impairment corresponds approximately to unbound exposures achieved by use of 60 mg and 30 mg respectively, in subjects with normal hepatic function.

Table 36. The Results of Steady State Darifenacin Pharmacokinetic Results in PM Subjects

	Raw Means		
Group	Child Pugh B (n=1)	Child Pugh A (n=2)	Healthy (n=0)
AUC_{24} (ng*hr/mL)	457	142	-
C_{max} (ng/mL)	28.0	8.0	-
C_{min} (ng/mL)	10.3	2.9	-
C_{av} (ng/mL)	19.0	5.9	-
CL/F (mL/min)	32.8	106.0	-
PTF (scalar)	0.93	0.87	-
T_{max} (hr)	10.0	9.0	-
Unbound AUC_{24} (ng*hr/mL)	13.7	3.30	-
Unbound C_{max} (ng/mL)	0.840	0.184	-
Unbound CL/F (L/hr)	1094	5016	-

CYP2D6 Genotype

Darifenacin is metabolized via CYP3A4 and CYP2D6 enzyme pathways. Therefore, any alteration in CYP2D6 expression or activity is likely to affect the pharmacokinetics of darifenacin. To evaluate the impact of CYP2D6 genotype on darifenacin pharmacokinetics, subjects were categorized as EMs and PMs based on a pre-defined scheme for mapping CYP2D6 allele combinations to phenotype. Comparison of darifenacin exposure between predicted phenotype categories suggests that the difference between EM and PM populations at steady state diminishes with increasing dose. This trend appears to be related to a dose-dependent reduction in the relative contribution of CYP2D5-mediated metabolism where this pathway appears to get saturated at higher doses.

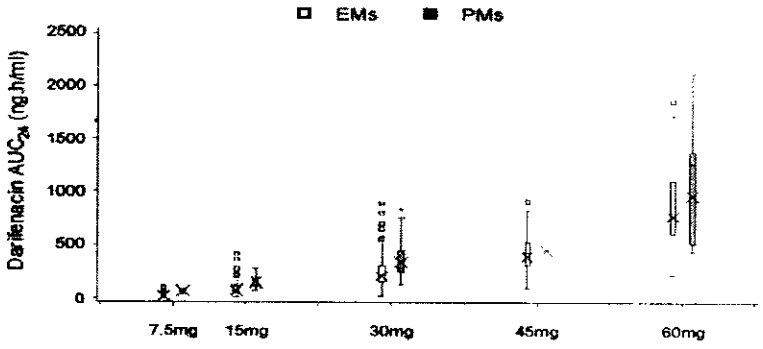
Table 37. Mean Steady State C_{max} and AUC_{0-24} of Darifenacin ER Tablets Based on Pooled Data by Predicted CYP2D6 Phenotype

		Darifenacin dose				
		7.5mg od	15mg od	30mg od	45mg od	60mg od
EM	N	95	104	185	22	30
	AUC_{24} (ng.h/ml)	26.3	74.9*	207.2	386.6	775.3
	C_{max} (ng/ml)	1.82	4.81	13.73	25.25	47.52
PM	N	6	10	40	1	5
	AUC_{24} (ng.h/ml)	69.6	149.1	327.6	449.6	964.3
	C_{max} (ng/ml)	4.46	9.11	20.59	26.20	64.54
PM:EM ratio	AUC_{24}	2.64	1.99	1.58	1.16	1.24
	C_{max}	2.45	1.89	1.50	1.04	1.36

* N=103

- Total exposure at steady state was on average 164% higher in PM subjects compared to EM subjects following administration of 7.5 mg ER tablets, and 99% higher following administration of 15 mg ER tablets.
- Corresponding values for mean peak exposures were 145% and 89%, respectively.

Figure 19. Steady State Darifenacin Exposure of Darifenacin ER Tablets Based on Pooled Data by Predicted CYP2D6 Phenotype



- Due to considerable inter-subject variability in darifenacin exposure in both EM and PM populations, AUC_{24} CV% across the dose range tested was 48-71% for EMs and 20-61% for PMs. Therefore, there was a high degree of overlap between ranges of individual exposures in EM and PM populations.

D. Extrinsic Factors

Drug Interactions

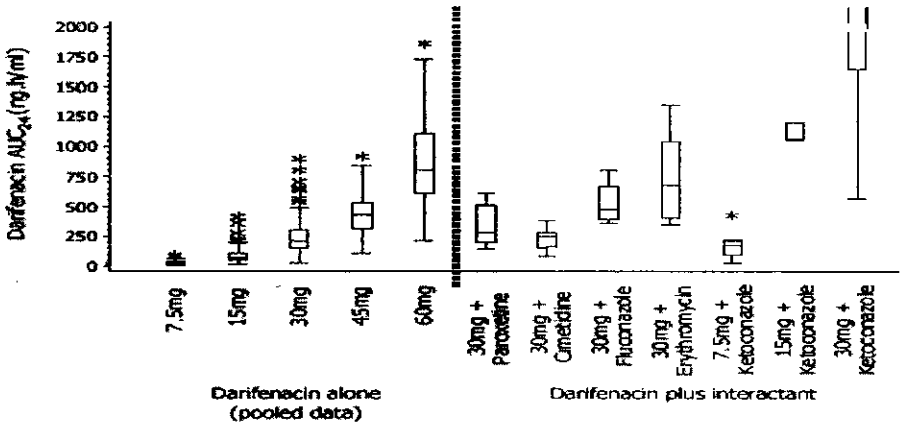
Table 38. The Summary of Drug-Drug Interaction Studies (CYP2D6 EM Subjects)

	Mean Ratio of AUC_{24}	Mean Ratio of C_{max}
Effect on Darifenacin		
Ketoconazole 400 mg QD	5.33 ↑ (7.5 mg) 11.6 ↑ (15 mg)* 10.6 ↑ (30 mg)	5.67 ↑ (7.5 mg) 10.0 ↑ (15 mg)* 9.5 ↑ (30 mg)
Erythromycin 500 mg BID	1.95 ↑ (30 mg)	2.28 ↑ (30 mg)
Fluconazole 200/100 mg QD	1.84 ↑ (30 mg)	1.88 ↑ (30 mg)
Paroxetine 20 mg QD	1.33 ↑ (30 mg)	1.36 ↑ (30 mg)
Cimetidine 800 mg BID	1.34 ↑ (30 mg)	1.42 ↑ (30 mg)
Effect of Darifenacin on		
Midazolam 7.5 mg oral	1.17 ↑ (30 mg)**	No Change (30 mg)
COC (0.15/0.03 mg LNG/EE)	No Change (10 mg TID)	No Change (10 mg TID)
Digoxin 0.25 mg	1.16 ↑ (30 mg)	1.20 ↑ (30 mg)
Imipramine 25 mg TID	1.7 ↑ (30 mg)***	1.57 ↑ (30 mg)
Desipramine	2.63 ↑ (30 mg)***	2.56 ↑ (30 mg)

Effect of Darifenacin on	Darifenacin 7.5 mg	Darifenacin 15 mg	Darifenacin 30 mg
Debrisoquine MR	2.2 ↑	3.25 ↑	7.25 ↑

*n=3, **mean ratio of AUC_{∞}, ***mean ratio of AUC_{72}

Figure 20. Darifenacin Total Exposure Following Co-administration of CYP P450 Inhibitors



THE EFFECTS OF CYP3A4 INHIBITORS ON DARIFENACIN AT STEADY STATE

Data from *in vitro* studies indicate that CYP3A4 is a major component of darifenacin metabolism. Therefore, four drug interaction studies were conducted with a selection of CYP3A4 inhibitors (ketoconazole, fluconazole, erythromycin) to evaluate the extent of inhibition of CYP3A4-mediated metabolism of darifenacin at steady state.

Study 1022: The Effects of Erythromycin on the Pharmacokinetics of Darifenacin at Steady State (Darifenacin 30 mg ER)

A randomized, placebo controlled, parallel group study was conducted in healthy white male subjects aged 18 to 55 years (23 EM, 7 PM) to evaluate the effects of erythromycin on the pharmacokinetics of darifenacin at steady state. In addition, the ratios of 3-hydroxyquinine/quinine and the pharmacokinetics of darifenacin were compared to determine if there were any correlations. Subjects were administered darifenacin ER 30 mg once daily on Days 1 to 13 and erythromycin 500 mg or placebo b.i.d. on Days 7 to 13. Seven to 10 days following the final dose subjects received a single oral dose of 600 mg quinine at the follow-up visit. Plasma concentrations of darifenacin were obtained pre-dose on Days 1 to 13 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36*, 48* (*Day 13 only) hours post-dose on Day 6 and Day 13. At the follow-up visit, blood samples were taken 6 hours post quinine dose for assay of quinine and 3-hydroxyquinine concentrations. For EM subjects only, darifenacin log-transformed AUC_{24}, C_{max} and untransformed T_{max} were analyzed using ANOVA. No formal was carried out on the quinine/3-hydroxyquinine ratio.

Table 39. The Results of the Statistical Analysis of Darifenacin Pharmacokinetic Parameters of 11 EM Subjects.

Parameter	Ratio/Difference (including 90% Confidence Interval) of/between adjusted means		Ratio/Difference*	90% Confidence Interval
	Day 13 – Day 6 Darifenacin + Erythromycin	Day 13 – Day 6 Darifenacin + Placebo	Day 13 – Day 6 Darifenacin + Erythromycin / Day 13 – Day 6 Darifenacin + Placebo	
AUC_{24} (ng.h/ml)	267 (214, 332)	136 (110, 170)	195	(143, 267)
C_{max} (ng/ml)	315 (254, 392)	138 (111, 172)	228	(167, 310)
T_{max} (h)	0.8 (-1.5, 3.1)	0.1 (-2.2, 2.4)	0.7	(-2.5, 4.0)

The ratios, expressed as percentages, are presented for AUC_{24} and C_{max}, and the differences for T_{max}.
*Ratio/Difference Between Adjusted Means

- On comparison of the darifenacin + erythromycin group with the darifenacin + placebo group from Day 6 to Day 13, AUC_{24} and C_{max} were greater in the darifenacin + erythromycin group by 95% and 128 %, respectively and T_{max} increased by about 40 minutes.

Table 40. The Darifenacin Pharmacokinetic Parameters at Steady State (22 EMs [11 per group], 7 PMs [4 in the darifenacin + erythromycin, 3 in the darifenacin + placebo]).

Parameter	Raw Means							
	Darifenacin + Erythromycin				Darifenacin + Placebo			
	EM		PM		EM		PM	
	Day 6	Day 13	Day 6	Day 13	Day 6	Day 13	Day 6	Day 13
AUC_{24} (ng.h/ml)	243	646	373	735	189	258	364	536
C_{max} (ng./ml)	15.9	50.0	22.6	47.5	13.4	18.5	24.2	34.8
T_{max} (h)	2.5	3.4	7.8	3.3	3.6	3.7	2.0	5.7

The means presented are geometric for AUC_{24} and C_{max} and arithmetic for T_{max}.

- In the darifenacin + erythromycin group (EMs), there was an increase in AUC_{24}, C_{max} and T_{max} of 167%, 215% and about 45 minutes, respectively, from Day 6 to Day 13.
- In the darifenacin + placebo group (EMs), there was an increase in AUC_{24} and C_{max} of 36% and 38% respectively, but no evidence of any change in T_{max} from Day 6 to Day 13.
- AUC_{24} and C_{max} of darifenacin were higher in the PMs than in the EMs on Day 6 and on Day 13 in both treatment groups
- The increases in concentration from Day 6 to Day 13 in each treatment group were proportionally similar for the EMs and PMs.

- On comparison of the darifenacin + erythromycin group with the darifenacin + placebo group, from Day 6 to Day 13, the darifenacin concentrations seen in the PMs did not increase as much as those seen in the EMs.

Table 41. The Ratio of Quinine/3-Hydroxyquinine in EM and PM Subjects

Quinine/3-hydroxyquinine Mean ± SD (range)			
EM		PM	
Darifenacin + Erythromycin (n=11)	Darifenacin + Placebo (n=11)	Darifenacin + Erythromycin (n=4)	Darifenacin + Placebo (n=3)
5.3 ± 1.5	6.6 ± 2.0	6.7 ± 2.3	9.4 ± 3.0

- No clear correlation was apparent between the ratio of quinine/3-hydroxyquinine and the change in darifenacin AUC_{24} from Day 6 to Day 13 in the presence and absence of erythromycin.

Study 1024: The Effects of Fluconazole on the Pharmacokinetics of Darifenacin at Steady State (Darifenacin 30 mg ER)

A randomized, placebo controlled, two-period crossover study was conducted in 17 white healthy male subjects (12 EM, 5 PM) aged 18 to 55 years to investigate the effects of fluconazole on the pharmacokinetics of darifenacin at steady state. Subjects were administered with darifenacin 30 mg and either fluconazole (a loading dose of 200 mg on Day 1 then 100 mg on Days 2 to 9) or placebo once daily on Days 1 to 9 after a minimum washout period of 14 days between the study periods. Plasma darifenacin concentrations were taken pre-dose on Days 1 to 9 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, and 48 hours post-dose on Day 9. The Darifenacin log-transformed AUC_{24}, C_{max} and untransformed T_{max} of EMs were analyzed using ANOVA.

Table 42. The Results of the Statistical Analysis of Darifenacin Pharmacokinetic Parameters of EM Subjects.

Parameter	Adjusted means		Ratio/difference between adjusted means[a]	90% confidence interval
	Darifenacin + Fluconazole	Darifenacin + Placebo		
AUC_{24} (ng.h/ml)	507	275	184%	(153, 222)
C_{max} (ng/ml)	35.5	18.9	188%	(152, 232)
T_{max} (h)	4.5	4.6	-0.1	(-1.5, 1.3)

[a] ratio (AUC_{24} and C_{max}); difference (T_{max})

- Co-administration of darifenacin with fluconazole increased darifenacin AUC_{24} and C_{max} by 84% and 88%, respectively, compared to co-administration of darifenacin and placebo.
- T_{max} was similar in the presence and absence of fluconazole.

Table 43. Summary of Darifenacin and UK-148,993 Pharmacokinetic Results in EM and PM subjects.

Parameter	Darifenacin Raw Means[a]				UK-148,993 Raw Means[a]			
	Darifenacin + Fluconazole		Darifenacin + Placebo		Darifenacin + Fluconazole		Darifenacin + Placebo	
	EM subjects (n=12)	PM Subjects (n=4)	EM Subjects (n=12)	PM Subjects (n=5)	EM subjects (n=12)	PM Subjects (n=4)	EM Subjects (n=12)	PM Subjects (n=5)
AUC_{24} (ng.h/ml)	507	1150	275	516	265	450	188	299
C_{max} (ng/ml)	35.5	68.6	18.9	33.4	16.6	30.4	12.5	19.1
T_{max} (h)	4.5	3.5	4.6	5.4	4.0	3.3	3.4	4.6
C_{min} (ng/ml)	14.2	29.5	7.6	13.6	N/C	N/C	N/C	N/C
C_{av} (ng/ml)	21.1	48.0	11.5	21.5	N/C	N/C	N/C	N/C
PTF (scalar)	0.97	0.80	0.83	0.73	N/C	N/C	N/C	N/C
CL/F (ml/min)	59.2	26.0	109.1	58.2	N/C	N/C	N/C	N/C
k_{el} (/h)	0.084[a]	0.060	0.090[e]	0.074[d]	0.041[e]	0.037[g]	0.054[f]	0.037[d]
$t_{1/2}$ (h)	8.2[b]	11.7	7.7[c]	9.4[d]	17.1[e]	19.0[f]	12.9[f]	18.7[d]

[a]means are, geometric (AUC_{24}, C_{max}, C_{min}, C_{av}, PTF and CL/F), arithmetic (T_{max} and $t_{1/2}$) and harmonic (k_{el}) [b] n=10; [c] n=11; [d] n=4, [e] n= 7, [f] n= 6, [g] n= 2, N/C = not calculated.

