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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-513

Medical Review(s)

NDA 21-513 ENABLEX® (DARIFENACIN)
MEDICAL OFFICER'S REVIEW

Application Information

NDA #	21-513
Sponsor	Novartis Pharmaceuticals Corporation
NDA PDUFA Goal Date	December 23rd, 2004
Review Status	Response to Approvable Action

Drug Name

Generic	Darifenacin
Proposed Trade Name	Enablex®

Drug Category

Chemical Classification	New Molecular Entity (NME)
Pharmacological Class	Muscarinic receptor antagonist
Proposed Indication	Treatment of Overactive Bladder
Proposed Dose Regimen	7.5 mg and 15 mg Tablets
Route	Oral

Reviewer Information

Clinical Reviewer	Suresh Kaul, MD, MPH
Medical Team Leader	Mark S. Hirsch, MD

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Executive Summary

I. Recommendations

In the opinion of this reviewer, from a clinical perspective, Enablex 7.5mg and 15mg tablets taken once daily **should be approved** for the indication of **treatment of overactive bladder (OAB) symptoms** in men and women of 18 years of age or older.

The evidence presented in this Response has adequately addressed the deficiencies outlined in the approvable action of October, 2003. The adverse events profile of Enablex appears similar to other approved anticholinergic drugs in its class. The safety exposure meets the ICH guidance for the number of subjects exposed to darifenacin and duration of exposure. The clinical, clinical pharmacology and biometrics review of study **DAR 328A2302** ("Thorough QT Study") showed no evidence of an effect on cardiac repolarization or conduction. The review of each bone fracture case provided no evidence of a linkage to Enablex, with virtually all cases demonstrating evidence for other etiologies.

II. Summary of Clinical Findings

A. Brief Overview

Darifenacin

Darifenacin (Enablex) is a muscarinic receptor antagonist developed for the treatment of overactive bladder (OAB). It has greater affinity for the M3 receptor than for M1, M2, M4 or M5. The proposed starting dose is 7.5-mg oral once daily and may be increased to 15-mg daily based upon individual response. Enablex should be taken once daily and may be taken without regard to food intake. Darifenacin is completely absorbed from the GI tract, and undergoes extensive first-pass metabolism. Bioavailability of darifenacin from 7.5 mg and 15 mg tablets is 15.4% and 18.6%, respectively at a steady state. Darifenacin is 98% bound to plasma proteins. It is extensively distributed into body tissues. It shows high systemic clearance via CYP3A4 and CYP2D6 pathways. In three, fixed-dose, pivotal, Phase 3 trials, darifenacin demonstrated a consistent dose-dependent increase in the volume of urine passed per void, and a decrease in daily micturitions and weekly incontinence episodes. This was demonstrated clearly in clinical studies A1371002, A1371007 and A1371015.

Regulatory History

NDA 21-513 received an approvable action on October 2, 2003. The Division requested that sponsor conduct a thorough QT study including both positive and placebo controls and including doses that would generate plasma concentrations comparable to those attained in a CYP 2D6 poor metabolizer taking ketoconazole (a potent inhibitor of CYP 3A4). The Division wanted to determine the independent effect of Enablex on cardiac

repolarization. The Division also requested changes to the label to highlight specific potential risks (urinary retention and constipation), and an updated database of product safety. Finally, the Division asked sponsor to clarify the potential association of darifenacin to cases of bone fracture noted in open-label trials in the original NDA, and if still appropriate following this review, to propose a Phase 4 study to address the issue.

Current Submission

In this Response, the sponsor submitted a study report for a **"Thorough QT-study"** (see medical officer's review in Appendix-A). In addition, sponsor submitted an update on safety for all patients in the darifenacin clinical program, a cardiovascular safety update, and an update on safety from the Open-Label Safety study report for 716 patients (see medical officer's review of all safety updates in Appendix–B). Finally, sponsor provided a careful analysis of each case of bone fracture and an overall discussion of the matter.

From the data submitted in the study report for **DAR328A2302 ("Thorough QT-study"),** the sponsor concluded that there was no evidence to associate darifenacin with any statistical or clinically relevant increase in the QT interval. There is clear evidence that therapeutic and supra-therapeutic doses of darifenacin (15mg and 75mg) resulted in no significant effect on cardiac repolarization (QT/QTc) or on cardiac conduction. The assay sensitivity of the study was demonstrated by an effect seen in the positive control group (moxifloxacin 400mg). Increased darifenacin exposure in poor CYP2D6 metabolizers was not associated with an increase in the risk of QT prolongation, nor was there a relationship between darifenacin plasma concentrations and change in QTc.

The safety update submitted by the sponsor provides overall safety information and also specifically addresses three adverse events (i.e. **constipation, urinary retention and bone fractures**) as pointed out in the action letter of October, 2003. The occurrence of both constipation and urinary retention was similar to that reported for other anticholinergic drugs in its class. Among 7,258 patients treated with darifenacin across the entire darifenacin clinical program, 18 cases of bone fracture were reported, representing an overall incidence of 0.2%. Most of these were reported in open-label, uncontrolled extension studies. No clear risk of fractures/accidental injuries related to treatment with darifenacin could be found. A complete review of all adverse events of fracture and accidental fall/injury revealed reasonable alternative etiologies for each case.

B. Safety

Safety data is drawn from a total of 7,368 subjects enrolled in three pivotal, fixed-dose studies, a dose-titration study, multiple clinical pharmacology studies, an open label extension study, and the thorough QT-study. The safety data for the three pivotal fixed-dose studies and dose-titration study was reviewed previously in the original NDA. Nevertheless, the clinical reviewers conducted another updated and careful review of safety during this review cycle. Overall, the evaluation of safety based upon the extensive database is acceptable.

Thorough QT Study

In the most recent submission of data from a QT study (**Study DAR328A2302**), a total of 179 healthy subjects received either darifenacin 15mg once daily (the maximum recommended dose), darifenacin 75mg once daily, moxifloxacin 400mg, or placebo for 6 days. The review of the clinical and clinical pharmacology data from this study revealed that darifenacin was not associated with any clinically or statistically significant QT/QTc prolongation nor with any cardiac conduction abnormalities.

At the time of maximum plasma darifenacin concentration (Tmax) on Day 6, there was no evidence of an effect of darifenacin on the uncorrected or corrected QT interval. For darifenacin **15mg**, the mean placebo-subtracted, change-from-(time-averaged) baseline to Tmax on Day 6 in uncorrected QT and QTcF was - 4.9 msec and -0.4 msec, respectively. For darifenacin **75mg**, the mean placebo-subtracted, change-from-baseline to Tmax in uncorrected QT and QTcF was -8.2 msec and -2.2 msec, respectively. The positive control demonstrated a clear increase from baseline to Tmax in QTcF of +11.6 msec, even after subtracting the placebo response. Therefore, assay sensitivity was demonstrated in the study, with no QT prolonging effect of darifenacin.

The sponsor did an additional analysis comparing the mean QT/QTc over the entire 24-hour collection period on Day 6 compared to the time-averaged baseline. Again, there was no evidence of QT or QTc prolongation with darifenacin treatment. For this analysis, after subtracting for placebo, the mean changes in QTcF from time-averaged baselines were –1.6 msec (90%CI: -4.2, 1.0) and –1.2 msec (90%CI: -4.6, 2.2) for 15 mg and 75 mg doses of darifenacin, respectively, and 6.9 msec (90%CI: 3.7, 10.1) for moxifloxacin 400mg.

In terms of categorical outlier analyses, none of the subjects in this study exhibited QTcF > 450 msec at the darifenacin therapeutic dose (15mg) or after placebo. However, there were two subjects, one in supra-therapeutic (75mg) darifenacin dose group and the other in the moxifloxacin group who had a single QT value >450 msec. Both these subjects were noted to have higher QT intervals at baseline. Overall, treatment with therapeutic and supra-therapeutic doses of darifenacin did not result in a greater frequency of individuals with absolute QTcF or with pre-determined changes-from-baseline (> 30 msec, > 60 msec) in QTcF when compared to placebo.

In view of these findings, this reviewer finds no realistic risk of QT prolongation or cardiac conduction abnormality associated with the use of darifenacin 7.5mg or 15mg once daily in patients with OAB.

Safety Update

The updated safety data is consistent with the data from the original NDA and reveals that the reported adverse events for darifenacin are consistent with known side effects of other approved anticholinergic drugs. No significant or unusual cardiovascular, hepatic, hematologic or renal toxicities were identified.

Important safety-related findings include:

- Dry mouth, constipation, dyspepsia, abdominal pain, nausea, headache, and urinary tract infection were the most frequently reported clinical adverse events in the pivotal studies and also in the long-term open label study. These events were generally reported as mild to moderate in severity with an onset within the first two weeks of treatment.

- The incidence of serious adverse events was similar between darifenacin and placebo. There have been a total of four deaths in the darifenacin clinical program to date. Three deaths were reported in darifenacin-treated patients (adenocarcinoma, suicide, and hepatic failure) and one was a placebo-treated patient. None of these were judged by the investigator as related to treatment. The safety update provided in the Response contained only one additional death from the long-term, open label safety study **DAR328A2301/1042.** This patient was diagnosed with widespread metastatic malignant melanoma while enrolled in the trial and this event was also judged unrelated to study medication.

- There was no evidence of an increased risk of cardiovascular conditions, including abnormalities of heart rate or heart rhythm. The effect of darifenacin on heart rate was very small, even at 5 times the maximum recommended dose. In the entire program, there were few discontinuations due to a cardiovascular adverse events, even in those patients with co-morbid cardiovascular conditions and in those patients taking concomitant cardiovascular medications.

- A total of 18 bone fracture adverse events were reported among 7,258 darifenacin-treated patients throughout darifenacin clinical program, representing an overall frequency of 0.2%. Most were derived from open-label, uncontrolled trials. None of the 18 cases were judged by the investigator to be related to treatment with darifenacin. Instead, each case was attributed to another clear etiology, including: falls related to advanced age, slippery surfaces, excessive consumption of alcohol, wheelchair accidents, or passengers in automobiles involved in an accident, among other incidents. In no case was dizziness, sleepiness, somnolence or blurred vision reported as part of the adverse event. Other cases were described as fractures of lumbar vertebrae attributed to advanced age. Overall, no increased risk of fracture/accidental injury associated with darifenacin treatment could be concluded.

C. Dosing

The 7.5mg and 15mg doses of Enablex were selected based on preliminary results in Phase 2 and Phase 3 studies. Enablex 3.75 mg demonstrated insufficient reduction in OAB symptoms and Enablex 30 mg was associated with a greater incidence of dry mouth, constipation and urinary retention. Therefore, Enablex 7.5mg once daily with the option to increase to 15mg once daily based upon individual response, was considered to

provide the best benefit to risk ratio for the treatment of overactive bladder (OAB). Enablex 7.5mg or 15mg dose may be taken without consideration of food intake.

D. **Special Populations**

Age, gender and race: Thirty percent of those treated with Enablex in controlled Phase 3 trials were over age 65. No overall differences in safety or in efficacy were observed between the elderly and those younger than 65 years of age. No dose adjustment is recommended in elderly patients. Enablex is effective in both men and women, although the lower dose (7.5mg) provides less symptomatic relief in men as compared to women. There is no dose adjustment recommended based upon gender. In terms of race, the majority of patients in Phase 3 trials were Caucasian. However, there is no reason to believe that efficacy or safety would differ based upon race.

Elderly: No overall differences in safety or in efficacy were observed between these patients and those younger than 65 years of age. The labeling recommends starting therapy with the low dose (7.5 mg) in all patients and increasing to 15 mg as individual response mandates. This seems medically prudent, especially in the elderly population who may be more sensitive to the known anticholinergic adverse event profile, including dry mouth, constipation, dyspepsia and urinary retention. No specific dose adjustment is recommended for elderly patients.

Renal impairment: No dose adjustment is recommended for patients with renal impairment. Darifenacin is metabolized primarily by CYP 2D6 and CYP 3A4 hepatic isoenzymes. A study conducted in patients with varying degrees of renal impairment demonstrated no clear relationship between renal impairment and clearance of darifenacin.

Hepatic Impairment: ENABLEX pharmacokinetics were investigated in subjects with mild (Child Pugh A) or moderate (Child Pugh B) impairment of hepatic function given ENABLEX 15 mg once daily to steady state. Mild hepatic impairment had no effect on the pharmacokinetics of darifenacin - no dose adjustment is recommended for those patients. However, in patients with moderate hepatic impairment, protein binding of darifenacin was affected. After adjusting for plasma protein binding, unbound darifenacin exposure was estimated to be 4.7-fold higher in subjects with moderate hepatic impairment than subjects with normal hepatic function. Therefore, the daily dose of ENABLEX should not exceed 7.5 mg once daily in those patients. Subjects with severe hepatic impairment (Child Pugh C) have not been studied, therefore ENABLEX is not recommended for use in these patients.

Pediatric: The safety and effectiveness of Enablex in pediatric patients have not been established. The sponsor has proposed an extensive pediatric drug development program to begin shortly after approval. Appropriate language regarding pediatric studies has been included in the action letter to meet PREA requirements.

Use in Pregnancy: There are no studies of darifenacin in pregnant women. ENABLEX is a Pregnancy Category C drug and the labels states that it should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus.

APPENDIX – A
Medical Officer's Review of Study DAR328A2302
"Thorough QT- Study"

Study Objective: To evaluate the effects of darifenacin at therapeutic and supratherapeutic concentrations on cardiac conduction in poor and extensive CYP2D6 substrate metabolizers as assessed by 12 lead ECGs and including both positive (moxifloxacin 400mg) and placebo controls.

Background:
On October 2, 2003, the Approvable action letter issued by the Division requested that sponsor submit the results from a prospective, randomized, double-blind "thorough" QT study including both positive and placebo controls, to evaluate the effect of darifenacin (using low and high doses) on cardiac repolarization. After several discussions with the Division regarding the protocol design, the sponsor proceeded to carry out an acceptable "thorough QT" study. The study report was submitted on May 26th, 2004. After conducting the initial filing review in July 2004, the Division agreed to proceed with the detailed review of the study results.

The original NDA contained a large amount of information related to the effect of darifenacin on cardiac conduction. Nevertheless, the Division found the data insufficient.

For example, sponsor conducted a pooled analysis of QT data from 964 darifenacin-treated subjects and 261 placebo-treated subjects from four studies (Study 137-684, A1371002, A1371007 and A1371015). From this data, the sponsor concluded, that there was no evidence to associate darifenacin with any statistical or clinically relevant increase in the QT interval. From this pooled analysis, the percentage of subjects with a maximum individual increase in QTcF from baseline of >60msec was the same for darifenacin and placebo. Also, there was no difference seen in either elderly or female subjects for any risk of QT prolongation. However, the Division found this pooled data analysis to be deficient. For example, it lacked a comparison with a positive control. Further, it was not clear how sponsor selected the studies for the pooled analysis. Some of the studies specifically excluded users of concomitant potent inhibitors of CYP 3A4, thereby limiting maximal potential systemic darifenacin exposure.

The sponsor also submitted detailed QT results from three specific Phase 1 studies (Studies 1007, 1035, and 1015). Again, the Division found the QT results from these studies insufficient.

Studies 1007 and 1035 were drug interaction studies which employed darifenacin doses of 30mg (Study 1007), or 7.5 and 15mg (Study 1035) in combination with ketoconazole or with placebo. The results of these two studies demonstrated a mean difference between darifenacin+ketoconazole and darifenacin+placebo of approximately 10-12 msec regardless of darifenacin dose. The Division concluded that these two studies were deficient for several reasons. Neither contained a positive control group for QT prolongation or a placebo+placebo group. Neither had multiple ECGs at baseline or at around the time of maximum darifenacin concentration. The number of patients included in the QT analysis was small and was less than the total number enrolled. The sponsor argued that the effect seen on QT in these two studies was due to ketoconazole. The Division concluded that insufficient information had been submitted to draw this conclusion.

Study 1015 was a Phase 1 study evaluating the safety, tolerability and pK for darifenacin doses of 30mg, 60mg and placebo daily for 14 days. Sponsor provided results from QT analysis of data from baseline and from Day 14 of this study that showed no apparent difference between groups. Again, the Division concluded that this study was not sufficient to rule out an independent effect of darifenacin. The Division argued that there was no positive control to document assay sensitivity. Further, ECGs were done only once at baseline and once at Hour 4 after dosing on Day 14. Finally, it was not clear that 60mg provided high enough systemic darifenacin exposure; for example, in the case of a CYP 2D6 poor metabolizer taking a potent 3A4 inhibitor.

Therefore, based upon this original NDA review, the Approvable action was issued, the "thorough QT protocol" was submitted and reviewed, the study was conducted, and the results were submitted in this Response.

Study Design:
This was a single-center, double-blind, placebo and active-controlled, randomized, and parallel-arm design, multiple-dose trial. Enrollment was stratified by cytochrome P450 CYP2D6 metabolic status, by age and by gender, with CYP 2D6 status taking priority. Subjects were randomized to receive placebo, moxifloxacin (Avelox® 400 mg) or darifenacin (15 or 75 mg) for 6 days. Serial digitized ECGs were collected in triplicate at 13 pre-specified time points on Day -1 and on Day 6. Blood samples were collected on Day 2-5 for trough measurements to verify attainment of steady-state. Blood collections were time matched to ECG on Day 6 to assess the relationship between darifenacin maximal concentrations and QTcF interval.

Total duration of the trial included one day of placebo run-in (Day -1) and 6 days of study drug treatment. 188 subjects were enrolled and completed the trial. ECG data analysis was conducted on 179 of the 188 completed subjects as 8 subjects (5174, 5181, 5191, 5230, 5239, 5241, 5252 and 5253) had multiple artifact recordings on either Days -1 or 6 and the Day 6 flash card (containing ECG data) for 1 (5236) subject was lost.

> *Reviewer's Comment: The reviewer requested and reviewed the actual ECGs for these 8 excluded subjects and agreed with sponsor's decision to exclude these individuals.*

The study was powered to detect a difference of 5 milliseconds between the darifenacin groups and placebo in the mean change from baseline to Tmax in QTcF, based upon a two-sided t-test at a 5% significance level. This critical study design element was recommended by the Division in December 2003, in accordance with current draft Agency recommendations for conducting a 'thorough" QT study.

Table 1: Overview of Study Procedures

Pre- Screening	Screening	Day -1	Days 1 & 2	Day 3	Day 4	Day 5	Day 6
CYP 2D6 Phenotype/ Genotype	CYP 2D6 Phenotype/ Genotype & PK	14 ECG's (Baseline) & PK	Pre-dose blood	Vital signs & Pre-dose blood	Pre-dose blood	Vital signs & Pre-dose blood	14 ECG's (Endpoint) & PK

Treatment Groups:
188 subjects were randomized to either group A, B, C or D to receive either darifenacin 15mg, darifenacin 75mg, Avelox 400mg (a positive control) or placebo, respectively. Ultimately, the total number of subjects in whom complete ECG data was available and was included in the primary analysis was 179, including 44 to 45 subjects per group. There were 44% males and 56% females, all between the ages of 45-65 years.

> *Reviewer's Comment: The study population is representative of the target population for the treatment.*

While the darifenacin 15 mg is the maxiumum recommended dose and represents the "therapeutic dose", the study also included a dose of 75 mg (5X the maximum recommended dose), which represents the "supratherapeutic dose". The 75mg dose was selected because it would allow an assessment of change in QT interval duration with change in darifenacin serum concentrations. In addition, 75mg was expected to achieve systemic darifenacin exposure comparable to that observed in CYP2D6 poor metabolizers (PMs) taking 15 mg darifenacin (the maximum recommended dose) in combination with ketoconazole.

> *Reviewer's Comments: In support of the 75mg dose:*
> *The actual pharmacokinetics observed in this study in poor CYP 2D6 metabolizers in the 75mg group was comparable to that observed in several CYP 2D6 poor metabolizers administered 15mg in combination with ketoconazole.*
>
> *As an additional precaution, the label states that the maximum recommended dose in patients taking concomitant potent 3A4 inhibitors is 7.5 mg, not 15 mg.*
>
> *Concentrations above those achieved with 75 mg are expected to be difficult to tolerate due to systemic anticholinergic effects such as dry mouth, constipation and blurry vision.*

Inclusion and Exclusion Criteria:

Basically, subjects were eligible for study participation if they were

- Healthy male or female volunteers 18-65 yrs of age
- Within +\-15 % of target weights on the Metropolitan Life weight scale.

Subjects were excluded from study participation if they presented with any of the following during screening assessments:

- Resting heart rate < 50 bpm
- Systolic blood pressure <90 mmHg or diastolic blood pressure <50 mmHg
- QT interval corrected with the Bazett's formula (QTcB) interval > 450 for males or >470 for females

> *Reviewer's Comment: The reviewer has presented only the major eligibility criteria. All inclusion and exclusion criteria were acceptable.*

Study Endpoints:

Primary Endpoint:

The primary endpoint in this study was the change from baseline to Day 6 in QTcF_tmax, where QTcF_tmax denotes the QTcF at the PK sampling time corresponding to the maximum plasma darifenacin concentration.

Secondary Endpoint:
The secondary endpoints were QT/QTc mean change-from-baseline to Day 6 (all 24-hour collection points taken into consideration), and the change from baseline to the mean maximum QT/QTc interval on Day 6.

> *Reviewer's Comment: Primary and secondary endpoints selected for this study are appropriate. Other endpoints were pre-defined and analyzed and these were also acceptable.*

Safety Assessments:
Safety and tolerability assessments included clinical adverse events, vital signs, laboratory data (biochemistry, hematology and urinalysis), physical examinations and ECG tracings.

ECGs:
Digital ECGs were obtained as 12-lead ECG's [ ] on Days –1 and 6 at pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 24 hours post-drug administration. Three ECG's were recorded at each pre-defined time-point. Therefore, a total of 39 ECGs (each ECG with a 3 beat reading) were extracted for each subject at pre-specified time-point during one 24 hour time period. Specifically, at the pre-specified ECG evaluation time-point, 3 ECGs were extracted in 20-second windows (e.g., 0-20 sec, 21-40 sec and 41-60 sec). If an ECG artifact was noted at the specified time point, replacement ECGs were extracted within a 5-minute window of the pre-specified ECG evaluation time-point (e.g., over minutes 55 to 65 for the pre-specified time-point of 1 hour).

Mean interval values were presented for each ECG evaluation time-point. The QT correction was based on Fridericia's, Bazett's and individual correction methods.

Lead II rhythm strip was used for the interval data in order to permit [ ] to make interval duration measurements on 3 consecutive beats. Manual digitization of up to 3 beats from Lead II for the RR, PR, QRS, and QT interval durations was performed using [ ] high-resolution digitized ECG measurement system. Digital ECG data was collected on flash cards and sent to [ ] for processing.

> *Reviewer's Comments:*
> *Except for 9 subjects, all extracted ECGs were used in the analysis. ECG data was lost on Day 1 for one of these subjects. The reason for exclusion of data for the other 8 subjects was presence of artifacts in the ECG's. The reviewer conducted a detailed review of these ECG's and all other clinical data for these eight subjects (using the case report forms) and agrees with sponsor that these exclusions were appropriate based upon ECG artifacts and not due to any other reason (e.g. cardiac adverse events).*

Demographics:
A total of 188 subjects were enrolled and randomized to groups A, B, C or D, as described previously. Demographics and subject stratification by age, gender and CYP 2D6 metabolic status are summarized in Table 2 below.

Table 2: Summary of Demographics

Mean ± SD *(range)*	Darifenacin 15 mg N=46	Darifenacin 75 mg N=48	Avelox 400 mg N=47	Placebo N=47
Age (yrs)	43 ± 10 (19-62)	44 ± 9 (23-65)	43 ± 10 (25-63)	44 ± 9 (18-64)
Weight (kg)	76 ± 12 (45-100)	75 ± 9 (52-96)	76 ± 12 (50-98)	76 ± 12 (55-100)
Height (cm)	170 ± 9 (150-188)	170 ± 10 (147-193)	170 ± 9 (152-188)	171 ±9 (152-193)
Gender (M/F)	22/25	18/28	22/26	21/26
CYP 2D6 Phenotype (PM/EM)	7/40	7/39	9/39	9/38

Clinical Adverse Events:
A total of 188 subjects were enrolled and completed the study. There were no subject discontinuations. There were no serious adverse events reported. Eighty-three subjects (44% of total enrolled) reported a total of 213 adverse events during the study.

The incidences of reported adverse events are described in Table 3 below. The most frequently reported adverse events were **dry mouth**, **headache**, and **dyspepsia**, irrespective of treatment group. The highest incidence of adverse events was observed when darifenacin was administered at 75mg, five times the recommended dose. In that group, the reported incidences of dry mouth, constipation, headache, dyspepsia were 48%, 20%, 20%, and 18%, respectively. However, when administered at 15mg, the maximum therapeutic dose, the incidences of these side effects were lower: dry mouth = 20%, constipation = 6%; headache =8%, dyspepsia = 6%.

There were no reports of blurred vision in the 15 mg group, but 4 out of 46 subjects (8.7%) in the darifenacin 75 mg reported blurred vision. Dizziness was reported by only one patient in the 15mg group and no patients in the 75 mg group.

Reviewer's Comments:
The reviewer agrees that no SAE's were reported in this study and that the adverse events reported (i.e. dry mouth, constipation and dyspepsia) were the

same as those reported for other anticholinergic drugs in the class. None of the AE's reported required any medical intervention.

It is noteworthy that there were no reports of urinary retention, blurred vision or chest pain at 15mg dose of darifenacin, which is similar to what was observed in the placebo group.

Table 3: Summary of Adverse Events in Study DAR328A2302, by Preferred Term

	----------Darifenacin----------		Avelox	Placebo
	15mg QD	75mg QD	400mg QD	
	N=47	N=46	N=48	N=47
Adverse Event	**N(%)**	**N(%)**	**N(%)**	**N(%)**
Neurologic				
Headache	4(8.5)	9(19.6)	11(22.9)	5(10.6)
Dizziness	1(2.1)	0(0.0)	3(6.3)	1(2.1)
Gastrointestinal				
Dry Mouth	9(19.1)	22(47.8)	2(4.2)	2(4.3)
Constipation	3(6.4)	9(19.6)	1(2.1)	1(2.1)
Dyspepsia	3(6.4)	8(17.4)	0(0.0)	2(4.3)
Eye				
Blurred Vision	0(0.0)	4(8.7)	0(0.0)	0(0.0)
Cardiovascular				
Chest pain	0(0.0)	1(2.2)	1(2.1)	0(0.0)

QT Results:

Corrected QT

The QT correction for RR dependency was based on Bazett's (QTcB) and Fridericia's method (QTcF), using the following formulae:

- $QTcB = QT.RR^{-1/2}$
- $QTcF = QT.RR^{-1/3}$

The QT correction for RR is necessary in order to adjust absolute QT values for increase in heart rate. According to the sponsor and the clinical pharmacology reviewer, the Bazett's method resulted in over correction, but the Fridericia's method was adequate. When the changes-from-baseline in heart rate were computed for the 24-hour duration on Day 6, the 15 mg and 75 mg doses of darifenacin resulted in mean increases of 8.4 ± 2.9 and 6.6 ±2.8 beats per minute (bpm), respectively. Placebo and moxifloxacin demonstrated increases from baseline in heart rate of 5.3 ± 2.4 and 3.3 ± 1.0 bpm, respectively.

Reviewer's comment: The effect of darifenacin 75 mg on heart rate was fairly small compared to placebo, even at five times the maximum recommended dose.

ECG data analysis was conducted on 179 of the 188 completed subjects as 8 subjects (5174, 5181, 5191, 5230, 5239, 5241, 5252 and 5253) had multiple artifact recordings on either Days -1 or 6, and in one subject (5236) the Day 6 flash card containing ECG data was lost. This analysis was conducted at a central facility [redacted]

Aside from the primary central tendency analysis (change-from-baseline to Tmax on Day 6), the following additional analyses were conducted:

- Mean maximum change from baseline on Day 6
- Mean change from baseline (over the 24-hour collection period) on Day 6
- Various categorical analyses
- Exploring the circadian effect on HR and QT/QTc.

Table 4 provides results for the primary endpoint, change from baseline at Tmax.

Table 4. Mean QT Interval Change from Baseline to Tmax on Day 6 - with Placebo Subtracted

Interval (msec)	Darifenacin 15 mg	Darifenacin 75 mg	Avelox® 400mg
QT	-4.9	-8.2	20.5
QTcF	-0.4	-2.2	11.6
QTcB	2.5	2.0	6.4

Table 5 provides results for a secondary analysis of QT data, mean change from baseline (over the 24-hour collection period) on Day 6.

Table 5. Mean QT Change from Baseline to Day 6 (Mean Over the 24-Hour Collection Period) – with Placebo-Subtracted

Interval (msec)	Darifenacin 15 mg	Darifenacin 75 mg	Avelox® 400 mg
QT	-4.0	-0.1	9.3
QTcF	-1.6	-1.2	6.9
QTcB	0.2	-1.2	5.8

It is clear from the results submitted that Avelox ® (moxifloxacin), the positive control, significantly prolonged the QT/QTc intervals, indicating that this study was capable of detecting a small increase in the QT interval. Thus, assay sensitivity was clearly established. For moxifloxacin, the mean, placebo-subtracted change in QT and QTcF from baseline to Tmax on Day 6 was 20.5 msec and 11.6 msec, respectively (Table 4). The mean, placebo-subtracted change in QT and QTcF from baseline to Day 6, over the 24-hour collection period, was 9.3 msec and 6.9 msec, respectively (Table 5).

In contrast, darifenacin did not result in an increase in QT interval compared to placebo at either the therapeutic or supratherapeutic dose strengths administered for 6 consecutive days. For 15mg, the mean, placebo-subtracted change in QT and QTcF from baseline to Tmax on Day 6 was –4.9 msec and –0.4 msec, respectively and for 75mg these values were –8.2 msec and –2.2 msec, respectively (Table 4). When baseline was compared to the mean of the 24-hour collection period on Day 6, the mean placebo-subtracted changes-from-baseline were -4.0 msec and -1.6 msec for QT and QTcF for darifenacin 15mg, and -0.1 msec and -1.2 msec for darifenacin 75 mg.

In fact, mean QTc intervals for both darifenacin treatment groups on Day 6 were found to be lower than the QTc intervals at baseline. Sponsor also points out that non-baseline subtracted QTcF intervals at steady state were comparable between placebo and the two darifenacin treatment groups.