- The relative increase in darifenacin and UK-148,993 was similar for EMs and PMs when darifenacin was co-administered with fluconazole compared with placebo. However, the exposure to darifenacin was approximately doubled in PMs compared to EMs.
- There was a small increase in $t_{1/2}$ when darifenacin was administered with fluconazole compared to placebo for both EM and PM subjects.

Table 44. Summary of Darifenacin PK Parameters in 5 PM Subjects

	AUC_{24} ng*hr/mL			C_{max} (ng/mL)		
Subject	Darifenacin + Fluconazole	Darifenacin + Placebo	Ratio	Darifenacin + Fluconazole	Darifenacin + Placebo	Ratio
12	[redacted]	[redacted]	2.07	[redacted]	[redacted]	2.19
13	[redacted]	[redacted]	NA	NA	[redacted]	NA
14	[redacted]	[redacted]	2.37	[redacted]	[redacted]	2.93
15	[redacted]	[redacted]	1.33	[redacted]	[redacted]	1.34
16	[redacted]	[redacted]	2.30	[redacted]	[redacted]	1.81

Study 1035: The Effects of Ketoconazole on the Pharmacokinetics of Darifenacin at Steady State (Darifenacin 7.5 mg and 15 mg ER)

A four-treatment, two-way, randomized, placebo controlled, two-period crossover study in two cohorts was conducted in healthy white male subjects aged 18 to 45 years to investigate the effects of ketoconazole on the steady state pharmacokinetics of darifenacin at doses of 7.5 mg and 15 mg. Subjects received darifenacin 7.5 mg or 15 mg once daily on Days 1 to 6 and either ketoconazole 400 mg or placebo once daily on Days 1 to 8 after a minimum washout period of 7 days between the study periods. Each dosing was administered ten minutes after a standard breakfast had been completed. A maximum of 24 subjects were planned to be enrolled for the study in two cohorts of 12 (10 EM and 2 PM). Plasma concentrations of darifenacin were obtained pre-dose on Days 1 to 6 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, and 72 hours post-dose on Day 6. At 4-hour post-dose on Day 6, an ECG recording was taken after each subject had been resting supine for five minutes. For EM subjects, darifenacin log-transformed AUC_{24}, C_{max} and untransformed T_{max} were analyzed using ANOVA.

Treatments:

A: Darifenacin 7.5 mg + ketoconazol 400 mg for 6 days followed by ketoconazole 400 mg alone on Days 7 and 8

B: Darifenacin 7.5 mg + placebo for 6 days followed by placebo alone on Days 7 and 8

C: Darifenacin 15 mg + ketoconazole 400 mg for 6 days followed by ketoconazole 400 mg alone on Days 7 and 8

D: Darifenacin 15 mg + placebo for 6 days followed by placebo alone on Days 7 and 8

Table 45. A Summary of Statistical Analysis of Darifenacin 7.5 mg Pharmacokinetic Results for EM Subjects

Parameter	Adjusted geometric mean		Difference/ratio (%)	90% CI (%)
	Darifenacin 7.5mg + Ketoconazole (n = 9)	Darifenacin 7.5mg + Placebo (n = 9)		
AUC_{24} (ng.h/ml)	139	26.1	533[2]	[386, 737]
C_{max} (ng/ml)	10.9	1.93	567[2]	[420, 764]
T_{max} (h)	4.79[1]	2.99[1]	1.80[3]	[0.38, 3.22]

[1]arithmetic mean (T_{max}); [2]ratio of means; [3]difference between means

- Co-administration of ketoconazole 400 mg with darifenacin 7.5 mg increased steady state darifenacin AUC_{24} and C_{max} by 5.3- and 5.7-folds, respectively compared with co-administration of darifenacin with placebo.
- Statistical analysis was not carried out on darifenacin 15 mg data as only 3 subjects were included in the statistical summaries. However, the mean data from the 3 subjects who received darifenacin 15 mg showed that AUC_{24} and C_{max} for darifenacin increased by a ratio of 11.6 and 10.0, respectively, in the presence of ketoconazole 400 mg compared with placebo.

Table 46. The Darifenacin Pharmacokinetic Results of EM Subjects

Parameter	Raw Means[1]			
	Darifenacin 7.5mg + Ketoconazole (n= 10)	Darifenacin 7.5mg + Placebo (n = 9)	Darifenacin 15mg + Ketoconazole (n = 3)	Darifenacin 15mg + Placebo (n = 3)
AUC_{24} (ng.h/ml)	143	25.8	1110	95.7
AUC (ng.h/ml)	179	37.6	1670	137
AUC_{last} (ng.h/ml)	174	32.2	1660	134
C_{max} (ng/ml)	11.2	1.91	67.6	6.77
C_{min} (ng/ml)	2.60	0.67	30.0	2.96
C_{av} (ng/ml)	5.94	1.08	46.2	3.99
T_{max} (h)	4.90	3.00	6.67	5.33
k_{el} (/h)	0.08	0.06(n=8)	0.09	0.09
$t_{1/2}$ (h)	8.67	11.9(n=8)	7.37	8.00
PTF	1.42	1.07	0.79	0.86
CL/F (l/h)	42.0	199	9.01	110

[1]geometric mean (AUC, AUC_{24}, AUC_{last}, C_{max}, C_{min}, C_{av}, $t_{1/2}$, PTF, CL/F), arithmetic mean (T_{max}); harmonic mean (k_{el})
Subjects with down-titrated doses of darifenacin are excluded.

- Four subjects in darifenacin 15 mg and ketoconazole treatment group and 2 subjects in darifenacin 15 mg and placebo treatment group had their dose of darifenacin reduced from 15 mg to 7.5 mg. Dose reductions were due to treatment related adverse events such as abnormal vision, dry mouth and constipation.

Table 47. Pharmacokinetic Data of Darifenacin in **PM Subjects**

Parameter	Raw Values[1]			
	Darifenacin 7.5mg + Ketoconazole (n= 1)	Darifenacin 7.5mg + Placebo (n = 1)	Darifenacin 15mg + Ketoconazole (n = 1)	Darifenacin 15mg + Placebo (n = 1)
AUC (ng.h/ml)	1600	139	1330	111
AUC_{24} (ng.h/ml)	939	79.9	931	87.7
AUC_{last} (ng.h/ml)	1560	128	1330	109
C_{max} (ng/ml)	55.4	5.85	58.9	6.17
C_{min} (ng/ml)	22.1	1.59	22.0	3.41
C_{av} (ng/ml)	39.1	3.33	38.8	3.65
T_{max} (h)	4.00	4.00	8.0	3.0
k_{el}(/h)	0.06	0.03	0.09	0.09
$t_{1/2}$ (h)	12.3	20.1	7.4	7.4
PTF	0.85	1.28	0.95	0.76
CL/F (l/h)	4.70	54.0	11.3	135

[1]geometric mean (AUC, AUC_{24}, AUC_{last}, C_{max}, C_{min}, C_{av}, $t_{1/2}$, PTF, CL/F), arithmetic mean (T_{max}); harmonic mean (k_{el})
The darifenacin dose was down-titrated in one CYP2D6 PM with darifenacin 15 mg.

Study 1007: The Effects of Ketoconazole on the Pharmacokinetics of Darifenacin at Steady State (Darifenacin 30 mg ER)

A randomized, placebo controlled, two-period crossover study was conducted in healthy white male subjects (12 EM, 4 PM) aged 20 and 52 years to investigate the effects of ketoconazole on the steady state pharmacokinetics of darifenacin. Subjects received darifenacin 30 mg once daily on Days 1 to 6 and either ketoconazole 400 mg or placebo once daily on Days 1 to 6 after a minimum washout period of 7 days between the study periods. Each dosing was administered 30 minutes after a standard breakfast. Plasma concentrations of darifenacin were obtained pre-dose on Days 1 - 6 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours post-dose on Day 6. A 12-lead ECG was performed within 3 weeks before the start of the study, 4 hours post-dose on Day 6, and at follow-up visit 14 days after the final dose. The original traces were sent to [redacted], for bitmapping, digitizing and analysis. For EM subjects, darifenacin log-transformed AUC_{24}, C_{max} and untransformed T_{max} were analyzed using ANOVA.

Table 48. A Summary of the Statistical Analysis of the Darifenacin Pharmacokinetic Results for EM Subjects, n=9 (no dose down titration).

Parameter	Adjusted geometric mean[a]		Difference/ratio	90% confidence intervals
	Darifenacin + ketoconazole	Darifenacin + placebo		
AUC_{24} (ng.h/ml)	2080	196	1061%[b]	[844. 1335]
C_{max} (ng/ml)	128	13.4	952.4%[b]	[781.6. 1160.6]
T_{max} (h)	7.2	3.2	4.0[c]	[2.8, 5.2]

[a] arithmetic mean (T_{max}); [b] ratio of means; [c] difference between means

- Co-administration of ketoconazole 400 mg with darifenacin 30 mg caused a 10.6 and 9.5 fold increase in steady state darifenacin AUC_{24} and C_{max}, respectively.

Table 49. Darifenacin Pharmacokinetic Parameters for EM/PM Subjects

	EM				PM			
PK Parameters[a]	D 30 + K (n=9)	D 30 + P (n=9)	D 15 + K[b] (n=3)	D 15 + P (n=2)	D 30 + K (n=2)	D 30 + P (n=3)	D 15 + K[b] (n=2)	D 15 + P (n=1)
AUC_{0-24}	2338.4	204.0	1889.3	180[c]	3496.0	331.0	1592.0	93.6
C_{max}	139.0	13.8	102.0	5.9	191.5	54.4	97.5	7.6
T_{max}	7.2	3.1	6.0	12.0	10	11.7	7.0	3.0

					(8, 12)	(3, 8, 24)	(4, 10)	

[a]Arithmetic mean
[b]Subjects were dosed darifenacin 30 mg + keto 400 mg Days 1-3, and darifenacin 15 mg + keto 400 mg Days 4-6
[c]AUC_{0-24} in one EM was not done, therefore n=1
D = darifenacin, K = ketoconazole, P = placebo

- The AUC_{24} observed in PM subjects was about 2 fold higher than the average seen in EM subjects (darifenacin + placebo treatment group).
- In the presence of darifenacin and ketoconazole compared to darifenacin and placebo, 2 PM subjects showed a 6.5 and 10.2 fold increase in AUC_{24}.
- Two out of 4 PM subjects (50%) had their dose down-titrated in the presence of ketoconazole compared with 25% of the EM subjects.
- The increases in AUC_{24} in PM subjects who did not down-titrate (n=2), in the presence of darifenacin and ketoconazole compared to darifenacin and placebo, were similar to those of the EM subjects.

Figure 21. Mean Plasma Concentrations of Darifenacin at Steady State on Day 6 (EM Subjects)

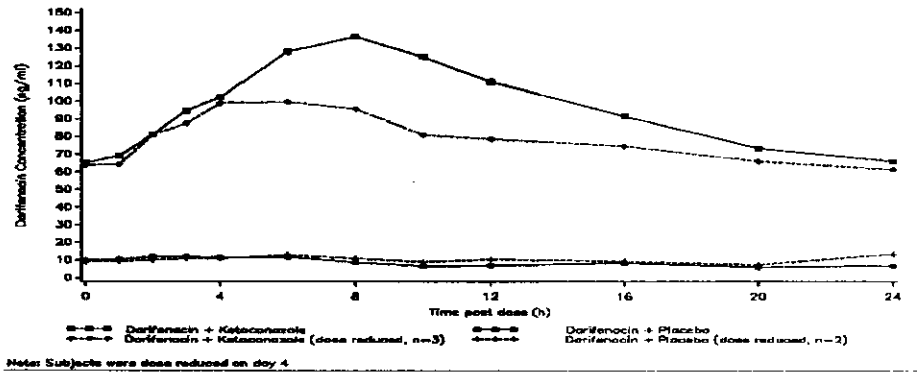
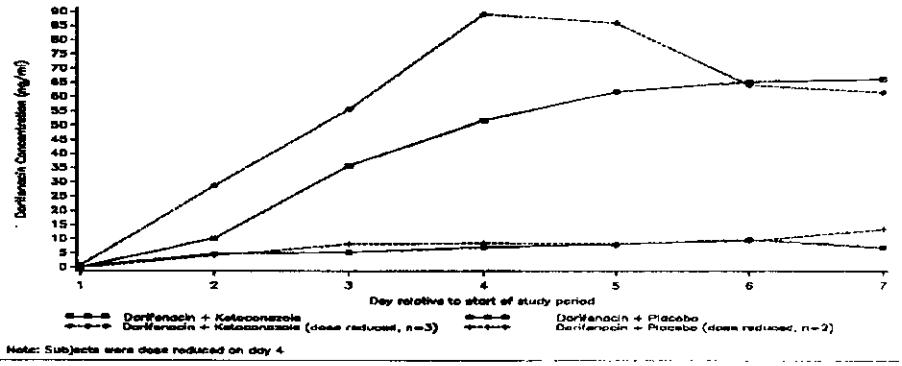


Figure 22. Mean Trough Plasma Concentrations of Darifenacin (EM Subjects)



- Plasma troughs on Days 1 to 4 were higher in the 3 EM subjects who dose-reduced (darifenacin and ketoconazole group)

THE EFFECT OF MIXED CYP P450 INHIBITOR, CIMETIDINE ON DARIFENACIN AT STEADY STATE

Study 1010: The Effects of Cimetidine on the PK of Darifenacin at Steady State

A randomized, placebo controlled, two-period crossover study was conducted in healthy white male subjects (16 EM, 4 PM) aged 18 to 55 years to evaluate the effect of cimetidine on the steady state pharmacokinetics of darifenacin. Subjects were administered darifenacin 30 mg ER tablet once daily and either cimetidine 800 mg tablet or placebo twice daily for 6 days. Treatment periods were separated by a minimum of 7 days washout period. Plasma concentrations of darifenacin were obtained pre-dose on Days 1 to 6 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours post-dose on Day 6. For EM subjects only darifenacin log-transformed AUC_{24}, C_{max} and untransformed T_{max} were analyzed using ANOVA.

Table 50. Comparisons of Darifenacin Pharmacokinetic Parameters in EM Subjects (n=13).

Parameter	Adjusted Means		Ratio of / Difference Between Means	90% Confidence Interval
	Darifenacin + Cimetidine	Darifenacin + Placebo		
AUC_{24} (ng.h/ml)	216	162	134%	110, 163
C_{max} (ng/ml)	17.1	12.0	142%	120, 168.
T_{max} (h)	6.80	5.34	1.5	-1.5, 4.4

The means presented are geometric for AUC_{24} and C_{max} and arithmetic for T_{max}. AUC_{24} and C_{max} are presented as ratios and expressed as percentages. T_{max} is presented as a difference.

-Two subjects excluded from the statistical analysis because data from both periods are not available.

- There was a 34% and 42% increase in mean darifenacin AUC_{24} and C_{max} respectively and a 1.5 hour increase in mean T_{max} following dosing with darifenacin + cimetidine compared to darifenacin + placebo in the EM subjects.

Table 51. Pharmacokinetic Results of Darifenacin at Steady State

Parameter	Darifenacin + Cimetidine		Darifenacin + Placebo	
	EM (N = 16)	PM (N = 4)	EM (N = 15)	PM (N = 3)
AUC_{24} (ng.h/ml)	216	281	166	209
C_{max} (ng/ml)	16.8	19.0	12.2	13.0
T_{max} (h)	6.4	5.3	5.3	11.0
$C_{ss,min}$ (ng/ml)	4.64*	7.12	4.05**	6.52
C_{ss} (ng/ml)	9.01	11.7	6.92	8.72
PTF	1.27*	0.99	0.97**	0.73
CL/F (1/h)	139	107	181	143

The means presented are geometric for AUC_{24}, $C_{ss,min}$, C_{max}, C_{ss}, PTF and CL/F and arithmetic for T_{max}. *N = 14; **N = 12

- The trends in darifenacin concentration seen in the EM subjects were similar to those seen in the PM subjects.

THE EFFECTS OF CYP2D6 INHIBITOR ON DARIFENACIN AT STEADY STATE

Study 1008: The Effects of Paroxetine on the PK of Darifenacin at Steady State

A randomized, placebo controlled, parallel group study was conducted in healthy white male subjects (18 EM, 8 PM) aged 18 to 55 years to evaluate the effects of paroxetine on the pharmacokinetics of darifenacin at steady state. Subjects received darifenacin 30 mg ER once daily on Days 1 to 16 and either oral paroxetine 20 mg or placebo once daily on Days 7 to 16. A standard breakfast was served 30 minutes prior to administration of darifenacin. Plasma concentrations of darifenacin were obtained pre-dose on Days 1 to 16 and at 1, 2, 3, 4, 6, 8, 10,

12, 16, 20, and 24 hours post-dose on Day 6 and Day 16. For EM subjects, darifenacin log-transformed AUC_{24}, C_{max} and untransformed T_{max} were analyzed using ANOVA.

Table 52. Results of the Statistical Analysis of Darifenacin Concentrations (18 EM, 9 per treatment group)

Parameter	Ratio/Difference (including 90% Confidence Interval) of/between adjusted Means		Ratio/Difference (90% Confidence Interval)
	Day 16 – Day 6 Darifenacin + Paroxetine	Day 16 – Day 6 Darifenacin + Placebo	(Day 16 – Day 6 Dari + Par) - (Day 16 – Day 6 Dari + Plac)
AUC_{24}(ng.h/ml)*	167 (131, 213)	125 (98, 160)	133 (94.4, 188)
C_{max}(ng/ml)*	173 (138, 217)	127 (101, 159)	136(98.7, 188)
T_{max}(h)**	-1.8 (-6.4, 2.8)	-3.0 (-7.6, 1.6)	1.2(-5.3, 7.7)

-The ratios, expressed as percentages, are presented for AUC_{0-24} and C_{max} and the differences for T_{max} are presented in hour.

- Co-administration of paroxetine increased the AUC_{24} and C_{max} of darifenacin at steady state by 33% and 36%, respectively.

Table 53. A Summary of the Raw Mean Darifenacin Pharmacokinetic Parameters (Day 6 and Day 16) for 18 EM Subjects (9 per treatment group) and 8 PM Subjects (4 per treatment group).

Parameter	Raw Means							
	Darifenacin + Paroxetine				Darifenacin + Placebo			
	EM		PM		EM		PM	
	Day 6	Day 16	Day 6	Day 16	Day 6	Day 16	Day 6	Day 16
AUC_{24}(ng.h/ml)	185	308	381	347	213	266	369	266
C_{max}(ng/ml)	11.5	19.9	26.2	25.3	13.8	17.5	22.0	19.8
T_{max}(h)	7.4	5.7	5.3	2.5	8.1	5.1	7.8	7.5

- The PM subjects have higher plasma concentrations of darifenacin than the EM subjects on Days 6 and 16 in both groups.
- The EM subjects have an increase in AUC_{24} and C_{max} from Day 6 to Day 16 in both groups
- The increases observed in the EM subjects are greater in the darifenacin + paroxetine group than in the darifenacin + placebo group.
- No formal analysis was performed in PM subjects after co-administration of a CYP2D6 inhibitor. However, visual inspection of data indicates that darifenacin exposure is not increased by paroxetine co-administration in PM subjects.
- The raw darifenacin means for AUC_{24} and C_{max} showed that darifenacin plasma concentrations were higher in PM subjects than in EM subjects. The raw means also showed that paroxetine caused an increase in darifenacin AUC_{24} and C_{max} in the EM subjects and not in the PM subjects.
- D + Paroxetine Group (6 EM and 3 HEM): 1 subject (ID 4420005, EM) with a negative difference of 72 ngh/mL in AUC and a negative difference of 4 ng/mL in Cmax
- The darifenacin + placebo group had 6 HEM and 3 EM.

Table 54. The Summary of Pharmacokinetic Parameters of Darifenacin in PM Subjects

Parameter	Ratio (test/ref) Range	Ratio (test/ref) Range

	Day 16 – Day 6 Darifenacin + Paroxetine	Day 16 – Day 6 Darifenacin + Placebo
AUC_{0-24} (ng*hr/mL)	0.7 – 3.2	0.6 – 2.4
C_{max} (ng/mL)	0.74 – 3.38	0.82 – 2.12

- Contribution of CYP2D6 to darifenacin metabolism at steady state is inversely related to dose, and is highest at low doses. Therefore, the difference in darifenacin exposure between EMs and PMs at steady state should be greater at lower doses.
- Total exposure from concomitant use of a CYP2D6 inhibitor with darifenacin in EM subjects cannot exceed that seen in the corresponding PM population.

THE EFFECTS OF DARIFENACIN ON CYP3A4 SUBSTRATES

In vitro human microsomal data have shown that darifenacin has the potential to inhibit CYP3A4 mediated metabolism (IC_{50} 1.2μM). Of the 3 probe substrates tested the greatest inhibition was observed for midazolam (DM-01137-01E). Therefore, midazolam was used as the probe substrate in a clinical study to determine the effect of darifenacin dosing on CYP3A4 activity *in vivo*. However systemic plasma concentrations of darifenacin achieved after proposed clinical doses are 0.609nM. Based on these data, darifenacin does not likely to inhibit the metabolism of midazolam *in vivo*.

Study 1031: Effect of Darifenacin on the Pharmacokinetics of Oral Midazolam

A randomized, double-blind, placebo controlled, two-period, crossover study was conducted in 30 healthy male subjects (14 EMs, 13 HEMs, 3 PMs) aged 18 to 45 years to investigate the effects of steady state darifenacin on the pharmacokinetics of a single oral dose of midazolam. Subjects received darifenacin 30 mg ER or a placebo once daily on Days 1 to 6 and a single oral dose of midazolam 7.5 mg on Day 6 only of each study period under fasting conditions. The treatment periods were separated by a minimum of 7 days washout period. Plasma concentrations of darifenacin were obtained pre-dose on Days 1 to 6 and plasma concentrations of midazolam were obtained pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours post-dose on Day 6. For all subjects with PK data, midazolam log-transformed AUC_{24}, C_{max}, and untransformed T_{max} were analyzed using ANOVA. No statistical analyses were performed for darifenacin.

Table 55. The Results of the Treatment Comparisons (EM/PM Subjects)

Parameter (units)	Adjusted Means		Ratio/ Difference	90% CI
	Midazolam + Darifenacin	Midazolam + Placebo		
AUC (ng.h/ml)	88.8	75.8	117%	107%, 129%
C_{max} (ng/ml)	34.2	34.7	98.6%	82.6%, 118%
T_{max} (h)	0.9	0.7	0.2	0.0, 0.3

Means are geometric for AUC and C_{max} and arithmetic for T_{max}.
The ratios, expressed as percentages, are presented for AUC and C_{max} and the differences for T_{max}.

- The co-administration of midazolam with darifenacin 30 mg at steady state resulted in 17 % increase in mean midazolam AUC and no effect on C_{max} and T_{max} compared to co-administration of midazolam with placebo.
- Both the EM and PM subjects were used in the PK analyses. The effects on the PK parameters were apparently similar for EM and PM subjects (considerable overlap for all of the parameters).

Table 56. The Midazolam Pharmacokinetic Parameters (EM/PM Subjects)

Parameter (units)	Midazolam + Darifenacin N=30	Midazolam + Placebo N=29
AUC_{24} (ng.h/ml)	84.5	72.6
AUC (ng.h/ml)	88.8	75.8
C_{max} (ng/ml)	33.8	34.7
T_{max} (h)	0.9	0.7
$t_{½}$ (h)	2.9	3.7
k_{el} (/h)	0.24	0.19

Means are geometric for AUC_{24}, AUC, and C_{max}, arithmetic for T_{max} and $t_{½}$ and harmonic for k_{el}

- There was an apparent decrease in midazolam $t_{1/2}$ following darifenacin administration.

Table 57. The Midazolam Pharmacokinetic Parameters of 3 PM Subjects

Parameter	Midazolam + Darifenacin Mean (range)	Midazolam + Placebo Mean (range)
AUC_{0-24} (ng*hr/mL)	103.3	79.6
AUC (ng*hr/mL)	108.2	83.1
C_{max} (ng/mL)	37.9	47.9
T_{max} (hr)	1.0	0.67
$t_{1/2}$ (hr)	2.8	4.1
k_{el} (hr^{-1})	0.245	0.174

THE EFFECTS OF DARIFENACIN ON ORAL CONTRACEPTIVES

Study 205: Effect of Darifenacin on the Pharmacokinetics of Oral Contraceptives

A double-blind, placebo controlled, two-period crossover study was conducted in 22 healthy sterilized white female subjects (11 EM, 7 HEM, 3 PM) aged 18 to 45 years to investigate the effect of orally administered darifenacin on the steady state plasma concentration profile of an OC. Subjects were administered a combined OC containing 0.15 mg LNG and 0.03 mg EE [ ] on Days 1-21, and 2 capsules of oral darifenacin 5 mg IR t.i.d. or placebo on Days 11-15. Days 22-28 were the washout period. Subjects then received OC on Days 29-43 and either placebo or 2 capsules of oral darifenacin 5 mg IR t.i.d. on Days 39-43. The morning dose of darifenacin or placebo was given with the OC and taken immediately after a standard light breakfast. Blood samples for LNG and EE were collected pre-dose, and at fixed intervals up to 24 hours post-dose (1, 2, 3, 4, 6, 8, 10, 14, 24 hours) on Day 15 and Day 43. Blood samples for darifenacin were also collected pre-dose and at intervals up to 8 hours post-dose (1, 2, 4, 8 hours). The log transformed AUC_{24} and C_{max} and untransformed T_{max} of LNG and EE were analyzed using an ANOVA.

Period 1				Period 2	
Days 1-10	Days 11-15	Days 16-21	Days 22-28	Days 29-38	Days 39-43
OC only	OC + Darifenacin or Placebo	OC only	Washout period	OC only	OC + Placebo or Darifenacin

The evening before the follow-up examination, subjects were administered 10 mg debrisoquine tablet after emptying their bladders. All urine produced in the following 12 hours was collected.

Table 58. Summary of the Effects of Darifenacfin on Pharmacokinetics of LNG and EE

Levonorgestrel	Darifenacin N=21	Placebo N=21	Ratio/difference of adjusted means	90% CI
AUC_{24} (ng.h/ml)[a]	137	142	0.961 (ratio)	0.912, 1.013
C_{max} (ng/ml)[a]	10.9	11.9	0.911 (ratio)	0.828, 1.004
T_{max} (hours)[b]	2.0	1.8	0.25 (difference)	-0.09, 0.58

[a] Adjusted geometric mean; [b] Adjusted arithmetic mean; CI = Confidence interval

Ethinyloestradiol	Darifenacin N=21	Placebo N=21	Ratio/difference of adjusted means	90% CI
AUC_{24} (ng.h/ml)[a,b]	894	906	0.987 (ratio)	0.947, 1.030
C_{max} (ng/ml)[a]	92.1	98.7	0.933 (ratio)	0.860, 1.012
T_{max} (hours)[c]	2.3	2.0	0.33 (difference)	0.02, 0.64

[a] Adjusted geometric mean; [b] For some subjects AUC_{16} was used instead of AUC_{24} because the concentration was below the level of quantification at 24 hours post dose; [c] Adjusted arithmetic mean; CI = Confidence interval

- There was no apparent effect of darifenacin on LNG or EE PK parameters
- Although this study was conducted using IR capsule formulation of darifenacin given three times daily, the data can be extrapolated to use of the proposed ER tablet dosing regimen since the interactions were explored at steady state darifenacin concentrations using a 30mg total daily dose.

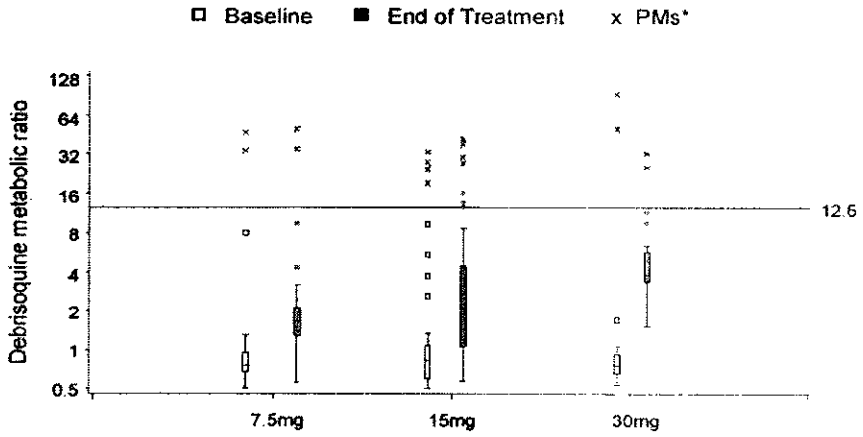
Table 59. A Summary of the Mean Pharmacokinetic Parameters for Darifenacin.

	Darifenacin N=21	UK-148,993 N=21	Ratio for darifenacin to UK-148,993 N=21
AUC_{0-t} (ng.h/ml)[a]	85.0	104	0.820
C_{max} (ng/ml)[a]	17.7	19.1	
T_{max} (hours)[b]	2.8	2.6	

THE EFFECTS OF DARIFENACIN ON CYP2D6 SUBSTRATES

In-vitro data has shown that darifenacin is a moderate inhibitor of CYP2D6 with an IC_{50} of 6μM.

Figure 23. Changes in Debrisoquine Metabolic Ratio Produced by Repeated Darifenacin Dosing (Studies 1023, 1038, 1045)



Source: Appendix B Figure A.4.1

* Subjects with baseline debrisoquine metabolic ratio >12.6, not included in summary statistics. Median indicated by a horizontal line within box. Top and bottom of box represent 75th and 25th percentiles and whiskers indicate the 1.5 interquartile range. Any individual value outside this range is marked with a symbol.