Categorical analyses of the QT data were also conducted. Some of these are depicted in Tables 6 and 7.

Table 6. Number (%) of Subjects with Change from Baseline for QTcF >30 msec or >60 msec

DAY	Treatment	>30 msec N(%)	>60 msec N(%)
Day 6	Darifenacin 15 mg	8 (17%)	0
	Darifenacin 75 mg	8 (19%)	0
	Avelox 400 mg	18 (39%)	2 (4%)
	Placebo	9 (20%)	0

Table 7. Number (%) of Subjects with Change from Baseline for QTcB >30 msec or >60 msec

DAY	Treatment	>30 msec N(%)	>60 msec N(%)
Day 6	Darifenacin 15 mg	17 (36%)	1 (2%)
	Darifenacin 75 mg	14 (33%)	0
	Avelox 400 mg	26 (56%)	5 (11%)
	Placebo	22 (49%)	3 (7%)

Sponsor reports that there were no subjects with QT/QTc intervals >500 msec on Day 6 of the treatment. There were two subjects, one in the darifenacin 75 mg group and one in Avelox 400 mg group with a reported QT interval >450msec. However, the subject in darifenacin group had a higher baseline QT of 455 msec with a Day 6 value of 469 msec. When Fridricia's correction was used, there were two subjects in the high dose darifenacin group with QTcF >450 msec and none in the other groups. It is possible that this reflects the higher baseline QT vales in the 75 mg group compared to the other groups. All groups were similar when Bazzet's correction factor was applied for categorical analyses.

Table 8 provides a brief summary of the trough darifenacin plasma concentrations presented by study day – for EMs and for PMs. Additional pharmacokinetic data (i.e. Cmax, Tmax, and AUC) may be found in the clinical pharmacologist's review.

Table 8. Mean Darifenacin Trough Plasma Concentrations by Study Day

Dose	CYP2D6	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
15 mg	**EM**	2.3	2.6	2.9	3.1	2.6	3.2
	PM	4.8	5.9	4.9	4.4	4.2	4.6
75 mg	**EM**	18.1	25.2	30.4	30.0	27.2	31.2
	PM	21.4	41.1	30.9	39.1	41.4	45.1

From Table 8, it is apparent that the steady state for darifenacin was achieved by Day 3 for both 15 mg and 75 mg.

Reviewer's Comment:
Based upon the results shown (i.e., lack of QT prolongation in both darifenacin groups observed with both uncorrected and corrected intervals), it is the opinion of this reviewer that darifenacin at both low and high dose strengths showed no QT prolongation and no cardiac conduction defects when compared to a positive control (moxifloxacin) and to placebo.

This reviewer also acknowledges that mean QTc for darifenacin on Day 6 was actually lower than baseline QTc. Such an observation can be attributed to "regression towards mean" effect, as suggested by sponsor, or to a modest increase in heart rate at Day 6.

Summary of Medical Officer's Review of Study DAR328A2302:
This thorough QT- study (DAR328A 2302) confirms that darifenacin does not result in any QT/QTc prolongation at therapeutic and clinically relevant supratherapeutic concentrations (i.e. after 6 consecutive days of darifenacin at 5-times the maximum recommended therapeutic dose with approximately 20% of subjects being poor metabolizers of CYP 2D6).

There were no SAE's or subject discontinuations reported, even at 5 times higher therapeutic doses. Adverse events reported most frequently were related to the expected anticholinergic effects (i.e. dry mouth, constipation and dyspepsia), and these were observed in both darifenacin groups in a dose-dependent manner. There were no reports of urinary retention, blurred vision, chest pain or tachycardia in those patients who received 15mg darifenacin or placebo. Blurred vision was reported in some patients administered 75 mg.

The systemic exposure of darifenacin achieved in this study either was comparable to or exceeded a clinically relevant range of plasma concentrations. Moreover, the systemic exposures achieved in this study was comparable to or exceeded exposures previously observed after the co-administration of 7.5 mg and 15 mg doses of darifenacin with the potent CYP3A4 inhibitor ketoconazole.

Based on this new data, and the previous data showing that co-administration of darifenacin with ketoconazole resulted in QTcF increases of 10-12msec without a dose-response effect for darifenacin (up to a dose of 30 mg), the sponsor's suggestion that ketoconazole and not darifenacin contributed to QT/QTc prolongation is reasonable.

Therefore, the results of study DAR328A2302 provide definitive evidence that darifenacin at substantial multiples of the anticipated maximum therapeutic dose in either extensive or poor CYP2D6 metabolizers of both genders did not result in QT/QTc prolongation or any defined cardiac conduction abnormality.

<u>Medical Officer's Conclusions Regarding Study DAR328A2302:</u>

- **This study has demonstrated that multiple doses of darifenacin (15mg or 75mg) are not associated with prolongation of QT/QTc intervals and have no clinically meaningful effect on cardiac conduction or ventricular repolarization.**

- **Avelox ® (Moxifloxacin), a positive control, significantly prolonged the QT/QTcF interval by 9.3/6.9 msec, consistent with previous observations and validating the sensitivity of this study.**

- **The systemic exposures achieved in this study were comparable to or exceeded darifenacin exposures previously observed after the co-administration of 7.5 mg and 15 mg darifenacin and the potent CYP3A4 inhibitor ketoconazole.**

- **Treatment with darifenacin did not result in a significant increase of mean cardiac conduction intervals (QT, QTcF, QTcB, QRS) at doses of 15 and 75 mg in extensive or poor metabolizers of CYP 2D6.**

- **Darifenacin treatment did not result in a significant increase of QT, QTcF, or QTcB at doses of 15 and 75 mg when analyzed at peak plasma exposure after 6 consecutive days.**

- **Both darifenacin and Avelox ® treatments were generally well tolerated in this study.**

APPENDIX -B

Medical Officer's Review of Safety Update and Specific Adverse Events

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A. Brief Statement of Conclusions

The adverse event profile for darifenacin appears similar to that for other anticholinergic drugs in its class. As per the review of original NDA submission, dry mouth, constipation and dyspepsia are the most frequently reported adverse events. There is no evidence of drug-related cardiovascular side effects. There have been 18 cases of bone fracture among 7,258 darifenacin recipients reported to date (0.2%), with most reported in open-label, uncontrolled trials, and none determined to be related to the drug.

The results of the thorough QT-study (DAR328A2302), in which subjects received up to five times the therapeutic doses of darifenacin i.e., 75 mg once daily, suggests no signal of cardiac safety concern. There was neither statistical nor clinically relevant effect on QT-interval and/or cardiac conduction due to darifenacin treatment nor any relationship between darifenacin exposure and changes in the QT-interval.

B. Source of Updated Safety Data and Patient Exposure

The safety update submitted by the sponsor contains safety data for studies **CDAR328A2301** (a long-term open label safety study) and **CDAR328A2302** (a randomized, placebo and active-controlled study to evaluate the effect of darifenacin on QT-interval). As per this submission, a total of 7363 subjects have been exposed to darifenacin to date.

In addition, the sponsor provided additional analyses to address the following three specific adverse events: constipation, urinary retention and bone fractures.

C. Specific Adverse Events

1. Constipation

According to the sponsor, there have been 7,258 subjects treated with darifenacin, 2343 subjects treated with placebo, and 887 subjects treated with an active comparator included in all phase 1, 2 and 3 trials combined.

There were 6 cases of constipation reported as serious adverse events among darifenacin-treated patients (0.083%), 1 among placebo-treated patients (0.043%) and none among patients treated with an active comparator. All 6 cases were classified as treatment-related by the investigators.

Of these six cases, two occurred at doses in excess of the maximum recommended dose, including one healthy volunteer exposed to 60 mg in Study A1371015 (Subject 1130-88) and one OAB patient taking 30mg daily. Two other cases were reported in patients taking part in studies for treatment of Irritable Bowel Syndrome (Study 137351 Subject 2670240 and Study 137356 Subject 1010750). A fifth case was reported in a patient taking part in a study for the treatment of Benign Prostate Hyperplasia (Study A1371026 Subject 0441-51).

Therefore, of all 6 cases of constipation as a serious adverse event, only one was in an OAB patient taking the recommended doses. This patient complained of nine months of chronic constipation of moderate severity. She was hospitalized briefly to undergo investigation by colonoscopy. She was released from the hospital promptly without further intervention.

In the recent QT study DAR328A2302, where doses of 15mg and 75mg were administered for 6 consecutive days to healthy volunteers, the reported incidences of constipation were 6.4% and 19.6%, respectively, compared to 2.1% for placebo. None of these events were classified as serious.

Reviewer's Comment: Constipation is a frequently reported adverse event with almost all drugs in this class (anticholinergics). Still, there has been only one serious adverse event (SAE) of constipation reported in OAB patients treated with the recommended doses. This was coded as serious only because routine investigation of symptoms, including colonoscopy, was conducted in-hospital. Throughout the clinical development of darifenacin, for all doses and all indications, constipation was reported as an SAE in a total of 6 darifenacin patients (0.083%) and one placebo patient. In the opinion of this reviewer, the incidence of this expected adverse event is not unreasonable and does not preclude approval. Labeling will clearly describe this potential risk.

2. Urinary Retention

Urinary retention was reported as an adverse event at a frequency of < 1% in the entire darifenacin clinical program. From the NDA safety database, a total of 49 (0.7%) darifenacin-treated subjects, 2 (0.1%) placebo-treated subjects, and four (0.5%) subjects treated with an active comparator reported an adverse event coded as urinary retention (Table 9). However, detailed review of these cases revealed that only sixteen of the 49 darifenacin cases were actually "acute urinary retention" (AUR), as generally recognized in the urologic community. The remaining 33 cases were reported as the sensation of incomplete bladder emptying that required neither catheterization nor intervention.

Of the 16 darifenacin cases that were considered to reflect acute urinary retention, only seven (0.11%) were reported as an SAE. Out of these seven cases:

- one case was reported in a 62 year old male patient with BPH taking part in an IBS (irritable bowel syndrome) study,
- one case was reported in a healthy 76 year old male with BPH taking part in a healthy volunteer study,
- one case was reported in a 75 year old male patient with detrusor hyperreflexia secondary to stroke.
- The remaining four serious cases were reported in OAB studies, but all four occurred in patients taking a daily dose of 30mg. In one of these cases, an 83 year old Japanese women with OAB was found to have acute renal failure and bilateral hydronephrosis as a consequence of acute urinary retention.

Of the remaining nine cases, none were reported as serious adverse events. Six of these cases occurred in patients taking 30mg daily. Only three occurred in OAB patients taking the recommended doses, as follows:

- 80 year old female had AUR after pre-planned hand surgery and required bladder catherization for 1 day.
- 74 year old Japanese male with BPH had AUR and required bladder catheterization for 2 days.
- 41 year old female with childhood enuresis, recurrent UTIs, and history of detrusor instability *and* urinary outflow obstruction had dry mouth, dry eyes and AUR. The AUR required only a single emptying of the bladder by straight catheterization (not an indwelling catheter).

The rate of urinary retention AE reports have not changed since the original NDA submission (Table 10). Four adverse events reported as urinary retention were reported during the long-term open-label safety study 2301/1042. All four cases were considered mild and no medical intervention was required. No new urinary retention SAE has been reported.

Table 9. Adverse Events of Urinary Retention in All Phase 1, 2 and 3 Studies (Original NDA Submission)

Urinary Retention	**Darifenacin N=6655** N(%)	**Placebo N=2216** N(%)	**Active Comparator N= 887** N(%)
AE	49 (0.74%)	2 (0.09%)	4 (0.45%)
SAE	7 (0.11%)	0 (0.00%)	0 (0.00%)

Table 10. Adverse Events of Urinary Retention in All Phase 1, 2 and 3 Studies (Updated Safety Data)

Urinary Retention	**Darifenacin N=7258** N(%)	**Placebo N=2343** N(%)	**Active Comparator N=887** N(%)
AE	53 (0.73%)	2 (0.09%)	4 (0.45%)
SAE	7 (0.10%)	0 (0.00%)	0 (0.00%)

Reviewer's Comment: There have been no new cases of acute urinary retention since the original NDA submission and none reported in the long-term, open-label safety study of 716 OAB patients taking darifenacin 7.5 or 15 mg. This adverse event is recognized as a potential consequence of most anticholinergic treatment, especially in those patients with pre-existing bladder outlet obstruction. The incidence of the events is not unreasonable. Overall, this issue does not preclude approval. Still, it is the opinion of this reviewer that the issue should be described prominently in labeling, with special consideration for patients with co-morbid bladder outlet obstructive disorders, i.e., urinary retention.

3. **Bone Fracture:**

The medical review of the original NDA revealed 16 cases of bone fracture reported as an SAE in all darifenacin-treated subjects versus no such reports in those patients treated with placebo. Most of these occurred in open-label, uncontrolled safety extensions. Still, there appeared to be a possible imbalance in the overall, adjusted incidence between darifenacin and placebo. Therefore, a more detailed review of this issue was undertaken during this review cycle.

As per the most recent safety data submission, there have been a total of 18 bone fracture cases reported as SAEs in 7,258 darifenacin recipient patients across the entire darifenacin clinical program, representing an overall frequency of 0.25% and an incidence of 0.82 cases per 100 patient-years of exposure. There have been no bone fracture SAE cases reported in placebo-treated (N= 2343) patients. When the exposure-adjusted incidence of SAE bone fracture was compared between drug and placebo, the difference was not statistically significant (p =0.11) and the 95% confidence intervals for the groups overlapped.

Ten of the 18 darifenacin cases (56%) occurred in open-label, uncontrolled trials (Studies 311, 1010, 1017, and 1042). Cases were reported with all four doses: 3.75, 7.5, 15, and 30 mg, with no apparent pattern of dose relationship. The amount of exposure prior to the event (number of days of treatment) was also widely distributed, without any pattern of clustering at the beginning of treatment or pattern of increase over time.

Reflecting the composition of the study populations, 12 of the 18 cases were in females. Eight of the eighteen cases were patients 65 years of age or older and two cases were patients 75 years of age or older. The increased frequency in older patients is consistent with observations in general population.

Nearly all of these cases were reported from study sites outside of North America. Out of 2074 subjects in North America who were exposed to darifenacin, there was one case (0.18%) of SAE fracture.

The incidence of 0.18 cases per 100 subject-years in North America was near 5-fold lower than the worldwide reported incidence of 0.82 per 100 subject-years. The geographic disparity in the fracture SAE reporting rate appears to suggest geographic difference in medical care. Whether an adverse event of fracture was coded as an SAE might have been influenced by geographical differences in standard of medical care, such as hospital admission policies.

In this review cycle, when all serious adverse events of accidental bone fracture were examined and adjusted for the amount of exposure, the confidence intervals for the darifenacin and placebo exposure-adjusted incidences overlapped and the p-value was not significant. This suggests that there is no independent contribution of darifenacin to SAE bone fractures.

Tables 11, 12, 13 and 14 provide the number of SAE bone fractures by dose, gender, age and geographic distribution, respectively.

Table 11. Number of SAE Bone Fractures By Dose

Darifenacin Dose	Number of SAE Bone Fractures
3.75 mg	2
7.5 mg	6
15 mg	6
30 mg	4

Table 12. Number of SAE Bone Fractures by Gender

Gender	Number of SAE Bone Fractures
Female	12
Male	6

Table 13. Number of SAE Bone Fractures by Age

Age	Number of SAE Bone Fractures
<65 years	10
>65 years	8

Table 14. Number of SAE Bone Fractures by Geographic Distribution

Geographic Location	Number of SAE Bone Fractures
North America	1
Europe	13
Japan	3
Israel	1

Table 15 provides a tabular list of all 18 bone fracture SAE cases in the NDA including: specific study number, subject ID number, subject age and gender, number of days of drug exposure, specific adverse event reported, investigator's judgement on causality, and country of origin. Eighteen individual patient narratives follow Table 15.