Study 1038: The Effects of Multiple Doses of Darifenacin 30 mg ER Tablets on the Debrisoquine Metabolic Ratio of Healthy Male Subjects

An open study was conducted in white healthy male subjects aged 18 to 45 years (11 EMs, 2 UEMs, 3 HEMs, 3 PMs) to compare the debrisoquine metabolic ratio (phenotype) pre-darifenacin dosing and at steady state following multiple doses of darifenacin 30 mg tablets. Each subject received 30 mg darifenacin once daily for 7 days and a single dose of 10 mg debrisoquine at Week -1 and on Day 7. Subjects were requested to void their bladders before being administered a single oral dose of debrisoquine. Plasma concentrations of darifenacin were taken at pre-dose on Days 1 to 5 and at pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours post-dose on Day 6. The total volume of urine excreted in the 8 hours post-debrisoquine dosing was collected at Week-1 and on Day 7. Statistical analyses were performed using ANOVA for the log-transformed metabolic ratio of debrisoquine and 4-hydroxydebrisoquine. The differences between treatment means of the metabolic ratio at baseline compared with the metabolic ratio post-treatment were compared. No formal analyses of darifenacin AUC_{24}, C_{max} and T_{max} were performed.

Table 60. The Statistical Analyses of the Debrisoquine Metabolic Ratio in EM Subjects

	Adjusted Means		Anti-log	
	Baseline N=16	Post-treatment N=16	Ratio of means	90% CI for ratio of means
Metabolic ratio	0.57	4.09	725%	(579%,906%)

Adjusted means presented are geometric, back transformed from the log-scale

- Administration of darifenacin inhibited metabolism of the CYP2D6 substrate debrisoquine.
- The estimated ratio of means for the debrisoquine MR between post-treatment and baseline was 725%.
- For EM subjects in general, there was a concentration dependent increase in debrisoquine MR with the greatest effects seen in those subjects with highest darifenacin exposure.
- The presence of darifenacin 30 mg did not result in any EM individual becoming phenotypically PM (MR>12.6).

Figure 24. Change in Debrisoquine/4-Hydroxydebrisoquine Ratio from Baseline to Post-Treatment

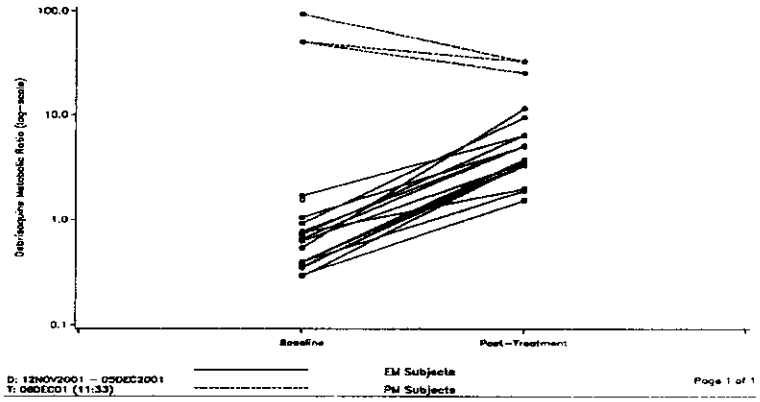


Table 61. The Darifenacin and UK-148,993 Pharmacokinetic Parameters

Parameter (units)	Darifenacin		UK-148,993	
	EMs N=16	PMs N=3	EMs N=16	PMs N=3
AUC_{24} (ng.h/ml)	130	350	132	270
C_{max} (ng.ml)	8.38	20.3	8.73	16.0
T_{max} (h)	6.8	6.0	5.2	5.3
C_{min} (ng/ml)	4.21	12.3	4.14	9.14
C_{av} (ng/ml)	5.41	14.6	5.51	11.3
PTF (scalar)	0.66	0.60	0.79	0.59

Means are geometric for AUC_{24}, C_{max}, C_{min}, C_{av} and PTF and arithmetic for T_{max}

STUDY 1023 (Refer to **Bioequivalence** section for study design)

Table 62. The Debrisoquine/4-hydroxydebrisoquine MR Data for the EM Subjects.

Treatment Group	Geometric Means		Ratio	90% CI
	Week -1	Day 7, Period 2		
Darifenacin 7.5mg (N=19)	0.9	2.0	2.2	2.0, 2.7
Darifenacin 15mg (N=17)	0.7	3.0	4.3	3.8, 5.4

- At steady state of darifenacin, the MR of debrisoquine to 4-hydroxydebrisoquine was about 2 fold greater for darifenacin 7.5 mg and about 4 fold greater for darifenacin 15 mg, compared to baseline (Week -1) values.
- One PM in the darifenacin 7.5 mg group had a MR of 1.06 whereas one PM in the darifenacin 15 mg group had a MR of 2.31.
- The debrisoquine/4-hydroxydebrisoquine MR data were pooled from two formulations of 15 mg ER tablets. However, since the two formulations of 15 mg ER tablets failed to show the bioequivalence, the MR data of debrisoquine should not be combined to assess the effects of darifenacin 15 mg on CYP2D6.

Study 1045 (Refer to **Bioequivalence** section for study design)
The effect of darifenacin on the debrisoquine MR and the duration of CYP2D6 inhibition after the discontinuation of darifenacin were investigated by comparing the debrisoquine metabolic phenotype pre-darifenacin dosing and at steady state for 15 mg darifenacin dose and at 1, 3, 5, and 7 days after the final dose of darifenacin.

Table 63. The Debrisoquine MR Data for the EM Subjects only

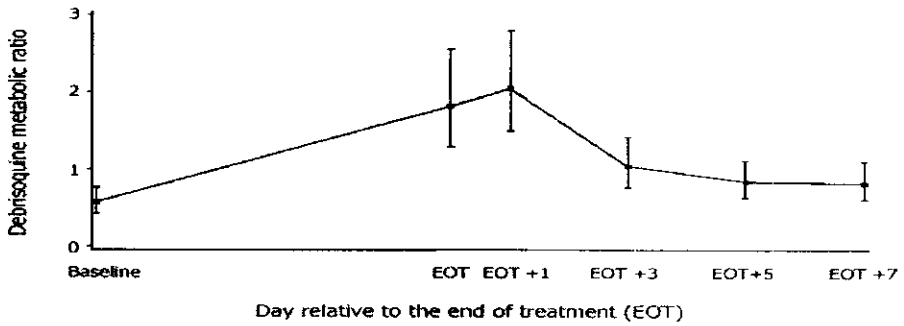
Timepoint	Geometric means[a] N = 24[b]	Ratio of change from baseline (test/reference)[c]	90% CI
Week -1 (Baseline)	0.57		
Day 7 (Period 2)	1.82	3.25	2.59, 4.08
Day 8 (Period 2)	2.05	3.66	3.01, 4.44
Day 10 (Period 2)	1.05	1.87	1.62, 2.16
Day 12 (Period 2)	0.85	1.51	1.36, 1.69
Day 14 (Period 2)	0.82	1.47	1.32, 1.64

[a] geometric means are back transformed from the log scale. [b] summary statistics are given for EM subjects only.
[c] test = MR post-treatment; reference=MR at baseline.
Debrisoquine MR data from both treatments were pooled for this table.

- Co-administration of darifenacin with debrisoquine inhibited the metabolism of debrisoquine but the 15 mg dose did not cause complete phenocoping of EM subjects to a PM phenotype (MR ≥ 12.6) except in 2 EM subjects.

- Inhibition of debrisoquine metabolism declined rapidly after cessation of darifenacin dosing and by 5 days after the end of treatment the mean inhibition was reduced to 1.5 times baseline value.
- In 4 PMs, ratios of change from baseline were as follows: 1.54, 0.91, 2.16, 0.97 on Day 7 of Period 2.
- There is a relationship between increasing darifenacin exposure (AUC and C_{max}) and increased CYP2D6 inhibition as seen by the consequent change in the MR of debrisoquine to 4-hydroxydebrisoquine.

Figure 25. Mean Debrisoquine Metabolic Ratio before Treatment and After Cessation of Darifenacin Dosing in EM Subjects



Source: Study A1371045 Figure 5.3
Error bars indicate 90% CIs.

Study 1009: The Effects of Darifenacin on the Pharmacokinetics of Imipramine at Steady State.

A randomized, placebo controlled, two-period, crossover study was conducted in healthy male subjects (12 EM, 2 PM) aged 18 to 55 years to evaluate the effects of darifenacin on the steady state pharmacokinetics of imipramine and desipramine. Subjects were administered darifenacin 30 mg ER or placebo once daily on Days 1 to 12 and imipramine 10 mg three times daily on Days 1 to 3 followed by imipramine 25 mg three times daily on Days 4 to 10 with a minimum of 14 days washout period between them. Pre-dose blood samples were obtained on Days 1 to 10 and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 18, 24, 48, and 72 hours post-dose on Day 10 for the measurement of imipramine and desipramine plasma concentrations. For EM subjects, the log-transformed AUC_{72}, C_{max} and untransformed T_{max} were analyzed using ANOVA. No statistical analyses were performed for the PM subjects.

Table 64. The Results of the Statistical Analysis for the Imipramine and Desipramine Pharmacokinetic Parameters in EM Subjects

Parameter (units)	Adjusted Means		Ratio/Difference of /Between Adjusted Means	90% Confidence Interval
	Imipramine + Darifenacin	Imipramine + Placebo		
Imipramine				
AUC_{72} (ng.h/ml)	302	178	170%	(142, 203)
C_{max} (ng/ml)	46.9	29.8	157%	(131, 189)
T_{max} (h)	3.1	2.7	0.4	(-0.9, 1.7)
Desipramine				
AUC_{72} (ng.h/ml)	509	140	363%	(287, 459)
C_{max} (ng/ml)	70.8	19.9	356%	(284, 447)
T_{max} (h)	4.2	4.1	0.1	(-1.8, 2.0)

- Co-administration of imipramine with darifenacin resulted in a 57% and a 70% increase in imipramine C_{max} and AUC_{72}, respectively and a 256% and a 263% increase in desipramine C_{max} and AUC_{72}, respectively.

Table 65. The Imipramine and Desipramine Pharmacokinetic Parameters for the EM and PM Subjects on Day 10.

Parameter (units)	Imipramine		Desipramine	
	Imipramine + Darifenacin	Imipramine + Placebo	Imipramine + Darifenacin	Imipramine + Placebo
EM Subjects (n = 12)				
AUC_{72} (ng.h/ml)	302	178	473	141
C_{max} (ng/ml)	46.9	29.8	66.2	19.9
T_{max} (h)	3.1	2.7	4.0	4.1
PM Subjects (n = 2)				
AUC_{72} (ng.h/ml)	173	196	465	523
C_{max} (ng/ml)	29.6	43.7	66.0	104
T_{max} (h)	3.3	2.8	5.3	2.8

The means presented are geometric for AUC_{72} and C_{max}, and arithmetic for T_{max}.

- There was reduced exposure to imipramine and desipramine in the presence of darifenacin in 2 PM subjects.
- The AUC_{72} results indicated that the plasma concentrations of imipramine were slightly higher in the PM subjects compared to EM subjects during imipramine and placebo dosing.
- When imipramine was co-administered with darifenacin, the plasma concentration of imipramine in the PM subjects slight dropped, whereas in the EM subjects it increased by 70%.
- The AUC_{72} showed that the plasma concentration of desipramine for the PM subjects was slightly lower during imipramine and darifenacin dosing compared to imipramine and placebo dosing. The desipramine plasma concentration in the EM subjects was 3.6 fold higher during imipramine and darifenacin dosing compared to imipramine and placebo dosing.
- The AUC_{72} showed that the plasma concentrations of desipramine were similar for the EM and PM subjects during imipramine and darifenacin dosing whereas they were approximately four fold higher in PM subjects when imipramine was dosed with placebo.

THE EFFECT OF DARIFENACIN ON WARFARIN

Study A1371030: Effect of Darifenacin on the Pharmacodynamics of Warfarin

This was a double blind, randomized, placebo controlled, two-way crossover study in 14 healthy male subjects aged 18 to 45 years to evaluate the effects of co-administration of darifenacin and warfarin on prothrombin time. Subjects were administrated oral administration of darifenacin 30 mg or placebo tablets once daily for 11 days and a single oral dose of warfarin 30 mg (6 tablets of warfarin 5 mg) on Day 6. Blood was collected to assess prothombin time at screening, pre-dose on Day 1, pre-warfarin dosing on Day 6 and at 6, 12, 24, 36, 48, 60, 72, 96, 120, and 144 hours post-warfarin dose and at follow up. AUEC for prothrombin time and the maximum change in prothrombin from baseline were analyzed using ANOVA.

Table 66. The Effects of Steady State Darifenacin on Pharmacodynamic Parameters Following a Single Warfarin Dose

	Unadjusted means		Difference between adjusted means (95% CI)
	Warfarin (N=14)	Warfarin + Darifenacin 30mg od (N=14)	
Baseline PT time (sec)	11.0	11.1	-
Max. change in PT time (sec)	9.4	9.2	-0.57 (-1.22, 0.07)
AUEC (sec.h)	2098	2144	16.9 (-51.5, 85.3)
PT INR (%)	0.91–2.34	0.94–2.75	-

Source: Study A1371030 Tables 5.1, 5.2 and Section 13, Table 24
INR, international normalized ratio

- Co-administration of darifenacin 30 mg with a single 30 mg dose of warfarin did not alter the pharmacodynamic effects of warfarin treatment.
- No significant differences in prothrombin time parameters were observed when warfarin was administered in combination with darifenacin compared with warfarin alone.

THE EFFECT OF DARIFENACIN ON DIGOXIN

Study 1021: The Effect of Darifenacin on the Steady State PK of Digoxin
A double blind, randomized, placebo controlled, parallel group study was conducted in 24 healthy male subjects aged 18 to 45 years to investigate the effect of multiple dose darifenacin on the steady state pharmacokinetics of digoxin. Subjects were administered digoxin 0.25 mg once daily on Days 1 to 17 and darifenacin 30 mg ER or placebo once daily on Days 8 to 17 one hour before breakfast. Plasma concentrations of digoxin were taken pre-dose on Days 1 to 17 and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours post-dose on Days 7 and 17. Urine samples for the measurement of digoxin were collected for 24 hours on Days 7 and 17 timed immediately before dosing of digoxin and ending exactly 24 hours later. The log-transformed AUC_{24}, C_{max}, and untransformed renal clearance and T_{max} of digoxin were analyzed using ANOVA.

Table 67. The Results of the Comparisons between Treatments

Parameter (units)	Comparison	Ratio/Difference Between Adjusted Means	90% CI
Plasma			
AUC_{24} (ng.h/ml)	(Day 17 - Day 7 darifenacin + digoxin) - (Day 17 - Day 7 placebo + digoxin)	116%	108%, 123%
	Day 17 - Day 7 darifenacin + digoxin	113%	108%, 119%
	Day 17 - Day 7 placebo + digoxin	98.1%	93.7%, 103%
C_{max} (ng/ml)	(Day 17 - Day 7 darifenacin + digoxin) - (Day 17 - Day 7 placebo + digoxin)	120%	106%, 135%
	Day 17 - Day 7 darifenacin + digoxin	106%	97.3%, 116%
	Day 17 - Day 7 placebo + digoxin	88.7%	81.6%, 96.5%
T_{max} (h)	(Day 17 - Day 7 darifenacin + digoxin) - (Day 17 - Day 7 placebo + digoxin)	0.2	0.0, 0.5
	Day 17 - Day 7 darifenacin + digoxin	0.2	0.0, 0.4
	Day 17 - Day 7 placebo + digoxin	-0.0	-0.2, 0.1
Urine			
CL_r (ml/min)	(Day 17 - Day 7 darifenacin + digoxin) - (Day 17 - Day 7 placebo + digoxin)	22.9	8.10, 37.6
	Day 17 - Day 7 darifenacin + digoxin	7.64	-3.02, 18.3
	Day 17 - Day 7 placebo + digoxin	-15.2	-25.4, -5.02

Source: Table 5.3
The ratios, expressed as percentages, are presented for AUC_{24} and C_{max} and the differences are presented for T_{max} and CL_r.

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- Comparison of digoxin AUC_{24} and C_{max} as the differences from Day 7 to Day 17 in the absence and presence of darifenacin indicated small increases of 16% and 20 %, respectively, in the presence of darifenacin. The renal clearance increased by 22.9 mL/min but T_{max} did not change in the presence of darifenacin.
- Co-administration of darifenacin on Days 8 to 17 produced a small increase in the digoxin trough levels. The effects observed on the digoxin PK were not considered to be clinically relevant.

Figure 26. Mean Trough Plasma Concentrations of Digoxin

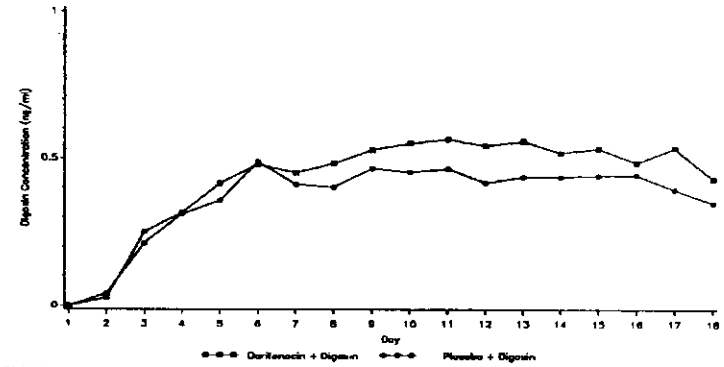


Table 68. The Digoxin Pharmacokinetic Parameters

Parameter (units)	Darifenacin + Digoxin		Placebo + Digoxin	
	Day 7 N=12	Day 17 N=11	Day 7 N=12	Day 17 N=12
Plasma				
AUC_{24} (ng.h/ml)	13.6	15.1	12.3	12.0
C_{max} (ng/ml)	1.85	1.94	1.75	1.55
T_{max} (h)	0.9	1.1	1.0	1.0
Urine				
CL_r (ml/min)	167	175	189	174

Means are geometric for AUC_{24} and C_{max} and arithmetic for T_{max} and CL_r

Table 69. Individual PK Parameters of PM Subjects (Darifenacin + Digoxin Group)

Subject	AUC_{24} (ng*hr/mL)			C_{max} (ng/mL)		
	Digoxin Day 7	Darifenacin + Digoxin Day 17	Ratio	Digoxin Day 7	Darifenacin + Digoxin Day 17	Ratio
001	[	]	1.09	[	]	0.69
003			1.08			1.12
018			1.19			1.05

Table 70. Individual PK Parameters of PM Subjects (Placebo + Digoxin Group)

Subject	AUC_{24} (ng*hr/mL)			C_{max} (ng/mL)		
	Digoxin Day 7	Placebo + Digoxin Day 17	Ratio	Digoxin Day 7	Placebo + Digoxin Day 17	Ratio
017	[	]	1.09	[	]	1.11
024			0.90			1.05

- The effects on the PK parameters of digoxin were apparently similar for EM and PM subjects (ie, there was considerable overlap for all the parameters investigated).
- In the darifenacin + digoxin treatment group the ratio of Day 7 to Day 17 for the PMs for AUC_{24} ranged between 1.08 and 1.19 and fell within the range of the ratios calculated for the EM and HEM subjects ([ ]) and for C_{max} ranged between 0.69 and 1.12 for the PMs (overall EM and HEM range: [ ]).
- In the placebo + digoxin treatment group, AUC_{24} ratios for the PMs were 0.90 and 1.09 and fell within the range calculated for the EM and HEM subjects ([ ]) and for C_{max} they were 1.05 and 1.11 which fell within the EM and HEM subjects range of [ ]

E. General Biopharmaceutics

Pfizer production facilities using the proposed commercial process have been utilized (1. Brooklyn, USA, [redacted] 3. Illertissen, Germany). However, only the Brooklyn and [redacted] sites are the proposed manufacturing sites for the USA supply.

What are the differences between clinical formulation and to be marketed formulation? Is to be marketed formulation bioequivalent to clinical trials formulation?

The TBM formulation is bioequivalent to clinical trial formulation (clinical research formulation) at steady state. Throughout the development of the proposed commercial ER formulation the tablet core composition has not been modified, qualitatively or quantitatively. Some modifications were made to the clinical research tablet to ensure commercial acceptability. [redacted] The core tablet and the matrix release system were not changed (see **Formulations** for more detail).

Three bioequivalence studies at steady state were conducted [redacted] Study 1016 was conducted to evaluate the bioequivalence between the initial formulation developed (early clinical research formulation), the formulation used in the Phase 2/3 clinical studies (clinical research formulation) and the TBM formulation, at a dose of 30 mg. Studies 1023 and 1033 evaluated the bioequivalence of the 7.5 and 15 mg formulations, respectively. Study 1023 failed to demonstrate the bioequivalence between the proposed commercial 15 mg ER tablet and the clinical research formulation. Using the same lots of drug product, Study 1033 subsequently demonstrated the bioequivalence of the two 15 mg ER formulations. This study included a greater number of subjects to provide a more precise estimate of any difference between the two formulations.

In the absence of an established IVIVC model, two additional bioequivalence studies were conducted to confirm the bioequivalence of batches of the proposed commercial 7.5 mg (Study 1040) and 15 mg (Study 1045) ER tablets produced at the Brooklyn [redacted] sites.

1. Bioequivalence

Study 1023: Bioequivalence Study of Darifenacin ER 7.5 mg and 15 mg at Steady State (TBM vs. Clinical Research Formulations)

An open, randomized, two-way crossover, two cohort study was conducted in healthy male subjects aged 20 to 40 years to compare the steady state PK of darifenacin following multiple oral doses of the 7.5 mg and 15 mg TBM tablets and the 7.5 mg and 15 mg clinical research tablets in the fasted state. In addition, the debrisoquine metabolic phenotype pre-darifenacin dosing and at steady state for both 7.5 mg and 15 mg doses were compared. Darifenacin was administered once daily for 6 days in Period 1 and for 7 days in Period 2 with a minimum of 7 days washout between the treatment periods. Subjects were administered debrisoquine 10 mg tablet orally once at Week -1 prior to Period 1 and on Day 7 of Period 2 after voiding their bladders. In each study period, a pre-dose blood sample was taken on Days 1 to 6 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours post-dose on Day 6. The total volume of urine excreted in the 8 hour post debrisoquine dosing was collected at Week -1 and on Day 7 of Period 2. Darifenacin log-transformed AUC_{24}, C_{max} and untransformed T_{max} were analyzed using ANOVA. There were 14 HEM, 20 EM, 2

UEM (one in each cohort) and 2 PM subjects (one in each cohort). The mean MR of debrisoquine to 4-hydroxydebrisoquine data were summarized for EM subjects only. No formal analysis was done in 2 PM subjects.

Table 71. The Comparisons of Darifenacin Pharmacokinetic Parameters in EM/PM Subjects

Parameter (units)	Adjusted Means		Ratio/Difference	90% Confidence Interval
	Commercial Tablet	Clinical Research Tablet		
Darifenacin 7.5mg (N=20)				
AUC_{24} (ng.h/ml)	29.7	30.7	96.7%	88.2, 106
C_{max} (ng/ml)	1.94	2.08	93.6%	84.6, 104
T_{max} (h)	8.1	7.3	0.8	-1.2, 2.7
Darifenacin 15mg (N=18)				
AUC_{24} (ng.h/ml)	63.2	74.9	84.4%	75.8, 94.0
C_{max} (ng/ml)	4.14	4.91	84.3%	72.7, 97.9
T_{max} (h)	6.9	6.3	0.6	-0.6, 1.7

The means presented are geometric for AUC_{24} and C_{max} and arithmetic for T_{max}
The ratios, expressed as percentages, are presented for AUC_{24} and C_{max} and the differences for T_{max}

- For darifenacin 7.5 mg, the ratios and 90% CIs for AUC_{24} and C_{max} were within the 80-125% limits. The 7.5 mg TBM and clinical research tablets were considered to be bioequivalent at steady state.
- For darifenacin 15 mg, the lower 90% CIs for both AUC_{24} and C_{max} were outside of the lower limit of the bioequivalence range and therefore, the two formulations failed to show the bioequivalence.
- For both darifenacin 7.5 mg and 15 mg, there was no difference in T_{max} between the formulations.

Figure 27. Mean Plasma Concentrations of Darifenacin at Steady State on Day 6

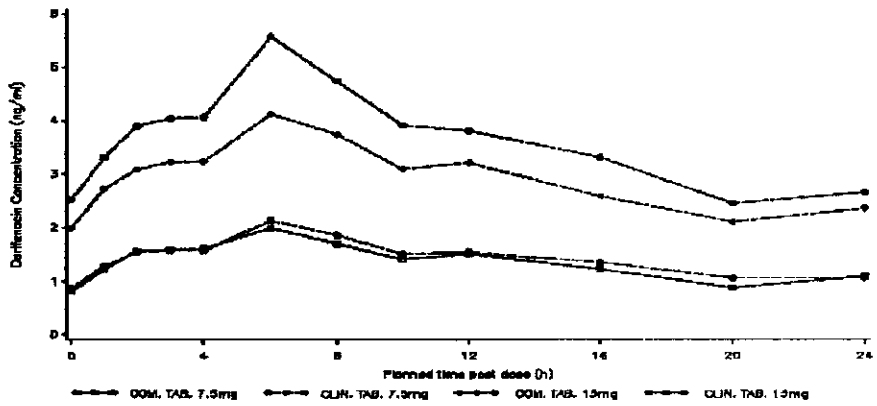
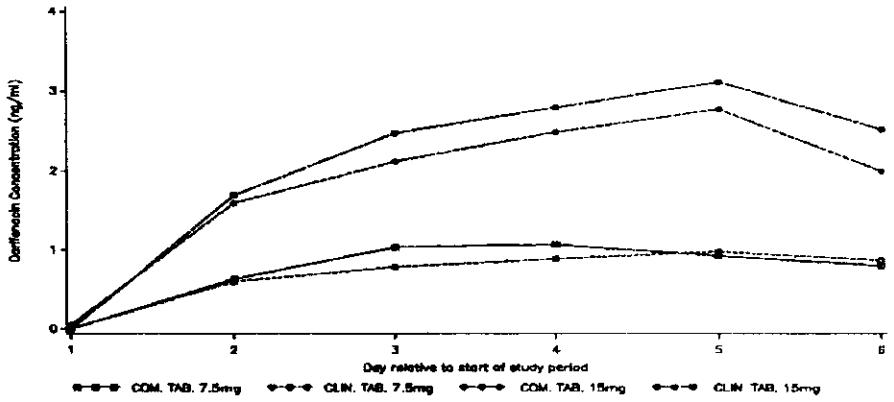


Figure 28. Mean Trough Plasma Concentrations of Darifenacin



Study A1371033: Bioequivalence Study of Darifenacin 15 mg at Steady State (TBM vs. Clinical Research Formulations)

An open, randomized, two-way crossover study was conducted in healthy male subjects aged 19 to 44 years to compare the steady state pharmacokinetics of darifenacin following multiple oral doses of the 15 mg TBM tablet and the 15 mg clinical research tablet in the fasted state. Darifenacin was administered once daily for 6 days in each period with a minimum of 7 days washout between the treatment periods. In each study period, a pre-dose blood sample was obtained on Days 1 to 6 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours post-dose on Day 6. Darifenacin log-transformed AUC_{24}, C_{max} and untransformed T_{max} were analyzed using ANOVA. There were 16 EM, 15 HEM, 5 PM and 1 UEM subjects.

Table 72. The Darifenacin Pharmacokinetic Parameters at Steady State on Day 6

Parameter	Adjusted Means		Ratio, Difference	90% Confidence Interval
	Commercial Tablet	Clinical Research Tablet		
AUC_{24} (ng.h/ml)	85.0	85.0	100%	(91.4%,110%)
C_{max} (ng/ml)	5.76	5.58	103%	(91.1%,117%)
T_{max} (h)	6.0	7.5	-1.54	(-3.15, 0.07)

The means presented are geometric for AUC_{24} and C_{max} and arithmetic for T_{max}. The ratios expressed as percentages are presented for AUC_{24} and C_{max} and the differences for T_{max}.

- The ratios and 90% CIs for AUC_{24} and C_{max} were within the 80-125% limits. The 15 mg TBM and clinical research tablets were considered to be bioequivalent at steady state.

Figure 29. Mean Plasma Concentrations of Darifenacin 15 mg at Steady State on Day 6

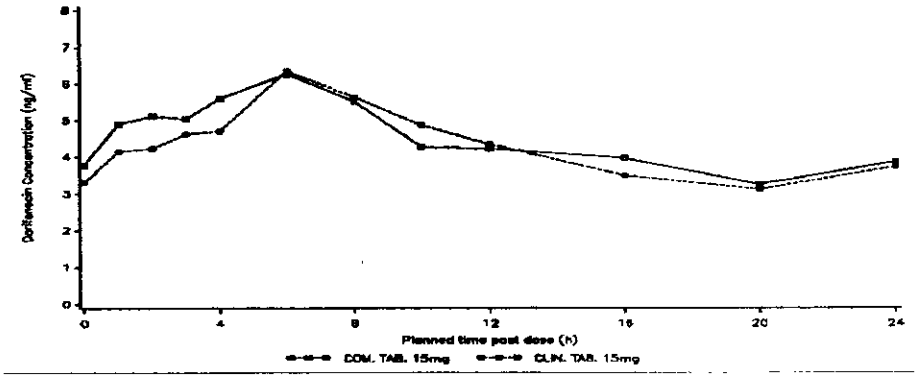
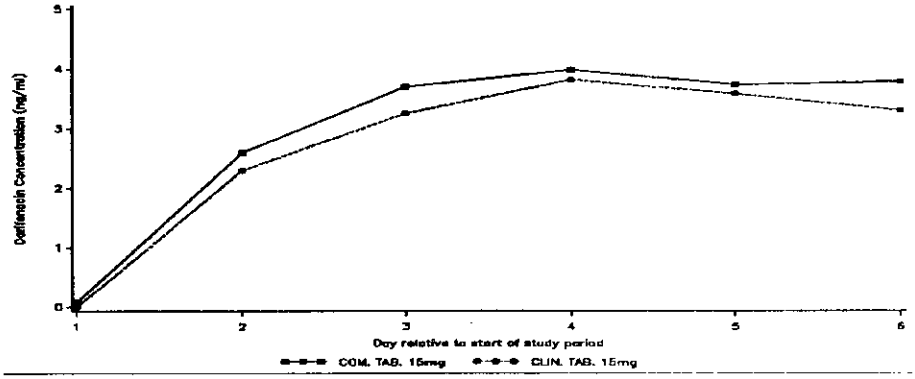


Figure 30. Mean Trough Plasma Concentrations of Darifenacin



Study A1371016: Bioequivalence Study of Darifenacin 30 mg at Steady State (TBM vs. Early Clinical Research vs. Clinical Research Formulations)

An open, randomized, multiple oral dose, three way crossover study was conducted in white healthy male subjects aged between 19 to 40 years to determine the bioequivalence of darifenacin at the steady state following multiple oral doses of the TBM tablet, the clinical research tablet, and the early clinical research tablet in the fasted state. Subjects received darifenacin 30 mg once daily for 6 days with a minimum of 7 days washout between the treatment periods. In each study period, a pre-dose blood sample was taken on Days 1 to 6 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours post-dose on Day 6. Darifenacin log-transformed AUC_{24}, C_{max} and untransformed T_{max} were analyzed using ANOVA. The comparisons were made between TBM tablet vs. clinical research tablet, clinical research tablet vs. early clinical research tablet, and TBM tablet vs. clinical research tablet.