Table 15. Bone Fracture SAE cases in Darifenacin-Treated Patients

Study	Subject ID	Age	M/F	Dose	Day #	Event	Causality (Investigator)	Country
305	00550108	73	F	7.5 mg	80	Fracture lumbar spine	"Suspected osteoporosis"	Sweden
305A	01145066	28	M	15 mg	218	Compression fracture lumbar spine	"Road traffic accident"	France
311	00260016	55	F	15 mg	61	Broken left wrist	Slipped on ice	UK
311	03010192	46	F	30 mg	40	Fracture pelvis	Fell down stairs (Multiple sclerosis)	UK
356	03110245	25	F	3.75 mg	53	Nose fracture; neck injury	"Traffic accident"	Sweden
1001	5060839	89	F	30 mg	8	Fracture right ankle	Slipped on wet kitchen floor	US
1002	0456810	44	F	15 mg	54	Fracture 12th thoracic vertebra/liver injury	Thrown from horse	Sweden
1010	10280002	32	M	30 mg	8	Fracture hip and right distal radius	Motorcycle accident	Spain
1013	10590341	70	M	30 mg	75	Fracture right femur	"Heavy alcohol intake"	Norway
1017	50817068	70	M	7.5 mg	107	Fracture right hip	"Got drunk and fell from a window"	Japan
1017	50777016	65	F	15 mg	39	Compression fracture	"Accidental fall"	Japan
1017	51327127	83	F	15 mg	12	Fracture right tibia and fibula	Electric wheelchair fell down at home	Japan
1041	11260128	55	F	3.75 mg	11	Fracture left tibial plateau	"Attacked by a dog"	Australia
1041	04610481	68	M	7.5 mg	54	Fracture right distal radius	"Transient cerebral ischemia"	Denmark
1042	1140410223	68	F	7.5 mg	69	Fracture hip	"Fell"	Poland
1042	1141410193	46	M	7.5 mg	99	Fracture right leg	"Accident" (paraplegic)	Poland
1042	04520311	41	F	15 mg	424	Fracture right ankle	Post-poliomylelitis	Israel
1042	1175410389	58	F	7.5 mg	340	Fracture right hand bone	"Had an accident"	

Patient Narratives/SAE Bone Fractures in Darifenacin-Treated Patients (N=18)

Study # 305 Case # 00550108

A 73 year old female on Sweden with suspected osteoporosis reported a fracture of her lumbar spine on study Day 80, which occurred on rising from a sun chair. She was hospitalized. Concurrent medical history included anemia, chronic cystitis, hiatus hernia and UTI. Concomitant medications included trimethoprim, ferrous fumarate, omeprazole, pivampicillin and L-thyroxine. The adverse event was not suspected to be related to study treatment by the investigator

> *Reviewer's Comment: The reviewer agrees with the investigator that this case is likely a compression fracture of a lumbar vertebrae related to osteoporosis. It is not possible to implicate darifenacin in this case.*

Study # 305A Case # 01145066

A 28 year old man in France was involved in a "road accident" on study Day 218 and reported a compression fracture of the lumbar vertebrae L3. The fracture was of moderate severity. He was hospitalized and made a complete recovery. Past medical history was significant for incomplete tetraparesia secondary to an accident in 1992. Concomitant medications included baclofen, tetrazepam and clonazepam. The adverse event was not suspected to be related to study medication by the investigator.

> *Reviewer's Comment: This patient was in a "road accident". No additional information was available. It is not known whether he was a driver or a passenger. However, this young man was previously injured in 1992, leaving him with a neurological deficit described as " tetraparesia". His medical condition required use of baclofen, tetrazepam and clonazepam (and now darifenacin). The reviewer believes that it is not likely that this patient was driving the automobile. Regardless, the reviewer believes that it is not likely that the road accident was related in any way to darifenacin.*

Study # 311 Case # 00260016

A 55 year old female in U.K. slipped on ice on study Day 61 and reported a fracture of her left wrist. She was hospitalized and an external fixation procedure was performed. The patient made a complete recovery. Past medical history was significant for injury and subsequent frozen left shoulder (1992), slight osteoarthritis of the right thumb, peptic ulcer and rectal bleeding. At the time of the event, the patient was on no reported concomitant medications. The event was not suspected to be related to the study medication by the investigator.

> *Reviewer's Comment: The reviewer agrees with the investigator in this case. This patient slipped on ice and fractured her left wrist, apparently in an attempt to stop the fall.*

Study # 311 Case # 03010192

A 46 year old U.K. female with Multiple Sclerosis (MS) fell down the stairs on study Day 40 and reported a fractured pelvis and also injury (but no fracture) to the ribs. The pelvic fracture was of moderate severity. The patient reported that she caught her foot in the carpet which resulted in the fall. The patient walked with difficulty and was very weak in the legs, normally attending the clinic in a wheelchair. She was hospitalized and treated for pain. The patient made a complete recovery. Past medical history was significant for multiple sclerosis (since 1976), depression (for 20 years), hiatus hernia (since 1994), tension headaches, and shortness of breath (for 30 years). Concomitant medications included: Algonac acid/aluminum hydroxide/sodium bicarbonate/magnesium trisilicate, acetaminophen and albuterol. The event was not suspected to be related to the study medication by the investigator.

> *Reviewer's Comment: The reviewer agrees with the investigator. The patient had Multiple Sclerosis with leg weakness and was wheelchair-bound while attending clinic. It appears that she tripped on carpeting and fell down stairs.*

Study # 356 Case # 03110245
A 25 year old female in Sweden fractured her nose and sustained a neck injury during a "traffic accident" on study Day 53. Both injuries were of moderate severity. She was hospitalized for only two days, but during the subsequent two weeks she returned twice for outpatient surgical repair of her nose. Concurrent medical history included irritable bowel syndrome and umbilical fistula NOS with umbilical operation performed in 1988. Concomitant medications included ethinyl estradiol/levonorgestrel and acyclovir. The adverse event was not suspected to be related to study treatment by the investigator, and the study drug was continued.

> *Reviewer's Comment: No additional information was available in the CRF to better explain the etiology of this case. It is not known whether the patient was a driver, passenger or pedestrian. Nevertheless, there was no report of dizziness, sleepiness or blurred vision in association with the accident.*

Study # 1001 Case # 50600839
An 89 year old female in the United States slipped and fell on a wet kitchen floor on study Day 8 as she was rushing to answer the telephone. This resulted in a severe fracture to the right ankle. The patient had no vertigo or syncope at the time of the fall. She was hospitalized and had a surgical repair. She made a complete recovery. Significant past medical history included arthritis of right big toe (1988), bunion repair with artificial joint in right big toe (1990), osteoarthritis (1965), osteoporosis (1999), left cataract removal (1995), right cataract removal (1994), hypertension (1985), gastro-esophageal reflux (1985), tension headaches six times per year (1985) and occasional lightheadedness (1998). Concomitant medications included verapamil, aspirin, omeprazole, acetaminophen, multivitamin preparation, vitamins C and E and calcium salts. The adverse event was not suspected to be related to study treatment by the investigator.

> *Reviewer's Comment: The reviewer agrees with the investigator. This 89 year old woman slipped on a wet kitchen floor while rushing to answer the telephone. She reported no dizziness or blurred vision in association with the fall.*

Study # 1002 Case # 0456810
A 44 year old female in Sweden fell from a horse on study Day 54 and sustained an uncomplicated fracture of her 12th thoracic vertebra and a secondary subcapsular liver hematoma. The fracture was severe. The horse apparently turned suddenly, causing the fall. She was hospitalized for pain management, intravenous fluids and observation. The patient made a complete recovery. Concomitant medications included ibuprofen. The adverse event was not suspected to be related to the study medication by the investigator.

> *Reviewer's Comment: The reviewer agrees with the investigator. This young woman fell from a horse that had turned suddenly. She reported no dizziness, sleepiness or blurred vision in association with the accident.*

Study # 1010 Case # 10280002
A 32 year old man in Spain participated in a cimetidine interaction study as a normal volunteer. On study Day 8, he was riding a motorcycle and lost control on a very dangerous curve. The motorcycle fell to one side and he crashed into an iron ball placed to separate the pedestrian way. There was no other vehicle involved in the accident. He was fully conscious at all times, and he did not have blurred vision, dizziness or other pathology that would explain the accident. Injuries included a fractured hip & fractured right arm. He was hospitalized for surgical repair of both fractures. He made a complete recovery. Past medical history was significant only for Hepatitis A during childhood. Concomitant medications included cimetidine 1600 mg. The adverse event was not suspected to be related to study medication by the investigator.

> *Reviewer's Comment: The reviewer agrees with the investigator. This young man lost control of his motorcycle while riding on a dangerous curve. He reported no dizziness, sleepiness or blurred vision in association with the accident.*

Study # 1013 Case # 10590341
A 70 year old male in Norway fell and fractured the neck of his right femur on study Day 75 after "heavy alcohol intake". It is unknown if he lost consciousness during the event. The patient could not remember what happened. The fracture was of moderate severity. He was hospitalized and his fracture required surgical repair. He recovered completely. Significant past medical history included: duodenal ulcer (2001), cerebral stroke with right-sided hemiparesis (1995) described as "recovered", renal cell carcinoma with right-sided nephrectomy (1994) and allergies (pollen, tomatoes). His concomitant medications included mometasone antazoline/tetrahydrozoline ophthalmic preparation, beclomethasone (respiratory), fexofenadine, and lansoprazole. The adverse event was not determined to be related to study treatment by the investigator.

> *Reviewer's Comment: The reviewer agrees with the investigator. This 70 year old man with a past medical history of cerebral stroke with right-sided weakness fractured his right femur after "heavy alcohol intake". There are no additional details and the subject cannot remember what happened. It is not possible to implicate darifenacin in this case.*

Study # 1017 Case # 50817068
A 70 year old man in Japan got drunk and fell from a window on study Day 107, resulting in a fractured right hip. He was hospitalized for surgical repair. The patient made a complete recovery. He had multiple co-morbid medical conditions including myotonia NOS, osteoporosis, peripheral neuropathy, gastritis NOS, total gastrectomy and iron deficiency anemia. Concomitant medications included alfacalcidol, ambroxol, carbocisteine, ferrous citrate, levofloxacin, ketoprofen, fexofenadine, chondroitin sulphate, mecobalamin, zaltoprofen, triazolam, tizanidine hydrochloride, rebamipide, organ lysate, mofezolac and mepivacaine. The event was not suspected to be related to the study medication by the investigator.

Reviewer's Comment: The reviewer agrees with the investigator. This 70 year old man with a past medical history of peripheral neuropathy, myotonia and also taking triazolam "got drunk and fell from a window". There are no additional details provided. It is not possible to implicate darifenacin in this case.

Study # 1017 Case # 50777016

A 65 year old female in Japan had "an accidental fall" resulting in a compression fracture of L3 and L4 on study Day 39. No cause for the fall was reported. However, it was reported that at the time of the fall the patient did **not** experience any dizziness, vertigo or light headedness. The patient rested at home but had persistent pain, and was hospitalized four months later for a detailed pain work-up. The patient made a complete recovery. Past medical history was significant for gastric ulcer and appendicitis. Concomitant medications included sucralfate and ranitidine. The adverse event was not determined to be related to study treatment by the investigator.

Reviewer's Comment: It is notable that in this case, the case narrative states that there was no dizziness, vertigo or light headedness at the time of the fall. No further details are given.

Study # 1017 Case # 51327127

An 83 year old female in Japan broke her right lower limb on study Day 12 when her electronically-powered wheelchair fell down at home. The fracture was of moderate severity. She was hospitalized and open reduction was performed. The patient made a complete recovery. Concurrent medical history included constipation, osteoarthritis and headaches, gastric cancer and right femur fracture. Concomitant medications included loxoprofen and magnesium oxide. The event was not determined to be related to the study medication by the investigator.

Reviewer's Comment: It is notable that this patient's electric wheelchair "fell down" at home, causing a fracture of her right lower limb. Darifenacin cannot be implicated in this case.

Study # 1041 Case # 11260128

55 year old female in Australia got attacked by a dog on study Day 11 and fractured her left lateral tibial plateau. The fracture was severe. Although she was initially treated and released from the Emergency Room, she required surgery the following month. The patient made a complete recovery. Past medical history was significant for eye muscle and bilateral squint (1950, 1955, 1970, repair of squint). At the time of the event, the patient was on no reported concomitant medications. The adverse event was not determined to be related to the study medication by the investigator and study medication was continued.

Reviewer's Comment: It is notable that this patient was attacked by a dog, injuring her left tibial plateau. Darifenacin cannot be implicated in this case.

Study # 1041 Case # 04610481
A 68 year old male in Denmark fell at home on study Day 54 and fractured his distal right radius. The fracture was of mild severity. The investigator judged that the fall was a result of transient cerebral ischemia. The patient was hospitalized and had osteosynthesis under local anesthesia. He made a complete recovery. Mild transitory cerebral ischemia had been reported previously as an adverse event (Study Days 33-34). Concurrent medical conditions included small thrombosis of the right big toe, intermittent claudication (since 1988) and intermittent dyspepsia. Past medical history was significant for cerebral infarction with hemiparesis and acute myocardial infarction (1992). Concomitant medications included acetylsalicylic acid and cimetidine. The investigator did not suspect the event to be related to the study drug, which was continued.

> *Reviewer's Comment: In this case, the investigator attributed the fall to "transient cerebral ischemia". The patient had intermittent claudication, previous acute MI, previous thrombosis of the right great toe, previous cerebral infarction with hemiparesis, and previous "transitory cerebral ischemia" as an adverse event on study Days 33 and 34 of this same trial. The reviewer agrees with the investigator's assessment.*

Study # 1042 Case # 1140410223
A 68 year old female in Poland "fell" on study Day 69 and fractured her hip. No cause of the fall was reported. She was hospitalized for surgical repair. The patient made a complete recovery. The investigator attributed causality to other co-morbid illnesses i.e., carcinoma of the lung, bronchitis, coronary artery insufficiency and hypertension. Concomitant medications included enalapril and verapmil. The adverse event was not suspected to be related to study treatment by the investigator.

Study # 1042 Case # 1141410193
A 46 year old male in Poland "had an accident" on study Day 99 and sustained an undisplaced simple fracture of the upper right leg. He was hospitalized and a closed reduction was performed. He made a complete recovery. Past medical history was significant for fractured spinal column with injury to the spinal cord T4-6, paraplegia (1988), and muscular atrophy of the lower limbs. The patient was on no reported concomitant medications. The adverse event was not suspected to be related to study medication treatment by the investigator.

> *Reviewer's Comment: It is notable that this patient was paraplegic, status-post fracture of the spinal column and injury to the cord at T4-6. The reviewer agrees with the investigator's assessment.*

Study # 1042 Case # 04520311
A 41 years old female patient in Israel with a past medical history including poliomyelitis reported swelling and pain in her right ankle due to a sharp movement, and was subsequently admitted to the hospital. She was diagnosed with a right ankle fracture on

study Day 424 and underwent surgical fixation of the ankle. She wore a cast for six weeks, and at the time of reporting, the patient's condition was improving. The investigator did not suspect a relationship between this event and the study medication, and causality was attributed to post-poliomyelitis.