Table 73. The Darifenacin Pharmacokinetic Results at Steady State on Day 6

Parameter (units)	Commercial Tablet 30mg N=21	Clinical Research Tablet 30mg N=20	Early Clinical Research Tablet 30mg N=21
AUC_{24} (ng.h/ml)	201	199	191
C_{max} (ng/ml)	13.0	12.5	12.4
T_{max} (h)	8.3	9.3	9.7
C_{min} (ng/ml)	4.33	6.54	5.41
C_{av} (ng/ml)	8.39	8.29	7.97
PTF (scalar)	0.85	0.63	0.78

The means presented are geometric for AUC_{24}, C_{max}, C_{min}, C_{av} and PTF and arithmetic for T_{max}

Table 74. The Results of the Comparisons between Formulations at Steady State on Day 6

Parameter (units)	Comparison	Ratio/Difference Between Adjusted Means	90% Confidence Interval
AUC_{24} (ng.h/ml)	Comm. tab *vs.* clin. res. tab.	100.1%	(88.3%, 113.5%)
	Clin. res. tab. *vs* early clin. res. tab.	105.0%	(92.6%, 119.1%)
	Comm. tab *vs.* early clin. res. tab.	105.1%	(93.0%, 118.9%)
C_{max} (ng/ml)	Comm. tab *vs.* clin. res. tab.	103.4%	(89.6%, 119.2%)
	Clin. res. tab. *vs* early clin. res. tab.	101.4%	(87.9%, 117.0%)
	Comm. tab *vs.* early clin. res. tab.	104.9%	(91.2%, 120.6%)
T_{max} (h)	Comm. tab *vs.* clin. res. tab.	-0.8	(-4.1, 2.6)
	Clin. res. tab. *vs* early clin. res. tab.	-0.6	(-3.9, 2.8)
	Comm. tab *vs.* early clin. res. tab.	-1.3	(-4.6, 1.9)

Key: comm=commercial; tab=tablet; *vs.*=*versus*; clin=clinical; res=research
The ratios, expressed as percentages, are presented for AUC_{24} and C_{max} and the differences for T_{max}

- For darifenacin AUC_{24} and C_{max} the 90% CI for all comparisons between formulations were within the range 80 % to 125%. All three formulations were considered bioequivalent to each other.

Study A1371040: Bioequivalence Study of Darifenacin 7.5 mg at Steady State (TBM formulations, manufactured at the Brooklyn and [redacted] sites)

An open, randomized, multiple dose, two-way crossover study was conducted in 26 healthy white male subjects aged 18 to 41 years to compare the steady state pharmacokinetics of darifenacin following multiple oral doses of the 7.5 mg commercial tablets manufactured at the Brooklyn and [redacted] sites in the fasted state. Darifenacin was administered once daily for 6 days with a minimum of 7 days washout between the treatment periods. In each study period, a pre-dose blood sample was taken on Days 1 to 6 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours post-dose on Day 6. Darifenacin log-transformed AUC_{24}, C_{max} and untransformed T_{max} were analyzed using ANOVA. There were 11 EM, 13 HEM and 2 PM subjects.

Table 75. The Comparisons of Darifenacin Pharmacokinetics between Formulations

Parameter (units)	Adjusted Means		Ratio/Difference Between Adjusted Means	90% Confidence Interval
	[redacted] Tablet 7.5mg N=26	Brooklyn Tablet 7.5mg N=25		
AUC_{24} (ng.h/ml)	27.5	25.7	107%	97.0%, 118%
C_{max} (ng/ml)	1.89	1.82	104%	92.8%, 116%
T_{max} (h)	6.0	6.8	-0.8	-1.7, 0.1

The ratios, expressed as percentages, are presented for AUC_{24} and C_{max} and the differences for T_{max}.

- The 7.5 mg darifenacin tablets manufactured at the [redacted] site were considered to be bioequivalent to the Brooklyn produced tablets.

Figure 31. Mean Plasma Concentrations of Darifenacin at Steady State on Day 6

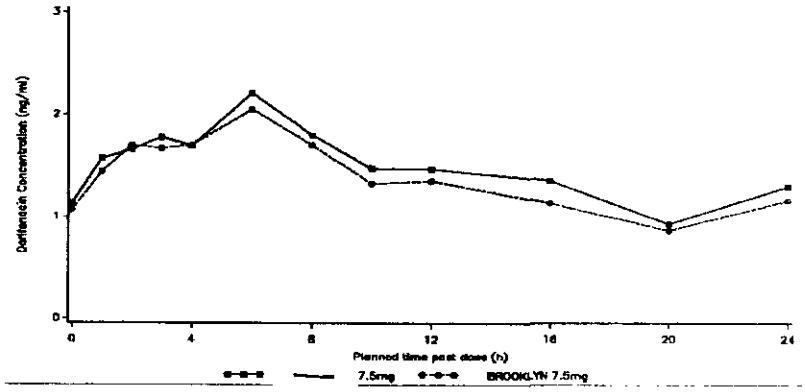
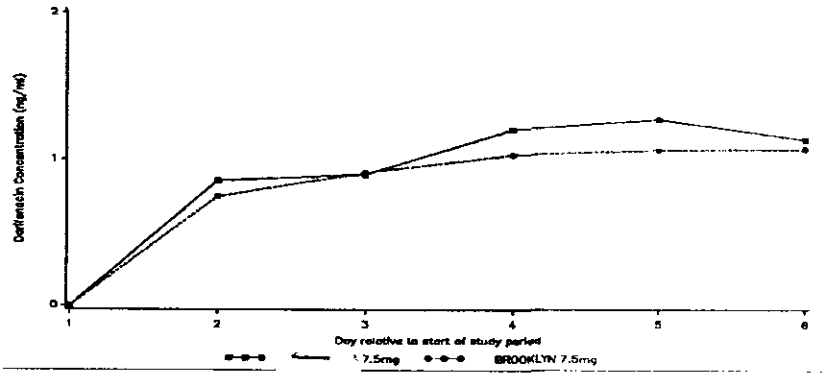


Figure 32. Mean Trough Plasma Concentrations of Darifenacin



Study A1371045: Bioequivalence Study of Darifenacin 15 mg at Steady State (TBM formulations, manufactured at the Brooklyn [redacted] sites)

An open, randomized, multiple dose, two-way crossover study was conducted in 26 healthy male subjects aged 19 to 43 years to compare the steady state PK of darifenacin following multiple oral doses of the 15 mg TBM tablets manufactured at the Brooklyn [redacted] sites in the fasted state. In addition, the effect of darifenacin on the debrisoquine MR and the duration of CYP2D6 inhibition after the discontinuation of darifenacin were investigated by comparing the debrisoquine metabolic phenotype pre-darifenacin dosing and at steady state for 15 mg darifenacin dose and at 1, 3, 5, and 7 days after the final dose of darifenacin. Darifenacin was administered once daily for 6 days in Period 1 and for 7 days in Period 2 with a minimum of 7 days washout between the treatment periods. Subjects were administered with debrisoquine 10 mg tablet orally once at Week -1 prior to Period 1 and on Days 7 (co-administered with darifenacin 15 mg), 8, 10, 12, and 14 of Period 2 after voiding their bladders. In each study period, a pre-dose blood sample was taken on Days 1 to 6 and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours post-dose on Day 6. The total volume of urine excreted in the 8 hours post-debrisoquine dosing was collected at Week-1, and in Period 2 only on Days 7, 8, 10, 12, and 14. Darifenacin log-transformed AUC_{24}, C_{max} and untransformed T_{max} were analyzed using ANOVA. There were 11 EM, 11 HEM and 4 PM subjects. The phenotyping data were analyzed for EM subjects only but no formal statistical analyses were done.

Table 76. The Results of the Statistical Analysis of the Darifenacin Pharmacokinetics

Parameter	Comparison	Adjusted means[a]	Ratio/ difference between geometric means[b,c]	90% CI
AUC_{24} (ng.h/ml)	/ Brooklyn	70.4 / 72.1	97.7%	(87.6%, 109%)
C_{max} (ng/ml)	/ Brooklyn	4.97 / 4.55	109%	(97.9%, 122%)
T_{max} (h)	– Brooklyn	7.7 – 6.8	0.8	(-1.0, 2.6)

[a] means are geometric (AUC_{24} and C_{max}) and arithmetic (T_{max}); [b] the ratios (expressed as percentages) and corresponding confidence intervals (CI), are back-transformed from the log scale for AUC_{24} and C_{max}; [c] difference between means (T_{max})

- The 15 mg darifenacin tablets manufactured at [redacted] were considered to be bioequivalent to the 15 mg darifenacin tablets manufactured at Brooklyn.

Figure 33. Mean Plasma Concentrations of Darifenacin at Steady State on Day 6

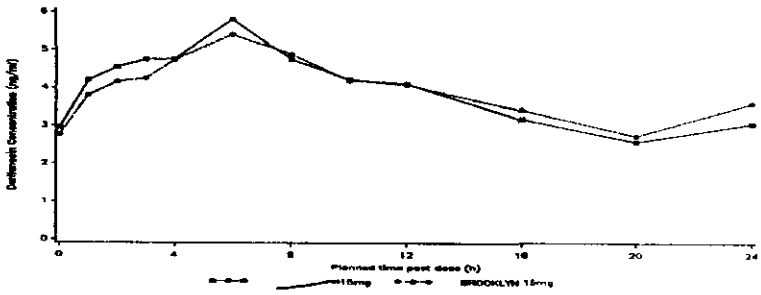
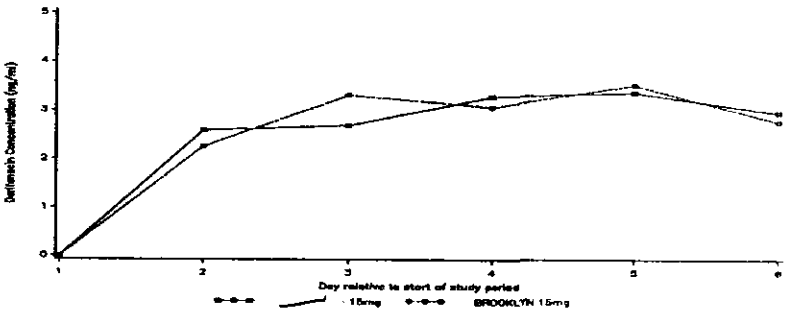


Figure 34. Mean Trough Plasma Concentrations of Darifenacin



2. IVIVC under fasting conditions

The sponsor stated that an IVIVC was investigated but was not achieved due to high predictability error.

To assist in setting the dissolution specification acceptance criteria and to facilitate potential post-approval changes to the formulation or manufacturing site, an IVIVC was investigated but was not achieved. Formulations were prepared with different release rates, using the 30 mg strength tablet. These formulations had release rates which were approximately 10 % different from the proposed commercial formulation. Data from the in-vitro dissolution study with the in-vivo data from the clinical study A1371036 generated a correlation which predicted the in vivo

performance of the formulations in terms of AUC but was not able to predict accurately the C_{max} for a rapidly releasing formulation. A rank-order relationship only was demonstrated.

Study 1036 described the development of a Level A IVIVC model for the 30 mg darifenacin ER formulations and the external validation of this model using the 7.5 mg ER formulation. The modeling incorporated obtaining impulse response parameter estimates from the dosing of darifenacin IR 12 mg tablets. (2 x 6 mg).

Overall, the internal predictability of the models was considered to be inconclusive. Therefore, evaluation of the external predictability of the models was undertaken. Prior to assessing the external predictability of the models, the results from the Study 1036 indicated that the 7.5 mg ER and 30 mg ER formulations had different relative BA at single dose. As the models were developed using the 30 mg ER concentration-time data, some correction of the model parameters were undertaken to predict the 7.5 mg ER formulation data. Therefore, both a_1 and a_2 were corrected by multiplying by the average BA of the 7.5 mg ER formulation relative to the three 30 ER formulations, based on the geometric AUC_{48} values for each formulation.

Both the individual two-stage approach and the mean convolution approach predicted both C_{max} and AUC for the 7.5 mg ER formulations within the limits (PE of 10 % or less) to establish external predictability. While the mean two-state model predicted C_{max} within 10 %, the PE associated with AUC was 11% outside the limits to demonstrate external predictability. The individual convolution-based IVIVC model failed to demonstrate external predictability for the 7.5 mg ER formulation, with a PE of about 17% for C_{max}.

Study 212: PK of Darifenacin after 6 days Oral Administration of Capsule 7.5 mg tid and 3 ER Matrix Tablets (20 mg)

An open, randomized four-way crossover pilot study was conducted in healthy male subjects aged 18 and 45 years to determine the optimum release rate from ER tablets for an once daily dosing regimen. The pharmacokinetics of darifenacin after multiple oral administrations of three ER matrix tablets (20 mg) and an IR capsule (7.5 mg t.i.d.) were compared. During each of the first 3 periods, subjects were dosed for 6 days with 3 ER darifenacin formulations (slow, medium and fast release). During the 4th period, all subjects received IR darifenacin capsules three times daily for 6 days. All four study periods occurred sequentially and continuously with no washout in-between. Plasma concentrations of darifenacin were obtained at intervals up to 24 hours on Day 6 of each period.

Fast release 20 mg darifenacin ER tablet: *in vitro* release of 4 hours
Medium release 20 mg darifenacin ER tablet: *in vitro* release of 8 hours
Slow release 20 mg darifenacin ER tablet: *in vitro* release of 18 hours

Table 77. Pharmacokinetic Results

Pharmacokinetic Results: Raw geometric means (N = 13)

Darifenacin:	Darifenacin CR Fast	Darifenacin CR Medium	Darifenacin CR Slow	Darifenacin IR
AUC_t (ng.h/ml)*	89.1	113	118	102
C_{max} (ng/ml)*	12.3	9.42	7.72	10.4
C_{24} (ng/ml)*	0.50	2.06	4.23	2.13
C_{avg} (ng/ml)*	3.71	4.72	4.93	4.23
C_{max}/C_{24}	24.5	4.57	1.82	4.86
PTFR**	3.16	1.48	0.52	1.85
T_{max} (h)***	3.7	6.7	6.4	1.2
Statistical Comparisons:	*Fast CR/IR*	*Medium CR/IR*	*Slow CR/IR*	
AUC_t*				
Ratio of Geometric Means (%)	88.4	110	117	
90% Confidence Intervals	76.4, 102	94.8, 127	101, 136	
C_{max}*				
Ratio of Geometric Means (%)	119	89.8	74.7	
90% Confidence Intervals	98.0, 146	73.7, 110	61.3, 90.9	
C_{24}*				
Ratio of Geometric Means (%)	24.0	94.3	200	
90% Confidence Intervals	16.8, 34.8	65.1, 137	138, 289	
C_{avg}*				
Ratio of Geometric Means (%)	88.5	110	117	
90% Confidence Intervals	76.3, 103	94.9, 128	101, 136	
C_{max}/C_{24}				
Ratio of Geometric Means (%)	497	95.2	37.4	
90% Confidence Intervals	325, 760	62.2, 146	24.5, 57.0	
PTFR**				
Ratio of Geometric Means (%)	168	81.1	27.9	
90% Confidence Intervals	121, 235	58.0, 113	19.8, 39.3	

*dose normalized to 7.5mg tid; **PTFR = Peak/Trough Fluctuation Ratio; ***arithmetic mean

- Bioavailability of the ER formulations of darifenacin relative to the IR formulation increased as release rate decreased while C_{max} was decreased.
- The slowest release 20 mg darifenacin ER tablet (*in vitro* release of 18 hours) showed the lowest C_{max}/C_{24} and PTFR.

Study 1036: The Effect of Varying In Vitro Dissolution Rates on the Single Dose PK of Darifenacin 30 mg ER Formulations

An open, randomized, five-way crossover study was conducted in healthy white male subjects (10 EM, 8 HEM, 2 PM) aged 18 to 45 years to determine the PK of darifenacin following single oral doses of three 30 mg ER formulations (TBM, fast-releasing and slow-releasing), a 7.5 mg TBM ER formulation, and 12 mg (2 x 6 mg) IR tablets in order to allow a comparison with the *in vitro* dissolution data associated with these formulations. Subjects were administered a single dose of darifenacin in a fasting state and remained fasted for 4 hours post-dose. The release rates for the slow and fast formulation were 80% in 20 and 9 hours, respectively. The treatment periods were separated by a minimum of 3 days or 7 days between doses, whichever was the longest. Plasma concentrations of darifenacin were obtained pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, and 48 hours post-dose.

Treatment groups:

A: Darifenacin 30 mg ER TBM tablet
B: Darifenacin 30 mg ER Fast-Releasing tablet
C: Darifenacin 30 mg ER Slow-Releasing tablet
D: Darifenacin 7.5 mg ER TBM tablet
E: Darifenacin 12 mg (2 x 6 mg) IR tablet

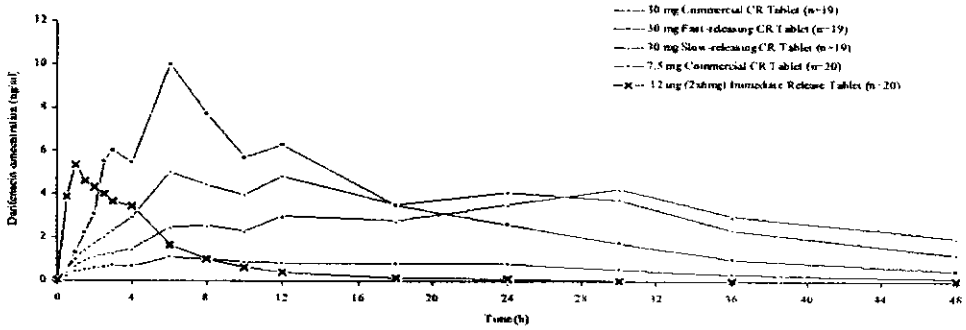
Table 78. The Darifenacin PK Parameters

Parameter (units)	Dari 30mg CR Comm. Tab.	Dari 30mg CR F-R Tab.	Dari 30mg CR S-R Tab.	Dari 7.5mg CR Comm Tab.	Dari 12mg (2 x 6mg) IR Tab.
AUC_{48} (ng.h/ml)	121 (N=19)	124 (N=19)	105 (N=19)	20.9 (N=20)	20.7 (N=20)
AUC (ng.h/ml)	110 (N=8)	130 (N=19)	91.5 (N=8)	28.2 (N=11)	21.1 (N=20)
C_{max} (ng/ml)	4.91 (N=19)	8.95 (N=19)	4.17 (N=19)	1.03 (N=20)	4.91 (N=20)
T_{max} (h)	13.3 (N=19)	6.4 (N=19)	22.8 (N=19)	9.6 (N=20)	1.4 (N=20)
k_{el} (/h)	0.0371 (N=17)	0.0701 (N=19)	0.0443 (N=14)	0.0426 (N=16)	0.2168 (N=20)
$t_{½}$ (h)	18.7 (N=17)	9.9 (N=19)	15.6 (N=14)	16.3 (N=16)	3.2 (N=20)

Means are geometric for AUC_{48}, AUC and C_{max}, arithmetic for T_{max} and $t_{½}$ and harmonic for k_{el}.
Key: Dari=darifenacin; Comm.=commercial; Tab.=tablet; F-R=fast-releasing; S-R=slow-releasing.

- The PK parameters for the ER formulations were the greatest for the fast-releasing formulation and then decreasing with the standard and slow-releasing formulations, respectively.

Figure 35. Mean Darifenacin Concentrations following a Single Oral Dose of Darifenacin



IVIVC

		Internal validation				External validation (%PE)
		%PE for CR tablet 30mg			MAPPE	
		Fast-releasing	Proposed commercial	Slow-releasing		
Mean two stage (deconvolution)	C_{max}	32.8	2.08	9.73	14.9	5.39
	AUC	0.49	4.54	3.00	2.68	11.06
Individual two stage (deconvolution)	C_{max}	28.3	9.05	14.6	17.3	3.22
	AUC	7.42	7.04	13.2	9.23	9.33
Mean one stage (convolution)	C_{max}	33.05	3.19	12.31	16.18	6.18
	AUC	3.09	2.81	3.83	3.25	8.22
Individual one stage (convolution)	C_{max}	35.12	19.52	22.45	25.70	16.72
	AUC	0.93	2.75	1.42	1.70	6.21

Source. Study A1371036 Section 11 Item 9
%PE, percent prediction error. MAPPE, mean absolute percent prediction error

Internal Predictability

- All 4 approaches predicted AUC for the 30 mg ER formulations within the limits to establish internal predictability.
- The two-stage IVIVC model, based on mean concentration-time data, failed to predict with sufficient accuracy C_{max} for the fast ER formulation (%PE=32.8).
- The two-stage model developed using individual deconvolution failed to predict C_{max} for the fast ER formulation (%PE =28.3)
- The IVIVC model determined using the convolution-based approach and mean concentration-time data failed to predict C_{max} for the fast ER formulation.
- The individual convolution-based model failed to predict the C_{max} for any of the three 30 mg ER formulations within the acceptance criteria for internal predictability.

External Predictability

Table 79. External Validation Statistics for the Mean Two-Stage IVIVC Model for the 7.5 mg ER Formulations

Treatment	C_{max} pred.	C_{max} obs.	C_{max} ratio	AUC pred.	AUC obs.	AUC ratio	C_{max} |%PE|	AUC |%PE|
7.5 mg	1.05	1.11	0.95	26.59	29.90	0.89	5.39	11.06

C_{max} units = ng/mL; AUC units = ng.h/mL

- The mean two-stage model, with correction of the a_1 and a_2 parameters for the difference in the BA of the 7.5 and 30mg ER formulations, predicted the C_{max} of the 7.5 mg ER formulation with the limit to establish external predictability. However, the %PE of 11.06% for AUC fell outside the limit to conclude external predictability.

Table 80. External Validation Statistical for the Individual Two-Stage IVIVC Model for the 7.5 mg ER Formulation

Treatment	C_{max} pred.	C_{max} obs.	C_{max} ratio	AUC pred.	AUC obs.	AUC ratio	C_{max} |%PE|	AUC |%PE|
7.5 mg	1.01	1.05	0.97	23.66	21.64	1.09	3.22	9.33

C_{max} units = ng/mL; AUC units = ng.h/mL

- The two-stage IVIVC model based on individual deconvolution satisfied the external predictability for both C_{max} and AUC.

Table 81. External Validation Statistics for the Mean Convolution IVIVC Mode for the 7.5 mg ER Formulation

Treatment	C_{max} pred.	C_{max} obs.	C_{max} ratio	AUC pred.	AUC obs.	AUC ratio	C_{max} |%PE|	AUC |%PE|
7.5 mg	1.05	1.11	0.94	27.44	29.90	0.92	6.18	8.22

C_{max} units = ng/mL; AUC units = ng.h/mL

- The mean convolution-based IVIVC model based on individual deconvolution satisfied the external predictability for both C_{max} and AUC.

Table 82. External Validation Statistics for the Individual Convolution-Based IVIVC Model for the 7.5 mg ER Formulation

Treatment	C_{max} pred.	C_{max} obs.	C_{max} ratio	AUC pred.	AUC obs.	AUC ratio	C_{max} |%PE|	AUC |%PE|
7.5 mg	0.87	1.05	0.83	20.29	21.64	0.94	16.72	6.21

C_{max} units = ng/mL; AUC units = ng.h/mL

- The individual convolution-based model failed to predict the C_{max} of the 7.5 mg ER formulations within the limit to establish external predictability.

3. Effect of Food

Is there any effect of food on the pharmacokinetics of ER formulation? How is it addressed in the label?

Total darifenacin exposure following administration of a single 30 mg ER tablet was not altered by the consumption of food while peak darifenacin exposure was 22% higher and T_{max} was 3.3 hours shorter in the presence of food. Once darifenacin plasma concentrations have reached steady state, ingestion of food had no effect on the pharmacokinetics of darifenacin from ER tablet dosing. Peak steady state darifenacin exposure and total exposure from dosing with 30 mg ER tablets was similar in both fed and fasted states.

The proposed label states that there is no food effect on multiple-dose pharmacokinetics from ER tablets. Therefore, darifenacin ER tablets may be taken with or without food, and should be swallowed whole and not chewed, divided or crushed.

Three food effect studies (Studies 226, 670, JP-95-502) on the pharmacokinetics of darifenacin following administration of ER tablets were reviewed. Two studies evaluated the effect of food following administration of a single ER tablet while Study 226 evaluated the effect of food at steady state. The composition of meals in three food effect studies was as follows:

- Studies 226 and 670: a standard high fat breakfast (a total of 1,000 calories with ~50% of the total calorific content from fat)
- Study JP-95-502: a low fat content (a total of 600 calories with ~15% of the total calorific content from fat)

Study 137-670: The Effect of Food on the Bioavailability of a Single Dose Darifenacin 30 mg

An open, single dose, randomized two-way crossover study was conducted in 24 healthy males (14 EM, 8 HEM, 2 PM) aged between 18 and 39 years to investigate the effect of food on the single dose bioavailability of 30 mg darifenacin. Subjects received oral darifenacin 30 mg once in the fasted or fed state after at least a 10-day washout between doses. Subjects in the fed group were dosed within 5 minutes after consuming a standardized high fat breakfast consisting of 2 slides white toast with butter, 2 eggs fried in butter, 2 slices of bacon, 2 ounces of hash brown potatoes and 8 ounces whole milk. Plasma concentrations of darifenacin were obtained pre-dose, and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, 72, 84 and 96 hours post-dose. Log transformed C_{max} and AUC and untransformed T_{max} were subject to ANOVA.

Table 83. Pharmacokinetic Parameters of Darifenacin after a Single Dose Darifenacin 30 mg

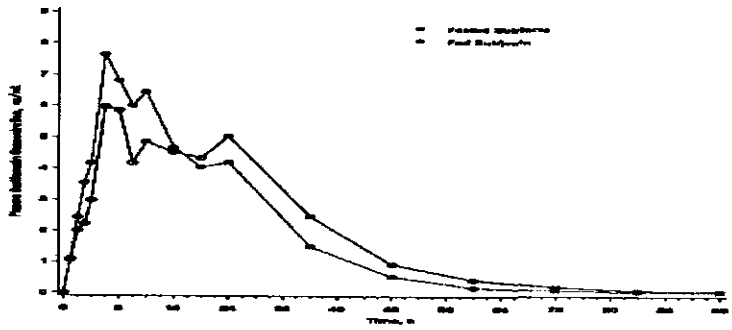
	Unadjusted means		Ratio or difference between adjusted means (90%CI)
	Fasted (N=23)	Fed (N=23)	
AUC (ng.h/ml)	145.4	134.1	0.93 (0.82, 1.05)
AUC_{24} (ng.h/ml)	144.5	133.5	-
C_{max} (ng/ml)	5.87	7.13	1.22 (1.09, 1.37)
T_{max}(h)	11.5	8.1	-3.3 (-6.4, -0.2)
$t_{1/2}$ (h)	7.5	7.2	-

Source: Study 137-670 Tables 5.1 and 5.2

Geometric mean for AUC, AUC_{24} and C_{max}. Arithmetic mean for T_{max} and $t_{1/2}$

- Single dose administration of 30 mg darifenacin with food resulted no change in AUC, a higher C_{max} (↑ 22%) and a shorter T_{max} (↓ 3.3 hrs) compared with administration in the fasted state.
- The CV% of AUC_{96} were 65.9% (fasted) and 73.3% (fed). The CV% of C_{max} were similar (70%) in fasted and fed states.
- There was no apparent change in the systemic clearance of darifenacin.

Figure 36. Mean Plasma Darifenacin Concentrations following a Single Dose Darifenacin 30 mg



Study JP-95-502: The Effect of Food on the Bioavailability of a Single Dose Darifenacin 15 mg (Japanese)

An open label, single dose, randomized two-way crossover study was conducted in 8 healthy Japanese males aged between 25 and 37 years to investigate the effect of food on the single dose bioavailability of 15 mg darifenacin. Subjects received oral darifenacin 15 mg once in the fasted or fed state with a 2-week washout between study periods. Subjects consumed a 600-calorie breakfast and were administered 15 mg darifenacin 30 minutes after (breakfast at 8:00 a.m., study drug at 9:00 a.m.). Subjects were to take a daily calorie intake of approximately 2,800 kcal during the hospitalization. Subjects were then prohibited from eating and drinking until 4 hours after administration. Plasma concentrations of darifenacin were obtained pre-dose, and at 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours post-dose. Urine collection was conducted 0-24, 24-48, and 48-72 hours post-dose, and urinary concentrations of darifenacin and UK-148,993 were measured. Log transformed C_{max} and AUC_{72} and untransformed T_{max} were subject to ANOVA.

Table 84. Pharmacokinetic Parameters of Darifenacin after a Single Dose Darifenacin 15 mg

	Unadjusted means		Ratio or difference between adjusted means (90% CI)
	Fasted (N=8)	Fed (N=8)	
AUC_t (ng.h/ml)	33.5	42.1	1.26 (0.91, 1.75)
C_{max} (ng/ml)	1.76	3.59	2.04 (1.37, 3.04)
T_{max} (h)	9.3	5.5	-3.8 (-7.5, 0.0)
MRT (h)	16.5	15.0	1.0 (0.7, 1.2)

Source: Study JP-95-502 Tables 5.1 and 5.2
Geometric mean for AUC_t, C_{max} and MRT. Arithmetic mean for T_{max}

- The bioavailability of darifenacin in the fed state was increased by 26%. Absorption of darifenacin was shorter in fed subjects but the C_{max} in the fed state were 2-fold higher to those in the fasted state.
- The CV% of AUC_{72} were 64% (fasted) and 37% (fed). The CV% of C_{max} were 79% and 58% in fasted and fed states, respectively.
- In the fasted treatment group, the mean cumulative urinary excretion rates of darifenacin and UK-148,993 with respect to administered dose up to 72 hours post-dose of darifenacin were 0.338% and 1.470%, respectively. In the fed treatment group, the mean cumulative urinary excretion rates of darifenacin and UK-148,993 were 0.381% and 1.881%, respectively.