> *Reviewer's comment: It is notable that this patient was post-poliomyelitis. This may have played a role in her ankle fracture as per the investigator.*

Study # 1042 Case # 1175410389
A 58 year old female "had an accident" on study Day 340 and sustained a fracture of right hand bone. Drug was temporarily stopped. The adverse event was not suspected to be related to study medication treatment by the investigator.

D. Summary (Bone Fractures)
As per the most recent submission of safety data, a total of 18 SAE bone fracture were reported in 7,258 darifenacin-treated patients across all studies in the darifenacin clinical program. The sponsor notes that the overall incidence of 0.82 cases per 100 subject-years of exposure does not appear to be significantly higher than the background rate in the general population. Further, and perhaps more importantly, even though there were no cases reported in the placebo group, the confidence intervals surrounding the placebo rate and the darifenacin rate for this adverse event overlap, and the p-value is not significant.

The distribution of the 18 SAE's suggested neither dose relationship nor exposure time relationship. The age distribution is consistent with the overall age distribution of the clinical database. There is no apparent relationship to gender.

The 18 SAE cases showed a lopsided geographic distribution with the incidence in North American subjects being 5-fold lower than the overall incidence. This may be related to medical practice policies in North Amerca versus other parts of the world, especially in regard to hospitalization. In North America, simple fracture cases often do not require hospitalization and therefore may not be classified as SAEs, by strict criteria.

Finally, each case of SAE bone fracture was individually reviewed and most could be attributed to another distinct cause. Darifenacin could not be directly implicated in any case.

> *Reviewer's Comments:*
> *After a detailed review of all 18 case reports, this reviewer believes that none of these cases was a result of taking darifenacin. Rather, they could be fairly attributed to other causes, including accidental falls subsequent to co-morbid medical conditions or age, or in some cases, secondary to heavy alcohol intake.*
>
> *Interestingly, there was only one case of bone fracture reported in the United States. Further, almost 60% of fracture SAE's were observed in non-controlled studies.*

Therefore, the concern raised in the original review has been satisfactorily resolved by the review findings in this safety update; specifically:

- *The confidence intervals between darifenacin and placebo groups for SAE bone fractures overlap*
- *The differences between darifenacin and placebo groups is not statistically significant.*
- *A case-by-case review of the 18 SAE's revealed reasonable alternative causes for each fracture.*

Therefore, this reviewer feels confident in ruling out a possible association between darifenacin and occurrence of bone fractures.

E. Cardiovascular Safety Update

The sponsor submitted a safety update for all reported cardiovascular adverse events. Table 16 below contains the reported cardiovascular adverse events (serious and non-serious) from all phase 2 and 3 OAB/IBS studies. According to sponsor, there is no increase in the incidence of tachycardia or arrhythmia in darifenacin treated patients compared to placebo-treated patients.

Table 16. Reported Cardiovascular Adverse Events in all OAB/IBS studies

Adverse Event	Darifenacin N=2101 N (%)	Active Comparator N=450 N (%)	Placebo N=830 N (%)
Palpitation	9 (0.4)	5 (1.1)	5 (0.6)
Tachycardia	5 (0.2)	4 (0.9)	1 (0.1)
Syncope	3 (0.1)	1 (0.2)	2 (0.2)
Angina pectoris	4 (0.2)	1 (0.2)	0 (0)
Arrhythmia	4 (0.2)	0 (0)	2 (0.2)
Hypotension	4 (0.2)	1 (0.2)	0 (0)
Bradycardia	3 (0.1)	0 (0)	0 (0)
Electrocardiogram abnormal	2 (0.1)	0 (0)	1 (0.1)
Myocardial infarct	1 (0.0)	0 (0)	0 (0)
Myocardial Ischemia	1 (0.0)	0 (0)	0 (0)
Atrial fibrillation	2 (0.1)	3 (0.7)	1 (0.1)
AV block	2 (0.1)	0 (0)	0 (0)
Coronary artery disorder	1 (0.0)	0 (0)	1 (0.1)
Bundle branch block	1 (0.0)	0 (0)	0 (0)
Ventricular arrhythmia	0 (0)	0 (0)	1 (0.1)

In the most recent safety update, a total of 31 serious cardiovascular adverse events were reported (equivalent to 1.8 cases per 100 subject years of exposure) in darifenacin-treated subjects in all Phase 1, 2, and 3 studies of darifenacin, compared to 9 cases (equivalent to 2.5 cases per 100 subject-years of exposure) in placebo-treated subjects. Only one of the events in darifenacin group was considered related to study drug.

Among the 31 cardiovascular SAE's in darifenacin-treated subjects, nine were in the heart rate/rhythm category (AV Block, Arrhythmia, Bradycardia, Atrial Fibrillation, Tachycardia). None of the placebo SAE's were in this category. Each of the cases in this category was individually examined and only four were found to be suggestive of a clinically significant arrhythmia. A brief summary of the information is provided for these 4 cases below.

- **Subject 50270999** in Study A1371001 was a 73 year-old female patient with OAB taking the active comparator tolterodine 2mg bid.

- **Subject 00230258** in Study 137-311 was a 71 year-old female patient with OAB taking darifenacin 15mg QD. After 156 days of therapy she was admitted to hospital with pericardial pain. She had a past history of aortic stenosis and valve replacement, left bundle branch block and a partial nephrectomy for a kidney tumor. Study drug was permanently discontinued and she made a full recovery. The investigator attributed the cardiac arrhythmia to other existing co-morbid illnesses i.e., (cardiovascular disease).

- **Subject 01650079** in Study 137-351 was a 56 year-old male patient with IBS taking darifenacin 3.75mg TID. After 78 days of blinded therapy he was admitted to hospital with tachycardia. He had a past history of myocardial infarction, coronary artery bypass graft, coronary angioplasty x 2, cholecystectomy and thyroid surgery. Study drug was temporarily discontinued during the hospital admission and he made a full recovery. The investigator attributed the tachycardia to other illness (coronary artery disease).

- **Subject 10770596** in Study A1371041 was an 83 year-old female patient with OAB taking darifenacin 7.5mg QD. After 50 days of blinded therapy she was admitted to hospital with second-degree AV heart block for which a pacemaker was implanted. She had past history of first-degree AV block. No action was taken with regard to study drug and she made a full recovery. The investigator attributed the second-degree AV heart block to study drug.

  Reviewer's Comment: Causality is difficult to discern in these cases, based upon complicated previous medical history and co-morbidity. Overall, there is no indication that darifenacin is associated with arrythmia.

Eight additional cardiovascular SAE's were reported in the long-term, open-label safety Study 2301/1402 to date. With the incremental increase of exposure time of more than 432.4 subject-years, the updated incidence of 1.85 per 100 subject years of exposure, is roughly the same as that in the original NDA (1.8 per 100 subject year of exposure) and shows no increasing risk associated with long-term exposure. Only two of the eight cases, Subject 12222395 and 12332302, were in the heart rate/rhythm category. Both were reports of atrial fibrillation in patients with pre-existing atrial fibrillation.

There were very few discontinuations due to cardiovascular adverse events from all darifenacin doses. The rates were similar to that in the placebo group and appeared lower than that of active comparator.

> *Reviewer's Comment: In the opinion of this reviewer, the clinical experiences accumulated throughout the darifenacin program showed no increased risk of cardiovascular disorders including heart rate or rhythm adverse events. There were few discontinuations due to such events in a diverse population, including a wide age range, multiple co-morbid medical conditions, and/or use of concomitant medications.*

F. Safety Report of Long-Term, Open-Label Study 2301/1042

The sponsor submitted the results from an open-label, multi-center, long-term safety study. These are reviewed herein.

1. Basic Study Design

Patients in this study were enrolled from two feeder studies, Studies A1371041 and A1371047. All qualified subjects in this study initially received 7.5mg darifenacin daily which was increased to 15mg daily after 2 weeks, for a total study duration of 24 months. Ten clinic/evaluation visits were pre-specified (at baseline, 2 weeks and every 3 months for 24 months).

2. Demographics

As of the interim cut-off date 716 patients were available for the analysis of safety. This group was predominantly female (14.9 % males and 85.1 % females) and middle-aged (mean age 57.6 years; range 20-89 years).

3. Exposure

Overall the median duration of treatment was 549 days (range 3-737 days). As reported by the sponsor, a total of 600 subject-years of exposure has been accured in the 716 subjects, resulting in an average of 0.84 years of exposure per subject. The median duration of treatment with darifenacin is close to one year. Approximately 10% of subjects have completed 18 months of treatment (see Table 17).

4. Subject Disposition

A total of 154 subjects (21.5%) have prematurely discontinued from Study 2031/1042. Most of the discontinuations occurred during the first six months of long-term treatment. Out of 578 patients who completed six months of treatment, only 30 (5.2%) discontinued upon further long-term treatment and follow up, suggesting no tolerability issues in those patients who tolerated an initial six months of therapy. Of note, the discontinuation rate was higher in subjects aged 65 years and older (26%) compared to subjects less than 65 years of age (20%). The reason for this difference in study discontinuation is primarily due to discontinuations due to adverse events in the older age group (11.8% versus 4.8%).

Table 17. Duration of treatment and number of subjects in Long-Term, Open-Label Study 2301/1042

Duration of treatment (days)	Number of patients
1	0
2-14	15
25-28	17
29-90	46
91-180	53
181-270	34
271-364	24
365-454	43
≥455	484

5. Adverse Events

The total number of subjects included in safety analysis was 716. The most commonly reported all-causality adverse events reported during long-term darifenacin treatment were dry mouth, constipation and dyspepsia (Table 18). The reporting rates of dry mouth and constipation in the all-subject analysis were 18.2% and 15.8%, respectively, which are rates comparable to or slightly lower than what was previously seen in the original, fixed-dose, phase 3, placebo-controlled studies and in all phase 2/3 OAB/IBS studies (Table 19).

Many reported adverse events that were reported at low incidences were not unexpected in the long-term follow-up of a study population with the demographic characteristics for the OAB indication. For example, the reported rates for the cardiovascular adverse arrhythmia, palpitations and tachycardia, were 0.1%, 0.7%, and 0.3%, respectively. This cardiovascular profile is similar to what was observed in darifenacin and placebo-treated subjects in phase 2/3 OAB/IBS clinical programs. The reporting rates for the neurological adverse events dizziness and somnolence, were 1.3% and 0.6%, respectively. These event rates were also comparable to or lower than those observed in darifenacin/placebo treated subjects in phase 2/3 OAB/IBS clinical programs (2.7%, and 1.1% for darifenacin-treated subjects for dizziness and somnolence, respectively, versus 2.1%, and 1.2% for placebo-treated subjects).

Table 18: Most Commonly Reported Adverse Events in Study 2301/1042

Adverse Event Term	Study 1042 7.5/15mg N=716 N(%)	Phase 3 Fixed- Dose 7.5/15mg N=671 N(%)	Phase 3 Dose-Titration 7.5/15mg N=268 N(%)	Phase 2&3 Darifenacin All Doses N=5398 N(%)	Phase 3 Placebo N=1910 N(%)
Dry Mouth	130(18.2)	186(27.7)	50(18.7)	2236(41.4)	224(11.7)
Constipation	113(15.8)	121(18.0)	56(20.9)	1227(22.7)	129(6.8)
Headache	29(4.1)	32(4.8)	18(6.7)	467(8.7)	170(8.9)
Dyspepsia	38(5.3)	37(5.5)	12(4.5)	461(8.5)	54(2.8)
Ur.Retention	4(0.6)	1(0.1)	0(0.0)	43(0.8)	3(0.2)
Abn. Vision	7(1.0)	7(1.0)	3(1.1)	240(4.4)	43(2.3)
Dizziness	9(1.3)	10(1.5)	5(1.9)	145(2.7)	40(2.1)
Somnolence	4(0.6)	4(0.6)	2(0.7)	61(1.1)	23(1.2)
Accidental Injury	17(2.4)	8(1.2)	8(3.0)	91(1.7)	21(1.1)

For all subject in Study 1042, the event rate of bone fracture was approximately 0.3%.

Four subjects reported urinary retention in Study 2301/1042, representing 0.6% and 1.2% of the subjects in all 1042 subjects, compared to 0.8% and 0.2% of the darifenacin-treated and placebo-treated patients respectively in phase 2/3/OAB/IBS studies.

The adverse event profile during long-term darifenacin treatment was further evaluated by the dose titration patterns. Out of 716 enrolled subjects, a total of 194 subjects (27.1%) stayed on 7.5 mg, 361 subjects (50.4%) titrated upward to 15 mg dose and stayed at the 15 mg dose level, and 161 subjects (22.5%) had further titrating. The incidence rates for commonly reported adverse events by dose are shown in Table 19. The event rates in the long-term study were generally similar to what was seen of the respective dose groups in phase 3, fixed-dose studies and in placebo.

Table 19: Commonly Reported Adverse Events by Dose, Study 2301/1402

Adverse Event Term	Study 1402 7.5mg N=194 N(%)	Study 1402 15mg N=361 N(%)	Study 1402 Mixed N=161 N(%)	Phase 3 Fixed 7.5mg N=337 N(%)	Phase 3 Fixed 15mg N=334 N(%)	Phase 3 Fixed Placebo N=388 N(%)
Dry Mouth	26(13.4)	60(16.6)	44(27.3)	68(20.2)	118(35.3)	32(8.2)
Constipation	31(16.0)	54(15.0)	28(17.4)	50(14.8)	71(21.3)	24(6.2)
Headache	8(4.1)	14(3.9)	7(4.3)	15(4.5)	17(5.1)	21(5.4)
Dyspepsia	5(2.6)	21(5.8)	12(7.5)	9(2.7)	28(8.4)	10(2.6)
Accidental Injury	4(2.1)	7(1.9)	6(3.7)	4(1.2)	4(1.2)	2(0.5)

The adverse event profile during long-term darifenacin treatment was further evaluated for age. Out of 716 enrolled subjects, a total of 496 subjects (69.3%) were less than 65 years of age and 220 subjects (30.7%) were 65 years or older. The occurrence rates of the more common adverse events in Study 1042 (reported by ≥ 2% subjects in either age group) are shown in Table 20. Age differences in event rates for dry mouth, constipation, and dyspepsia were minimal in this long-term study. However, the incidence of urinary tract infections was higher in the older group. Age differences in two events of special interest, accidental injury and urinary retention were small.

Table 20. Adverse Events Reported By Age

Adverse Event Term	Study 1402 Age <65 Years 7.5/15mg N=496 N(%)	Study 1402 Age ≥65 Years 7.5/15mg N=220 N(%)
Dry Mouth	89(17.9)	41(18.6)
Constipation	77(15.5)	36(16.4)
Urinary Retention	2(0.4)	2(0.9)
Dyspepsia	24(4.8)	14(6.4)
UTI	24(4.8)	17(17.7)
Accidental Injury	10(2.0)	7(3.2)

Overall, the rate of reporting any adverse event with long-term exposure in study 2301/1042 was slightly higher in the older age group compared to the younger age group, 59.5% versus 65.5%.

> *Reviewer's Comment: In the opinion of this reviewer, darifenacin is associated with commonly reported anticholinergic side effects such as dry mouth, constipation, dyspepsia and urinary retention. The analysis and severity of these adverse events, as reported in short and long-term studies, appears no different than any other drug in its class. These events can be bothersome to patients, but they rarely lead to significant clinical consequences and resolve when the drug is discontinued. It is therefore reasonable to expect that the majority of patients and prescribers would be able to recognize these events and stop taking the medication if and when necessary. Therefore, this reviewer has no major concerns regarding the adverse events listed above.*

6. Deaths

There have been a total of four deaths in the darifenacin clinical program. Three deaths were among darifenacin-treated patients and one in the placebo-treated patient group. No death was attributed to study drug. Since the original NDA submission, one additional death was reported recently in the long-term safety study DAR328A2301/1042.

Subject 1057/410891, a 50 year old male entered the extension study and began open-label treatment with darifenacin 7.5 mg once daily on 06-Sep-2002. His dose was increased to 15 mg once daily on [redacted] The patient's history included obesity, osteoarthritis, allergic rhinitis, and hypogonadism. Concomitant medications included

budesonide, ibuprofen, paracetamol, and testosterone. Four weeks later, the patient was hospitalized with abrupt onset of headache and nausea consistent with intracerebral bleeding. He also had left arm weakness. CT scan confirmed cerebral hemorrhage, possible metastatic malignant melanoma and lesions in the lung. A right frontal craniotomy and excision of a hemorrhagic intraventricular tumor was performed on [ ] and a ventricular drain was inserted. A postoperative CT scan on [ ] indicated remaining tumor and on [ ] a pathology report of the brain specimen confirmed the diagnosis of malignant melanoma. No obvious primary source of the melanoma was found. The patient was discharged from the hospital on [ ]

Initially, the investigator had discontinued the study drug on [ ] due to the above event. However, after consultation with the investigator the patient resumed study medication on [ ] because the patient had strongly requested to remain on the study drug due to marked improvement in his incontinence and general quality of life. The investigator decided to allow the patient to resume the study drug as it was felt that patient's safety was not compromised by continuing the study drug and due to the patient's poor prognosis, it was in the best interest of the patient's quality of life to continue on the study. The investigator did not consider this event to be related to study drug, and the causality was attributed to primary melanoma (source unknown).

On [ ] a CT scan confirmed metastases in chest, abdomen and pelvis. Radio and chemotherapy were administered. On [ ] the patient presented with pneumonia of the right lower lobe and right middle lobe and was admitted to hospital. The patient completely recovered from the pneumonia on [ ] On [ ] the patient died and the final diagnosis was metastatic melanoma with secondary hemorrhages.

> *Reviewer's Comment*:
> *It is the opinion of this reviewer that the cause of death in patient 1057/410891 was from metastatic malignant melanoma. This reviewer also agrees that it was in the best interests of the patient to continue the study medication as desired by the patient himself, even after the diagnosis of metastatic melanoma was established.*

7. Serious Adverse Events

A total of 21 SAE's in the entire darifenacin clinical program were judged by the investigator to be related to treatment with darifenacin. Considering only those subjects with OAB, a total of one, four, and nine SAE were recorded in subjects taking 7.5 mg, 15 mg, and 30 mg darifenacin, respectively. In the placebo group, four SAE's were judged by the investigator to be related to treatment.

Among the five serious adverse events reported in OAB patients taking the recommended dose, only one is notable. This suspected treatment-related case was a case of constipation that occurred during the long-term safety study 2301/1042. The patient profile and event history are discussed below.

Subject 1142/410214, a 69 year old female patient entered the extension study and began open-label treatment with darifenacin 15 mg/day on 12-Apr-2002. Her medical history included cataracts, hypercholesterolemia, hypertension, musculoskeletal pain, and myocardial ischemia. Concomitant medications included isosorbide, amlodipine, and perindopril. On [ ], the patient was admitted to the hospital for evaluation of chronic constipation (duration 9 months) of moderate severity. A colonoscopy was performed which showed a small polyp. A specimen for histo-pathological examination was taken. The patient was discharged from the hospital on [ ] The constipation was moderate and required pharmacotherapy with bisacodyl since [ ] The investigator did not suspect a relationship between the colonic polyp and the study medication. At the time of the report, her condition was stable.

> *Reviewer's comment*:
> *This reviewer agrees with the investigator's determination that the study drug did not contribute to development of a colonic polyp.*

Of note, the serious adverse event reporting for darifenacin from the most recent reporting period (July 31, 2003 to July 31, 2004) as compared to the time period prior to July 31, 2003 is unchanged. In addition, the most recent serious adverse event reporting in this open-label study was no different than what was seen in the original, fixed-dose, phase 3, placebo-controlled studies and in all phase 2/3 OAB/IBS studies.

G. Summary and Conclusions Regarding the Open-Label Safety Study

- **A total of 600 subject years of exposure to darifenacin 7.5mg or 15 mg has been accrued in 716 subjects enrolled in the long-term safety Study 2301/1042. A total of 322 subjects have been continuously exposed for one year or longer.**

- **The discontinuation rate of 21.5% or 25.6 per 100 subject years of exposure, and the rate of discontinuation due to adverse events, 6.4% or 7.7 per 100 subject years of exposure, are consistent with that observed previously for 7.5mg/15 mg during the darifenacin development program.**

- **Half of the discontinuations occurred during the first three months of treatment. The discontinuation rate decreased over time, suggesting that long-term treatment of darifenacin was well tolerated.**

- **The incidence of discontinuation due to adverse events in the age subgroup of subjects ≥65 years was slightly higher than that of subjects < 65 years of age. However, the placebo-treated subjects in the original, fixed-dose, phase 3 studies exhibited the same pattern. No increased risk as demonstrated by discontinuations due to adverse events was seen in the subgroup of subjects ≥ 65 years of age.**

- **The overall rate of any adverse events with long-term exposure was marginally higher in the age group of ≥65 years as compared to the subgroup of < 65 years, 65.5% versus 59.5%. Age differences in the adverse event rates for dry mouth,**

constipation, and dyspepsia were minimal in the long-term study 2301/1042, as well as in the phase 3, fixed-dose studies.

- **The adverse event rates during long-term treatment of 7.5/15 mg darifenacin have been similar to or lower than that observed for 7.5/15 mg during the darifenacin development program, with 18.2% for dry mouth, 15.8% for constipation and 5.3% for dyspepsia.**

- **The rates of newly reported adverse events decreased over time, suggesting very low risk of late-onset adverse events.**

- **The only death reported since the original NDA submission occurred in a patient due to widespread metastatic melanoma.**

- **No increase in the incidence of serious adverse events has been observed. There was only one new serious adverse event of note, i.e., a case of chronic constipation, where the patient required hospitalization for investigation.**

In conclusion, therefore, the safety data from long-term treatment with darifenacin, as submitted in this Response, is consistent with that presented in the original NDA. There is no evidence to suggest a safety concern associated with long-term treatment with darifenacin 7.5mg or 15 mg once daily.

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/s/

Suresh Kaul
12/21/04 09:15:15 AM
MEDICAL OFFICER

Mark S. Hirsch
12/21/04 09:51:02 AM
MEDICAL OFFICER
I concur.

NDA 21-513 ENABLEX™

Application Information

NDA #:	21-513
Sponsor:	Novartis Pharmaceuticals Corporation
Clock Date:	October 3, 2003
Review Status:	Standard (10 Months)
Related IND and NDA:	IND 45,457

Drug Name

Generic Name:	Darifenacin hydrobromide
Proposed Trade Name:	ENABLEX™

Drug Categorization

Chemical Classification:	New Molecular Entity (NME)
Pharmacological Class:	Selective muscarinic M_3 receptor antagonist
Proposed Indication:	Treatment for Overactive Bladder
Proposed Dose Regimen:	7.5mg and 15mg once daily
Strength and Dosage Forms:	7.5mg and 15mg extended release tablets
Route:	Oral

Reviewer Information

Clinical Reviewer:	Zili Li, MD, MPH
Medical Team Leader:	Mark Hirsch, MD
Completion Date:	September 25, 2003

CLINICAL REVIEW

Executive Summary Section

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Clinical Review for NDA 21-513

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a clinical standpoint, the evidence presented in this NDA submission is substantial and adequate in support of the effectiveness of darifenacin 7.5mg and 15mg for the treatment of overactive bladder in men and women of 18 years of age or older in the US. The adverse events profile of darifenacin appears to be similar to that of other marketed drugs in the same drug class. While safety evaluation, in general, meets ICH guidance in terms of the number of subjects exposed to darifenacin and the exposure duration, ECG data presented in this NDA does not allow this reviewer to confirm QT safety of this new drug with assurance at a range of plasma concentrations that is clinically relevant. The need for a high degree of assurance is supported by the drug's QT prolonging potential identified in pre-clinical studies and a possible drug-associated QT prolongation identified in two human PK/PD studies.

From a clinical perspective, this reviewer recommends that darifenacin for the treatment of overactive bladder indication receive an **approvable action**. The primary deficiency is: "lack of QT safety data from an adequate and well controlled clinical PK/PD study to rule out a clinically important QT prolongation at the range of plasma concentration that are clinically relevant". This is particularly true for those subjects who may take darifenacin and a potent CPY3A4 inhibitor together. This deficiency can be corrected by the sponsor's conducting an adequate, prospectively designed QT safety study. A brief discussion of the study design and conduct can be found under the Section X of this review.

Other clinical efficacy and safety issues that require further discussion with sponsor include:

? lack of direct clinical data to support the effectiveness of darifenacin 7.5mg and 15mg for the treatment of overactive bladder in the non-white population;

? a higher incidence of bone fracture requiring hospitalization in darifenacin-treated subjects, compared to placebo-controlled subjects, and

? the drug's potential to cause severe constipation and acute urinary retention, and labeling and risk management plans for these two adverse events.

In the opinion of this reviewer, these issues can be resolved through a combination of a Phase 4 study commitment, appropriate risk assessment and management program, and adequate product labeling. The proposed recommendations can be found under the Sections I (B) and/or X of this review.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

1. Phase 4 study commitments:
   A. The sponsor should conduct an adequate and well controlled clinical investigation to confirm the effectiveness of darifenacin for the treatment of overactive bladder in an appropriate non-white population;
   B. The sponsor should conduct a large simple safety trial to investigate the relationship between darifenacin and bone fractures.

2. Risk Management Program:
The sponsor should submit an adequate risk management plan, towards preventing serious sequelae of constipation and acute urinary retention that is possible with darifenacin . A detailed discussion of this requirement can be found under Section X.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Darifenacin (Enablex) is a selective anti-muscarinic M3 receptor antagonist for oral administration. The sponsor requested an approval of darifenacin 7.5mg and 15mg extended release tablets for the treatment of overactive bladder (OAB). [

]

As of 11 October 2002, the sponsor had completed a total of 94 Phase 1, 2 and 3 human clinical trials in the US and worldwide for [ ] OAB [ ]
A total of 6,655 subjects were exposed to at least one dose of darifenacin up to 60mg once daily with a cumulative exposure of 1,462 person-years. Of those 6,655 subjects, 5,398 enrolled into darifenacin groups of 38 Phase 2 and 3 clinical studies, including 601 and 363 subjects who were exposed to darifenacin for at least 6 months and 12 months, respectively. In addition, 792 subjects were treated with an active comparator and 1,910 with placebo.

For the efficacy determination, the sponsor has requested the Agency to consider the evidence presented in three Phase 3 controlled clinical studies in which OAB

patients were treated with a daily dose of darifenacin 3.75, 7.5, 15, and 30mg for 12 weeks (Study 1001, 1002 and 1041). A total of 337, 334 and 388 male and female OAB patients of 18 years of age or older were enrolled into darifenacin 7.5mg, 15mg and placebo groups of these three clinical studies. Additionally, a Phase 3 dose-titration study of 7.5mg to 15mg was also submitted for review (Study 1047).

B. Efficacy

The Agency has determined that all three Phase 3 studies (Study 1001, 1002 and 1041) were adequate and well controlled studies (pivotal studies) in support of this new drug application (NDA). The design and conduct of three studies were similar except that Study 1001 is the only study that included patients from US sites. Darifenacin 7.5mg was only studied in two of three pivotal studies (Study 1002 and 1041). Study 1047 (the titration study) included 7.5mg and was conducted in the US and Canada.

The primary endpoint of the studies was the change in average number of incontinence episodes per week from baseline to Week 12. This endpoint was thought to be appropriate and clinically meaningful. Based on the data presented in this NDA, this reviewer has concluded that the evidence is adequate and substantial in support of the effectiveness of darifenacin 7.5mg and 15mg for the treatment of overactive bladder in men and women of 18 years of age or older in the US, as demonstrated by darifenacin's ability in reducing incontinence episodes, urgency episodes, and micturition frequency.

The main efficacy conclusions are as follows:

- Over a 12-week treatment period, darifenacin 7.5mg and 15mg were associated with a median reduction of 2.0 and 3.2 incontinence episodes per week, respectively, from baseline. Statistical significance was achieved in two of three pivotal clinical studies at a predefined level.
- If a 50% reduction in incontinence episodes from baseline was used to define a clinical responder, the number needed to treat (NNT) was seven. In other words, seven OAB patients need to be treated for 12 weeks in order to produce one clinical responder. NNT for both darifenacin 7.5mg and 15mg dosages was the same;
- The treatment effect was observed as early as at Week 2. At this time, no controlled data are available to support the long-term effectiveness of the darifenacin 7.5mg and 15mg for the treatment of overactive bladder.
- For subjects treated with darifenacin 7.5mg or 15mg, the magnitude of the treatment effect was higher in female subjects and in older subjects (65 years of age or older). For subjects treated with darifenacin 15mg, the magnitude of treatment effect appeared to be greater for those who had more severe incontinence symptoms (> 21 incontinence episodes per week) at baseline. This difference was not observed for subjects treated with darifenacin 7.5mg.

? In addition to the reduction in the number of incontinence episodes, darifenacin 7.5mg and 15mg were also associated with reduction in number of micturitions and number of episodes of urgency. The treatment effect was approximately a change of 0.8 episode per day for both outcomes. The effect did not appear to be dose dependent;

Based on the data presented in this NDA, this reviewer believes that there is reasonable evidence to support the conclusion that that darifenacin 7.5mg is the minimally effective dose for the treatment of OAB from a clinical perspective.

C. Safety

As of 11 October 2002, a total of 6,655 subjects were exposed to at least one dose of darifenacin up to 60mg once daily with a cumulative exposure of 1,462 person-years. The safety evaluation, in general, appears to be adequate in terms of the number of subjects exposed to darifenacin and the exposure duration. The only deficiency in term of adequacy of safety testing was in the area of QT safety assessment.

The sponsor provided a pooled analysis from four clinical studies (two Phase 1 and two Phase 3 studies) to support QT safety of darifenacin. While no apparent safety signal was identified from the pooled analysis, a mean increase of 12 ms in QTcF from baseline was observed in 16 subjects treated with darifenacin 30mg and ketoconazole 400mg for 6 days in one of the four studies (Study 1007). The mean plasma concentration at time of ECG measurements was 103ng/ml. Due to lack of appropriate control groups in the study, no final conclusion can be made at this time regarding the clinical significance of this observation and whether the increase was caused by darifenacin. The possibility that darifenacin could cause a clinically significant QT prolongation at this plasma concentration, however, cannot be reasonably excluded, given that darifenacin inhibited HERG, competed for dofetilde binding sites, and increased action potential duration in pre-clinical studies.