Figure 37. Mean Plasma Concentrations of Darifenacin following a Single Dose 15 mg

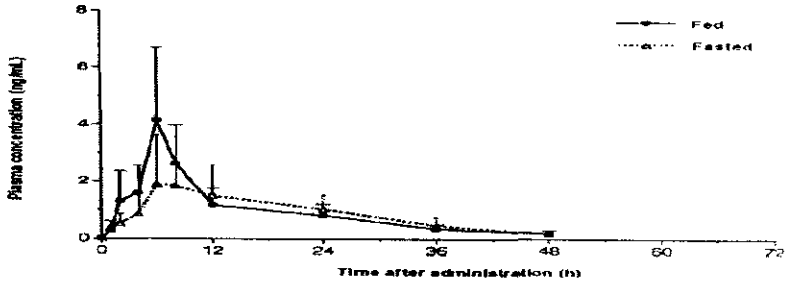


Table 85. Summary of Darifenacin Pharmacokinetic Parameters after a Single Dose of 15 mg Darifenacin

a) Fasted

Subject No.	C_{max} (ng/mL)	AUC_{0t} (ng.h/mL)	MRT_{0t} (h)	T_{max} (h)
1				
2				
3				
4				
5				
6				
7				
8				
Arithmetic Mean	2.14	42.2	17.2	9.3
SD	1.68	26.9	4.6	6.3
C.V.(%)	79	64	27	68
Geometric Mean	1.76	33.5	16.5	NC
Harmonic Mean	NC	NC	NC	7.4
Min.				
Max.				

NC: Not Calculated

b) Fed

Subject No	C_{max} (ng/mL)	AUC_{0t} (ng.h/mL)	MRT_{0t} (h)	T_{max} (h)
1				
2				
3				
4				
5				
6				
7				
8				
Arithmetic Mean	4.25	45.6	15.1	5.6
SD	2.46	17.0	2.1	1.4
C.V.(%)	58	37	14	25
Geometric Mean	3.59	42.1	15.0	NC
Harmonic Mean	NC	NC	NC	4.8

NC: Not Calculated

Study 137-226: The Effect of Food on the Bioavailability of Darifenacin 30 mg at Steady State

An open, randomized, two-way crossover, multiple dose study was conducted in healthy male subjects aged 18 to 45 years, in both the fed and fasted states to determine the relative bioavailability of oral darifenacin ER tablets at steady state. Subjects received oral darifenacin 30 mg once daily for 10 days in the fasted or fed state. Fed and fasted study periods were separated by at least a 10-day washout period. The high fat breakfast consisted of scrambled eggs (100g), two white bread rolls (100g), butter or margarine (20g) and whole milk (140mL). The approximate fat content of the meal was 53g. Within 5 minutes of completing the meal, darifenacin was administered and the subjects remained fasted for the next 4 hours. Plasma concentrations of darifenacin were obtained from blood collected pre-dose on Days 1, 4, 6, 8, and 10 and at fixed intervals post-dose (1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 hours) on Day 10. The log transformed AUC_{24}, C_{max}, C_{min}, C_{av} and peak:trough fluctuation for darifenacin were subject to ANOVA.

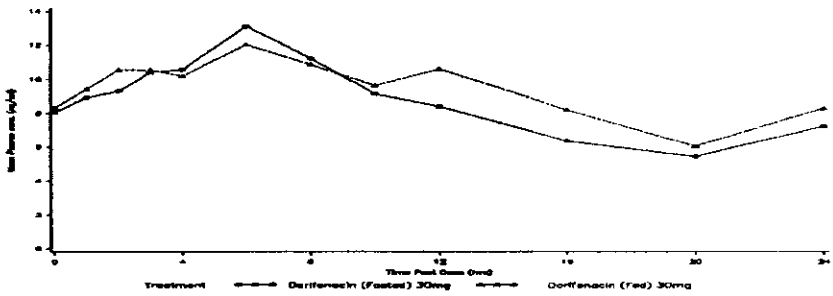
Table 86. The Mean Pharmacokinetic Data for Darifenacin in the Fed and Fasted States (n=24)

	Fasted	Fed	Ratio (%) between means	90% CI
$AUC_{24,ss}$ (ng.h/ml)[a]	180.88	182.90	101.1	92.3, 110.8
$C_{max,ss}$ (ng/ml)[a]	11.84	12.02	101.5	91.5, 112.6
$C_{min,ss}$ (ng/ml)[a]	4.50	4.47	99.2	84.8, 116.1
$C_{av,ss}$ (ng/ml)[a]	7.54	7.62	101.1	92.3, 110.8
Peak:Trough fluctuation[a]	0.94	0.92	98.2	82.5, 116.9
T_{max} (hrs)[b]	5.83	6.63	-	-

[a]Geometric mean, [b]Arithmetic mean

- There was no evidence of a food effect with respect to darifenacin, for any of the measured pharmacokinetic parameters.
- The CV% of AUC_{24} were 57% (fasted) and 66% (fed). The CV% of C_{max} were 65% and 73% in fasted and fed states, respectively.
-

Figure 38. Mean Plasma Concentrations of Darifenacin at Steady State on Day 10



4. In vitro Dissolution

In the absence of an IVIVC, the proposed dissolution specification acceptance criteria have been established following ICH Q6A guidance. The methodology selected utilized basket apparatus (USP apparatus I), rotating at rpm in [redacted] held at 37°C ± 0.5°C. The dissolution profile of darifenacin was determined at 1, 8, and 24 hours using [redacted] Darifenacin hydrobromide tablets are monolithic (non-dispersing) formulations where release rate is dependent on the exposed surface area to the medium. Basket apparatus was selected for agitation due to [redacted]

[redacted] A rotation speed of — rpm was selected in line with general pharmacopoeial practice since no major change in tablet dissolution profile was observed with a range of basket rotation speeds. In terms of dissolution medium, [redacted] was selected in light of solubility and ionic strength considerations. The solubility of darifenacin hydrobromide in [redacted] was — ng/mL.

Table 87. The Sponsor's Proposed In-Vitro Dissolution Acceptance Criteria

Test Time (hours)	Amount Dissolved (Q_i)		
	L_1 (Individuals)	L_2 (Mean)	L_2 (Individuals)
1		10 to 30%	
8		56 to 76%	
24		≥ 85%	

- The sponsor's proposed in-vitro dissolution specification is acceptable.

The specification ranges are based on the release data of batches used in Phase 2/3 clinical trials and stability data [redacted] obtained from tablets manufactured by the proposed commercial process. The release data of [redacted] batches of the 7.5 mg ER tablets and [redacted] batches of the 15 mg ER tablets were submitted. However, only the data from [redacted] batches of the 7.5 mg and 4 batches of the 15 mg were evaluated since the rest of the batches were either film-coated but not

over-coated with a clear film-coat, or they were manufactured from sites other than the proposed sites for the U.S. supplies.

Release Batches	Time Point (hr)	Darifenacin 7.5 mg	Darifenacin 15 mg
	1		
	8		
	24		
Stability Batches			
	1		
	8		
	24		

Dari 7.5 mg			Dissolution Rate		
Batch No	Site of Manufacture	BE Study	Time Point @ 1 hr	Time Point @ 8 hr	Time Point @ 24 hr
EPP 1014	[ ]	1040			
EPP 1015	[ ]	NA			
EPP 1099	[ ]	NA			
N0049	Brooklyn	1023, 1040			
N0051	Brooklyn	NA			
N0057	Brooklyn	NA			

Dari 15 mg			Dissolution Rate		
Batch No	Site of Manufacture	BE Study	Time Point @ 1 hr	Time Point @ 8 hr	Time Point @ 24 hr
EPP 1016	[ ]	1045			
N0053	Brooklyn	NA			
N0055	Brooklyn	1023, 1033, 1045			
N0059	Brooklyn	NA			

The mean release data for batch N0053 (15 mg) did not meet the acceptance criterion at 8 hours. However, the mean data for the core tablets and the registration stability data for this batch were within the acceptance range.

Figure 39. Baskets at — rpm — at . — pm in [ ] for Darifenacin Hydrobromide 7.5 mg MR Tablets.

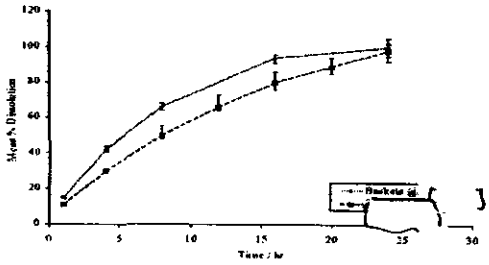
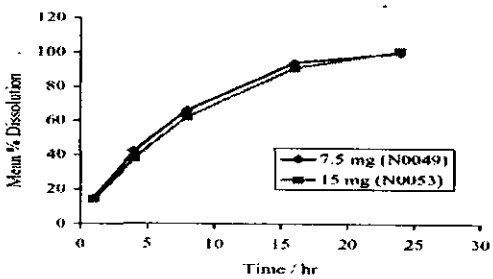


Figure 40. Dissolution Profiles for Darifenacin Hydrobromide MR Tablets, in [ ]



F. Analytical Methods

The method for analyzing darifenacin and UK-148,993 in plasma utilized [redacted] for sample preparation with separation and detection of the analytes and internal standards by [ ] The analytical procedure employed [ ] The overall method precision values for the analysis of plasma QC samples (CV's) were [ ] for darifenacin at target concentrations of 0.15, 3, 7, and 20 ng/mL (1:5 dilution), respectively and [ ] for UK-148,993 at target concentrations of 0.3, 6, 14, and 40 ng/mL, respectively. The mean accuracy for the assay at all concentrations ranged from 9.5 to 12.0 % for darifenacin and -11.3 to 9.0 % for UK-148,993. The lower limit of quantification for darifenacin and UK-148,993 concentrations in plasma was [redacted] ng/mL and [redacted] ng/mL, respectively. The upper limits of the calibration were [redacted] ng/mL and [redacted] ng/mL for darifenacin and UK-148,993, respectively.

IV. Appendix

A. Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-513**	**Brand Name**	**Enablex**
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Darifenacin Hydrobromide**
Medical Division	**DRUDP**	**Drug Class**	**M_3-selective muscarinic receptor antagonist**
OCPB Reviewer	**Myong-Jin Kim**	**Indication(s)**	**Treatment of Overactive Bladder**
OCPB Team Leader	**Ameeta Parekh**	**Dosage Form**	**Extended Release Tablet**
		Dosing Regimen	**7.5 mg/15 mg QD**
Date of Submission	**03-DEC-2002**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review		**Sponsor**	**Novartis Pharmaceuticals Corporation**
PDUFA Due Date		**Priority Classification**	**1S**
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X			
Blood/plasma ratio:	X	1		
Plasma protein binding:	X	5		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	9		
multiple dose:	X	7		
Patients-				
single dose:	X			
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	7		
In-vivo effects of primary drug:	X	7		
In-vitro:	X	5		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X	2		
renal impairment:	X	1		
hepatic impairment:	X	1		
PD:				
Phase 2:	X			
Phase 3:	X	4		
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	8		

Phase 3 clinical trial:	X	1		
Population Analyses -				
Data rich:				
Data sparse:	X	4		
II. Biopharmaceutics				
Absolute bioavailability:	X	2		
Relative bioavailability -				
solution as reference:	X	1		
alternate formulation as reference:	X	3		
Bioequivalence studies -				
traditional design; single / multi dose:	X	9		
replicate design; single / multi dose:	X			
Food-drug interaction studies:	X	7		
Dissolution:	X			
(IVIVC):	X	2		
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	X			
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		87		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**What are basic PK (ADME) characteristics of darifenacin?** **How does PK of ER formulation compare with IR formulation?** **What is the basis for dose-selection?** **How is exposure-response (efficacy and safety) relationship characterized?** **Is there a PK/PD relationship for efficacy and safety parameters?** **Is PK altered by various intrinsic and extrinsic factors?** **Is dose adjustment needed in special populations, based on CYP2D6 genotype or with concomitant medications, particularly in the presence of CYP3A4 or CYP2D6 inhibitors?** **Is to-be-marketed formulation bioequivalent to clinical trials formulation?**	
Other comments or information not included above	**The to-be-marketed and clinical trial formulations are linked via multiple-dose BE studies. This will be a review issue.** **At the Pre-NDA meeting on June 8, 2002, the following requests were made by the Clinical Pharmacology and Biopharmaceutics to submit the following information with the original NDA:** • **The solubility and permeability data of darifenacin hydrobromide.** • **The CYP2D6 genotype/PK/PD assessment to address the exposure response in terms of safety and efficacy; these data could be submitted to the Clinical Pharmacology section in ASCII or SAS format.** **Please submit these data for review. If these data have been already submitted with the original NDA, please provide the location of these data in the NDA submission.**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-513, HFD-850 (L. Lesko, S. Huang), HFD-580 (Z. Li, M. Hirsch), HFD-870 (A. Parekh, H. Malinowski, J. Hunt), CDR (B. Murphy)

CPB Briefing attendees on 09/29/03: S.Al-Habet, D.J.Chatterjee, M.Hirsch, S-M.Huang, V.Jarugula, L. Kenna, J.Lau, J.Lazor, P.Lee, L.Lesko, Z.Li, H.Malinowski, S.Nallani, A. Orencia, S.Oritz, A.Parekh, C. Sahajwalla.

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-513
Compound: Darifenacin Hydrobromide
Sponsor: Pfizer Global Research & Development

Date: 17-JAN-2003
Reviewer: Myong-Jin Kim

Background:

Darifenacin hydrobromide is an M3-selective muscarinic receptor antagonist which has been developed for the long-term treatment of overactive bladder. The sponsor is seeking approval of an extended release (ER) once a day matrix tablet formulation of 7.5 mg and 15 mg dosage strengths.

Formulations:
Seven (7) ER tablet formulations were used during the course of the darifenacin clinical program (4 h release, 8 h release, fast-releasing, slow-releasing, early clinical research, clinical research, and to-be-marketed). However, only data from the early clinical research, clinical research and to-be-marketed tablets are used to support the claims made in the proposed labeling. [

] To link these formulations of darifenacin, BE studies of steady state exposure have been conducted between the to-be-marketed and clinical research formulations at 7.5 mg, 15 mg, and 30 mg tablet strengths, and between the to-be-marketed and early clinical research formulations at 30 mg tablet strength. In addition, 2 BE studies were conducted to compare to-be-marketed tablet batches made at different manufacturing sites. A multiple-dose study design was used in these BE studies at steady state. It should be noted that the sponsor is seeking approval of 7.5 mg and 15 mg dosage strength.

Darifenacin is proposed to be a substrate of CYP3A4, CYP2D6 and P-gp. Thirteen studies are submitted to address DDI. CYP2D6 genotype and phenotype (debrisoquine 5mg or 10 mg) were determined for most subjects in the clinical program.

Three studies (2 studies with a single-dose, 1 study under steady state conditions) were conducted to examine the effect of food on the PK of darifenacin following administration of ER tablets.
Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical

Evaluation II find that the Human Pharmacokinetics and Bioavailability section for NDA 21-513 is fileable.

/S/

Myong-Jin Kim, Pharm.D. Date

/S/

Ameeta Parekh, Ph.D., Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Myong-Jin Kim
10/2/03 11:36:46 AM
PHARMACOLOGIST

Ameeta Parekh
10/2/03 02:28:22 PM
BIOPHARMACEUTICS
Labeling has not been worked on at this time.

NDA 21-513 Enablex Extended Release Tablets
Darifenacin hydrobromide, 7.5 and 15 mg

Controlled Substance Staff Review

Not applicable to this application.

/S/

9/31-3