Because of both pre-clinical and clinical findings, this reviewer believes that a high degree assurance is needed to confirm QT safety in a range of darifenacin plasma concentrations that is clinically relevant. The sponsor has argued that QT safety is supported by a placebo-controlled Phase 1 PK/PD study in which a total of 38 male and female subjects treated darifenacin 60mg once daily for 14 days . The mean change from baseline in QTcF after adjusting for placebo effect was 3 ms which was not statistically significant, and the mean plasma concentration of darifenacin at time of ECG measurements was approximately 45ng/ml. Due to lack of a positive control in the study design, this reviewer cannot conclude that darifenacin is not associated with a clinically significant QT prolongation at this plasma concentration based upon the results. Even if darifenacin is safe at this plasma concentration, there is still no assurance that this plasma concentration

represents the upper limit of a range that is clinically relevant. Preliminary data has suggested an individual's plasma concentration can easily exceed this limit if darifenacin 7.5mg or 15mg is co-administered with ketoconazole 400mg together.

Assurance of QT safety for darifenacin can only be met, in the opinion of this reviewer, by evidence presented in a "thorough" QT study with a positive control group. The dose tested should be sufficiently high to ensure QT safety in a range that is clinically relevant.

Other important safety-related findings are as follows:

- Dry mouth, constipation and dyspepsia were the three most frequently reported adverse events and they occurred in 20%, 15% and 3% of subjects treated with darifenacin 7.5mg for 12 weeks in three OAB pivotal trials;
- The majority of adverse events typically occurred in the first two weeks of treatment and they were dose-dependent. For subjects treated with darifenacin 15mg for 12 weeks, the incidence of the three most frequent adverse events increased to 35%, 21% and 8%, respectively;
- While the majority of adverse events were mild to moderate at onset, some adverse events had a significant percentage rated as severe (such as 17-33% of patients with dyspepsia rated the symptoms as severe);
- While the median duration for the majority of adverse event episodes was relatively short, some can last a long time. Despite anti-constipation treatment, 7 out of 11 subjects who developed severe constipation still suffered from the event at the end of the study;
- In three OAB pivotal studies, 5.6% and 12.9% of patients prematurely discontinued from the studies due to an adverse event in darifenacin 7.5mg and 15mg groups, respectively, compared to that of 8.0% in the placebo groups;
- Darifenacin appears to be associated with UTI though none of the subjects discontinued from the study or were hospitalized due to UTI. In three OAB pivotal studies, the incidence of UTI was 4.5-4.7% for the subjects treated with darifenacin 7.5 or 15mg, respectively, compared to that of 2.6% in the placebo groups;
- Darifenacin appears to be associated with the occurrence of urinary retention. Though the incidence of urinary retention was low (0.2%) in subjects treated with darifenacin in three OAB pivotal trials, one female subject in darifenacin clinical development program developed acute renal failure as a consequence of urinary retention 40 days after the initiation of darifenacin 7.5mg treatment, and six patients developed acute urinary retention requiring medical interventions;
- Of 6,655 darifenacin-treated subjects (1462 person years) in darifenacin clinical development program, 16 had a bone fracture requiring hospitalization though none of those events were assessed by PI as drug- related. No such a report was received in 2,216 subjects who received placebo (329 person years);

? Darifenacin does not appear to be associated with a clinically significant increase in liver enzymes. One subject in the darifenacin clinical development program had ALT > 10 times ULN without hyperbilirubinemia.

In the opinion of this reviewer, the sponsor needs to design and conduct a large simple safety study to investigate the relationship between darifenacin and accidental fall and/or bone fracture requiring hospitalization.

The sponsor also needs to develop a risk management plan towards preventing serious outcomes from drug-induced constipation and urinary retention, such an intestinal obstruction or acute renal failure.

The risk of constipation, acute urinary retention and UTI needs to be adequately stated in the product labeling. In the opinion of this reviewer, a warning or precaution would be appropriate.

D. Dosing

The sponsor proposes a starting dose of darifenacin 7.5mg once daily orally without regard to meals. The sponsor also stated that "for those patients starting on 7.5 mg daily and requiring greater symptom relief, the dose may be increased to 15 mg daily, as early as two weeks after starting therapy, based on individual response".

From an efficacy perspective, both darifenacin 7.5mg and 15mg once daily are efficacious for the treatment of OAB. Darifenacin 15mg appears to be associated with a greater improvement in number of incontinence episodes, compared to that of darifenacin 7.5mg (a reduction of 3.2 v.s 2.0 episodes per week from baseline, respectively). Such a dose-related improvement, however, was not noted for micturition or urgency endpoints.

It is possible that subjects who fail to respond to darifenacin 7.5mg may respond to darifenacin 15mg. It has not been demonstrated. however, that the subjects who respond to darifenacin 7.5mg would get "greater symptom relief" if they would have increased the dose to 15mg.

Common adverse events, such as dry mouth, constipation, dyspepsia appear to be dose related. Although the adverse event profile of darifenacin 7.5mg appears to be superior to that of darifenacin 15mg, availability of darifenacin 15mg to US market would not, in the opinion of this reviewer, significantly change overall benefit and risk ratio of this product. Unless a dose restriction is required due to a future safety concern, this reviewer recommends that both darifenacin 7.5mg and 15mg be made available to the US market.

This reviewer proposes the following statement for this section of the product labeling: [redacted]

E. Special Populations

Age, gender and ethnicity: Table II-E-1 shows the demographics for the subjects who participated in the darifenacin 7.5mg, 15mg and placebo groups of the three pivotal Phase 3 studies (Study 1001, 1002 and 1041). The patient population was predominantly white (94-96%) and female (84-85%). Approximately one third of the study participants was 65 years of age or older. It appears that the non-white population was under-represented in the NDA. While there is little reason to suspect that non-white population would have responded differently to darifenacin treatment, eventually such a statement needs to be confirmed by evidence from an adequate and well controlled study.

Table II-E-1 Demographics in the three Phase 3 pivotal studies (Study 1001, 1002 and 1041)

Demographics	Treatment Group		
	Darifenacin 7.5mg (n=337)	Darifenacin 15mg (n=334)	Placebo (n=388)
Number and percent of Female	288 (85%)	281 (84%)	331 (85%)
Number and percent of White	324 (96%)	320 (96%)	366 (94%)
Number of percent of 65 years of age or older	97 (29%)	110 (33%)	110 (28%)

Source Data: Table 2.1.1 of final study report of Study 1001, 1002 and 1041.

Table II-E-2 shows the treatment effect of darifenacin 7.5mg and 15mg in reducing the number of incontinence episodes per week by age and gender. Data appears to suggest that female subjects and subjects of 65 years of age or older would have a greater improvement, compared to their counterparts. Despite the differences, the only concern of this reviewer was the inconsistency in the direction of treatment effects observed in male subjects treated with darifenacin 7.5mg, compared to that of all other groups. This may become a problem if darifenacin 15mg cannot be approved for any reason. In that case, a separate clinical study in an appropriate male population may be needed to demonstrate the effectiveness of darifenacin 7.5mg for the treatment of OAB in male population.

Table II-E-2 Treatment effect of darifenacin 7.5mg and 15mg in reducing number of incontinence episode per week by age and gender

Treatment Group	Age		Gender	
	< 65	≥ 65	Female	Male
7.5mg	-1.0	-5.9	-2.7	1.0
15mg	-2.8	-4.1	-3.7	-1.3

Source Data: Table VI-C-8.1 and 8.2 of this NDA review.

Pregnancy and Nursing Mothers: Women who were pregnant or breast-feeding and women of childbearing potential who were not using a medically accepted means of contraception were excluded from participating in all darifenacin clinical trials. As a result, information on darifenacin-exposed pregnancy is limited. Of 6,655 subjects exposed to at least one dose of darifenacin, only two women known to be pregnant while being treated with darifenacin. No pregnancy-related outcomes were reported.

Darifenacin is excreted into the milk of lactating rats. Excretion of darifenacin into human milk has not been studied and breast-feeding while being treated with darifenacin is not recommended.

Renal Insufficiency: A study of subjects with varying degrees of renal impairment (creatinine clearance between 10 and 136ml/min) given darifenacin 15 mg once daily to steady-state demonstrated no relationship between renal function and darifenacin clearance.

Comments: *The sponsor proposed that* [redacted] *The clinical pharmacologist agreed with this statement. This reviewer has no objection to this statement, since only a small fraction of darifenacin is excreted through the kidney unchanged.*

Hepatic Insufficiency: Darifenacin pharmacokinetics were investigated in subjects with mild (Child Pugh A) or moderate (Child Pugh B) impairment of hepatic function given darifenacin 15 mg once daily to steady-state. Mild hepatic impairment had no effect on the pharmacokinetics of darifenacin. After adjusting for plasma protein binding, unbound darifenacin exposure was estimated to be 4.7-fold higher in subjects with moderate hepatic impairment than subjects with normal hepatic function. Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Comments: *The sponsor proposed that "the daily dose of darifenacin should not exceed 7.5 mg once daily for patients with moderate hepatic impairment (Child Pugh B).* [redacted]

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Darifenacin, a selective muscarinic M_3 receptor antagonist, is proposed to be indicated for the treatment of overactive bladder (OAB). While the clinical development program for darifenacin in OAB used both the immediate release (IR) and a controlled release (CR or extended release) formulations, the sponsor only requests the approval of two CR dosage formulations: 7.5mg and 15mg CR tablets. The OAB Phase 3 program used only the CR formulation.

The sponsor proposed a trade name of ENBLEX for darifenacin, which has been approved by ODS/DMETS, with the following treatment indication: "ENABLEX once daily Extended Release Tablets are indicated for the treatment of overactive bladder. Symptoms of overactive bladder include urgency, urge urinary incontinence, frequency and nocturia".

The proposed starting dose of ENABLEX Extended Release Tablets is 7.5 mg once daily without regard to meal. The sponsor also stated that ' [redacted]

]

The sponsor proposed no special dosing requirements for elderly patients, for patients with renal impairment or for patients with mild hepatic impairment (Child Pugh A). It was stated that the daily dose of ENABLEX should not exceed 7.5 mg for patients with moderate hepatic impairment (Child Pugh B) or when co-administered with potent CYP3A4 inhibitors.

B. State of Armamentarium for Indication(s)

The overactive bladder (OAB) syndrome was recently defined by the International Continence Society (ICS) as a medical condition consisting of the symptoms of urinary urgency and frequency, with or without urge urinary incontinence, when appearing in the absence of local pathological factors. This condition, now knows as overactive bladder, has had various different terminologies in the past, including bladder dyssynergia, detrusor instability,

uninhibited detrusor, and unstable bladder. While overactive bladder is still not a universally accepted term in the medical community even at this time, the introduction of this standardized terminology has provided a foundation for a better measurement of the prevalence and impact of this medical condition.

OAB prevalence data is not available for CDC's National Health Interview Survey. Based on a telephone interview of 5,000 English speaking adults in the US (18 years of age or older), it was estimated that the prevalence of OAB was approximately 16.9 % in women and 16.0% in men in the US. A similar survey in Western Europe revealed a prevalence of 16.6% for adults of 40 years of age or older.

The two main treatment options for overactive bladder are bladder retraining and anticholinergic drugs. By blocking the parasympathetic pathway, the anticholinergic drugs attempt to reduce the irregularity of detrusor muscle contraction, which is believed to be the underlying abnormality in OAB patients.

Currently two anticholinergic drugs (tolterodine and oxybutynin) have been approved for the treatment of overactive bladder in the US adult population. Both drugs have a controlled release formulation available. The studies showed that tolterodine 4mg once daily was associated with a mean reduction of 4.8 incontinence episode per week from baseline and placebo. There are no long-term effectiveness data available for either drug.

C. Important Milestones in Product Development

3 June 1994	Initial IND 45,457 opened for studying [ ] indication;
[	IND]
	[ ]
1 June 1999	End of Phase 2 Meeting (EOPII Meeting) for OAB indication
14 December 2000	The sponsor requested that the proposed indication for IND 45,457 be changed to "overactive bladder" (OAB)
18 June 2002	Pre-NDA meeting for OAB indication
December 2002	Submission of NDA 21,513 for OAB indication

Darifenacin has not been approved or marketed in any countries at this time.

D. Other Relevant Information

None

E. Important Issues with Pharmacologically Related Agents

As stated earlier, two pharmacologically related agents have been approved and are currently marketed in the US. Table I-E-1 provides basic information on the two drugs. They are non-selective anti-cholinergic antagonists and the both have extended release formulation available. The magnitudes of treatment effects and frequency of common adverse events are not presented because the cross-study comparisons of efficacy and common adverse events among the three products are inappropriate, given the differences in the study design, conduct and populations.

Table I-E-1. Drug products (controlled release only) that are currently marketed for the treatment of OAB in the US

Drug Products	Detrol LA	Ditropan XL
Generic Name	Tolterodine	Oxybutynin
Formulation	Capsule	Tablet
Dosages	2 and 4 mg	5, 10 & 15mg

The most common adverse events are dry mouth and constipation. Other clinically significant events include urinary retention and vision abnormality.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Clinically relevant findings from the reviews of other disciplines are as follows:

1. **Chemistry:** Both 7.5mg and 15mg tablets are acceptable from a chemistry perspective.

2. **Pharmacology and Toxicology:** The clinically relevant findings are as follows:
   - ? Based on pre-clinical data, there is strong evidence to support that darifenacin is a highly selective M3 receptor antagonist;
   - ? Pre-clinical data suggest that darifenacin has a potential to cause QT prolongation. At a plasma concentration of 357ng/ml, darifenacin was associated with a statistically significant increase (9.9%) in monophastic action potential duration from baseline in an in vivo dog study (N=4). At a plasma concentration of 107 ng/ml, little effect was observed.
   - ? Pre-clinical data suggest no other safety concerns or potentials that were not observed in human clinical trials;

3. **Biostatistics:** The statistical reviewer concurs with the sponsor and this reviewer's statistical analysis of the three pivotal studies.

4. **Clinical pharmacology:** At time of this review, the clinical pharmacologist had not made final recommendations in regard to QT safety and use of the drug in patients with hepatic impairment.

5. **Office of Drug Safety:** The ODS has recommended approval for the trade name of Enablex.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The basic PK profile of darifenacin is as follows:

- ? Darifenacin is rapidly and completely (>98%) absorbed after oral administration. The estimated mean oral bioavailability of darifenacin in EMs at steady-state is 15% and 19% for 7.5 and 15 mg extended release tablets, respectively.
- ? Following administration of the extended release tablets maximum plasma levels are reached approximately 7h after dosing;
- ? The estimated $T_{1/2}$ for the extended release table is 12.8 to 18.7 hrs and steady-state plasma levels are achieved by the sixth day of dosing;
- ? Darifenacin is 98% bound to plasma protein, primarily to ? -1-acid glycoprotein;
- ? Darifenacin's metabolism is mediated by cytochrome P450 enzymes CYP2D6 and CYP3A4.
- ? Following administration of an oral dose of ^{14}C-darifenacin solution to healthy volunteers, approximately 60% of the radioactivity was recovered in the urine and 40% in the feces. Only a small percentage of the excreted dose was unchanged darifenacin (3%).

The following factors may affect the PK profile of darifenacin:

CYP2D6 inhibition: Darifenacin exposure following 30 mg once daily dosing was 33% higher in the presence of the potent CYP2D6 inhibitor paroxetine.
CYP3A4 inhibition: When a 7.5 mg once daily dose of darifenacin was given to steady-state and co-administered with the potent CYP3A4 inhibitor ketoconazole, mean darifenacin exposure was increased 5.3-fold, while individual darifenacin exposures following 15 mg dosing were increased between 10- and 14-fold.

Table III-A-1 and A-2 show mean steady state peak (Cmax) for darifenacin7.5mg and 15mg CR tablets by CPY2D6 genotype and CYP3A4 inhibition.

Table III-A-1 Mean Steady State Peak (Cmax) for darifenacin CR Tablets – a pooled analysis of 20 Phase 1 Studies without CYP3A4 inhibition

Darifenacin Cmax (ng/ml)	Darifenacin 7.5mg	Darifenacin 15mg
EM	1.8 (n=95)	4.8 (n=104)
PM	4.5 (n=6)	9.1 (n=10)

Source Data: Table 5 of 2.5 Clinical Overview

Table III-A-2 Mean Steady State Peak (Cmax) for darifenacin CR Tablet with ketoconazole (CYP3A4 inhibitor) – Study 1035

Darifenacin Cmax (ng/ml)	Darifenacin 7.5mg	Darifenacin 15mg
EM	11.2 (n=10)	67.6 (n=3)
PM	55.4 (n=1)	58.9 (n=1)

Source data: Page 31 and 32 of Final Study Report of Study A1371035

Food - The effect of food on the pharmacokinetic profile of darifenacin was established in three studies. Although co-administration of food with a single 15mg or 30mg CR tablet produced a higher peak darifenacin concentration (C_{max} ratio fed/fasted = 1.22), once darifenacin plasma concentrations had reached steady state, ingestion of food had no effect on the pharmacokinetics of darifenacin.

Age: Modeling suggests that there is a small reduction in the clearance of darifenacin with increasing age (6.2% for every decade).

Gender: A population pharmacokinetic analysis of patient data indicated that darifenacin exposure at steady state was 28% lower in males than in females.

Race: No specific pharmacokinetic study was conducted to investigate the effect of race on the PK profile of darifenacin.

Renal Insufficiency: A study of subjects with varying degrees of renal impairment (creatinine clearance between 10 and 136ml/min) given darifenacin 15 mg once daily to steady-state demonstrated no relationship between renal function and darifenacin clearance.

Hepatic Insufficiency: Darifenacin pharmacokinetics were investigated in subjects with mild (Child Pugh A) or moderate (Child Pugh B) impairment of hepatic function given darifenacin 15 mg once daily to steady-state. Mild hepatic impairment had no effect on the pharmacokinetics of darifenacin. After adjusting for plasma protein binding, unbound darifenacin exposure was estimated to be 4.7-fold higher in subjects with moderate hepatic impairment than subjects with normal hepatic function. Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

A detailed discussion of PK profile of darifenacin and the factors that may affect the PK profile can be found in clinical pharmacologist's review.

B. Pharmacodynamics

Please refer to clinical review section (safety) for a detail discussion on darifenacin's potential effects on QT prolongation and heart rate.

No direct study on orthostatic effects of darifenacin was conducted. However, the sponsor submitted a Phase 1 PK/PD study report (Study 1009) in which orthostatic blood pressures were measured for subjects taking darifenacin and imipramine vs. imipramine and placebo.

This was a randomized, double blind and cross-over clinical trial in which 14 (12 EM and 2 PM) healthy male subjects (18-49 years of age) took imipramine and darifenacin 30mg qd (Period 1) or imipramine and placebo (Period 2) for 12 days each. Imipramine was given 10mg tid for 3 days and then followed by 25mg tid for 7 days.

Orthostatic blood pressures were taken at pre-dose and 2, 4, and 6 hours post dose at Day 1 and Day 10. Table III-B-1 shows summary of mean orthostatic systolic blood pressures for 12 EM subjects at baseline (pre-dose at day 1) and 2, 4 and 6 hours post-dose at Day 10.

Treatment		Baseline	Time Post Dose on Day 10		
			2 hours	4 hours	6 hours
Imipramine + Darifenacin	N	12	12	12	12
	Mean	119.1	117.6	115.6	117.1
	Std. Dev	10.8	13.2	14.1	12.4
Imipramine + Placebo	N	12	12	12	12
	Mean	119.7	118.9	118.9	120.0
	Std. Dev.	8.6	9.7	9.3	12.4

Source Data: Table 5.19.1 of Study Report of Study 1009

Comments: *Data do not suggest that darifenacin 30mg was associated with any orthostatic effect when it was co-administrated with imipramine, compared to imipramine alone. Data provide indirect, but adequate, assurance with regard to orthostatic safety.*

IV. Description of Clinical Data and Sources

A. Overall Data

The review is based solely on the studies conducted by the sponsor in this NDA submission and no information from other sources, such as literature reports, was used in the review. The sponsor requests that the Agency consider the information presented in three Phase 3 studies (Study 1001, 1002 and 1041) as the primary evidence for determining the efficacy and safety of darifenacin 7.5mg

and 15mg once daily for the treatment of overactive bladder (OAB). In addition, a Phase 3 flexible dosing study (Study 1047) was submitted as supporting evidence. For the safety evaluation, data from 94 human Phase 1, 2 and 3 studies were submitted in which a total of 6,655 subjects had been exposed to at least one dose of darifenacin up to 60mg once daily.

B. Tables Listing the Clinical Trials

Table IV-B-1 shows the key Phase 2 and 3 studies used to support the efficacy and safety of darifenacin (CR formulation) for the treatment of overactive bladder.

Table IV-B-1. Phase 2 or 3 studies conducted for overactive bladder indication, CR formulation only

Study Protocol (County)	Length (week)	% of Female (Age)	Total Subjects	Treatment Groups Daily Dose (mg)								
				0	3.75	7.5	7.5/15	15	15/30	30	30/15	45
Phase 3 Fixed Dose Placebo-Controlled Studies												
1001 (US)	12		680	X				X		X		
1002 (Non-US)	12		439	X		X		X		X		
1041 (Non-US)	12		561	X	X	X		X				
Phase 2 and Phase 3 Flexible Dose Placebo-Controlled Studies												
601 (Japan)			60			X		X		X		
312			42	X				X				
315			127	X		X		X		X		X
666			268	X				X		X		
1011	12		561	X							X	
1013	12		229	X					X			
1012 (Japan)	6		389	X		X		X		X		
1019			72	X						X		
1047 (US)	12		395	X			X					
Long-term Open Label Studies												
311			324				X			X		
1041			453							X		
1017 (Japan)	Ongoing		Pending			X		X		X		
1042	Ongoing		Pending				X					

Source Data: Table 1, 2 and 3 of 2.7.3 Summary of Clinical Efficacy and Table 2 of FDA statistical review

C. Postmarketing Experience

Darifenacin is not currently marketed in any country

D. Literature Review

Since darifenacin has not been approved or marketed in any country, all information was submitted by the sponsor. No additional literature review is planned.

V. Clinical Review Methods

A. How the Review was Conducted

The efficacy and safety reviews were conducted separately. Only the three Phase 3 pivotal trials (1001, 1002 and 1041) were considered in determining darifenacin's efficacy for the treatment of overactive bladder. Study 1047 was used to strengthen the applicability of efficacy results to US population. No pooled analysis was allowed for the efficacy determination. Once the efficacy was determined for each individual Phase 3 trial, a pooled analysis of the three Phase 3 studies was employed to provide (1) a more reliable estimate for the magnitude of the treatment effect, and (2) statistical power to conduct a subgroup analysis.

The safety review was not limited to the three pivotal Phase 3 trials but priority was given to OAB trials. Death and serious adverse event cases from all clinical trials regardless of treatment indications were evaluated. A pooled analysis was employed to calculate the frequency of the safety outcomes of interest.

B. Overview of Materials Consulted in Review

All submissions to this NDA were reviewed, including:

1. The original submission of NDA 21513 dated 3 December 2002
2. The 120-day safety update to the original submission dated 16 April 2003
3. The response to 74-day filing letter issue dated 16 April 2003
4. The response to request for information dated 20 August 2003, 5 September 2003, 11 September 2003, 12 September 2003 and 19 September 2003
5. The copy of proposed product labeling dated 29 August 2003

All submissions were made electronically.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The following strategies were employed to evaluate data quality and integrity:

1. Conducted an independent analysis based on the original data sets provided by the sponsor;
2. Examine the patient's safety information (death and serious AE) in Case Report Forms (CRF);
3. Audited a selected number of principal investigator to ensure that the data submitted is consistent with the original records in the physician's office (DSI).

Two clinical sites in Poland associated with this NDA were inspected by DSI which concluded that data submitted in support of this NDA from those sites appeared to be acceptable.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards?

All pivotal studies were conducted in compliance with Institutional Review Board/Independent Ethics Committee (IRB/IEC), informed consent and ICH GCP guidelines. In addition, all local regulatory requirements were adhered to. The studies were conducted according to the revised Declaration of Helsinki (Revised, Somerset West, Republic of South Africa, 1996), and with local laws and regulations relevant to the use of new therapeutic agents in the countries of conduct.

E. Evaluation of Financial Disclosure

Financial disclosure was made from all required studies. The disclosure appears to be adequate and no evidence suggests that financial relationship had any impact on the study findings.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Based on the data presented in this NDA, this reviewer concludes that the evidence is substantial in support of the effectiveness of darifenacin 7.5mg and 15mg for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in men and women of 18 years of age or older.

It needs to be emphasized in the product labeling that the drug is indicated for the treatment of overactive bladder in men and women 18 years of age or older. The effectiveness of the drug for the treatment of overactive bladder in a pediatric population has not been studied.

B. General Approach to Review of the Efficacy of the Drug

General approach to the efficacy review is as follows.

1. Review the proposed indication;
2. Identify all Phase 3 pivotal studies used to support the indication;
3. Conduct a detailed review of each of the pivotal studies;
4. Declare that darifenacin is effective if at least two pivotal trials shows that the drug is efficacious at a predefined level of statistical significance for the primary endpoints. No data pooling from multiple studies or trials is allowed in the efficacy determination;
5. Conduct an appropriately pooled analysis to determine the magnitude of the treatment effect once the efficacy is demonstrated;
6. Conduct an appropriately pooled analysis to determine the factors that may affect the magnitude of the treatment effect;
7. Determine whether a reasonable effort was made to determine the minimally effective dose.

C. Detailed Review of Trials by Indication

1. What is the proposed indication for darifenacin under this NDA?

The sponsor proposed the following treatment indication for ENBLEX:

[ ]

Comments: *This reviewer suggests the following revisions to the proposed indication in order to maintain consistency with treatment indication of the similar drugs in the same drug class, and to emphasize that the effectiveness of darifenacin for the treatment of overactive bladder in a pediatric population has not been studied.*

MO proposed treatment indication:

[ ]

2. What is the evidence that sponsor wishes to use to support the proposed indication?

The sponsor requested that the Agency consider the evidence presented in three randomized, placebo-controlled, fixed dose Phase 3 clinical studies (1001, 1002 and 1041) as the basis of approving darifenacin 7.5mg and 15mg for the proposed indication. These three Phase 3 studies were random zed, double-blind, placebo controlled and fixed dose studies in man and women of 18 years of age or older with the symptoms of overactive bladder. The patients were treated with a dose of darifenacin ranged from 3.75mg to 30mg for a period of 12 weeks, and the

primary endpoints were changes in number of incontinence episode per week from baseline to Week 12. The sponsor also submitted US study 1047, a dose-titration trial, as supporting evidence.

Comments: *This reviewer considers Study 1001, 1002 and 1041 as the pivotal studies for the purpose of determining the effectiveness of darifenacin 7.5mg and 15mg for the treatment of overactive bladder in the US. Study 1047 serves as supporting evidence.*

3. What are the highlights in the design and conduct of the three Phase 3 pivotal clinical studies?

All three pivotal studies were multi-center, double blind, randomized, placebo controlled, parallel group studies of a 12-week duration. They all collected the same primary and secondary efficacy endpoints using the same instrument (an electronic patient diary), had identical key inclusion and exclusion criteria, and utilized a once daily dosing of the controlled release (CR) formulation of darifenacin.

Design: multi-center, randomized, double-blind, placebo-controlled, parallel studies with no stratification.

The studies consisted of three phases and a total of five visits:

? Phase 1: 2-week pre-screening/washout for subjects on excluded medication (Visit 1);
? Phase 2: 2-week treatment free or placebo run-in (Visit 2);
? Phase 3: 12-week double-blind therapy, including randomization (baseline at Visit 3) and then 3 follow-up visits at Week 2, 6 and 12 (Visit 4, 5, and 6).

Key Inclusion Criteria:

Patients were male or female (non-childbearing potential or using effective contraception) and 18 years of age or older. They had to be in good health and capable of taking study medication on an outpatient basis, as well as capable of independent toileting and of independently completing the electronic patient diary.

Patients were expected to have all 3 cardinal symptoms of OAB (urgency, urge incontinence and micturition frequency) for at least 6 months and were expected to exhibit these symptoms at the specified levels as defined below during the run-in period.

? Incontinence: 5-50 episodes of urinary incontinence per week.
? Micturition frequency: at least 8 micturitions per 24 hours.
? Urgency: at least once per 24 hours.

Key Exclusion Criteria:

? Patients with clinically significant stress incontinence, significant bladder outlet obstruction and/or a post void residual (PVR) volume of greater than 200mls.

? Patients with significant urogenital disease, such as recurrent urinary tract infection (UTI) or interstitial cystitis;

? Patients who had undergone hysterectomy or prostatectomy in the past 6 months;

? Patients taking prohibited medication included drugs with significant anticholinergic or antispasmodic effects, potent inhibitors of CYP3A4 enzyme systems (ketoconazole, itraconazole, miconazole, troleandomycin and nefazodone), estrogens if taken for less than 2 months as well as opioids and other drugs that could cause significant constipation. Bulking agents and stool softeners were allowed for the treatment of constipation.

Comments: *A detailed list of inclusion and exclusion criteria can be found in Appendix A. It is noted that the patients who had received previous therapy for OAB were not excluded from these studies. In particular, Study 1041 allowed patients who had had participated in previous controlled, double blind darifenacin studies to be enrolled as long as there were a 4-month waiting period. Though the sponsor stated that the intentional randomization of patients known to be responsive to, or tolerant of, anticholinergic therapy was avoided, the impact of this practice will be carefully examined in the efficacy analysis.*

The exclusion of patients taking potent CYP3A4 inhibitors might have served to lessen overall adverse reactions, including serious ones.

Treatment Groups and Dosage Tested: Treatment groups and dosages tested in the three pivotal trials were different (Table VI-C-3.1). Darifenacin 7.5mg was tested in two studies and 15mg in all three studies.

Table VI-C-3.1 The treatment groups in three pivotal studies (Study 1001, 1002, and 1041)

Treatment Groups	Study 1001	Study 1002	Study 1041
Darifenacin			
3.75 mg			X
7.5 mg		X	X
15 mg	X	X	X
30 mg	X	X	
Tolterodine 2mg bid	X		
Placebo	X	X	X

Source Data: Tables 1.1 in Final Study Report of A1371002, A1371001, and A1371041.

Comments: *The sponsor only requested the approval of darifenacin 7.5mg and 15mg. They are the focus of this review.*

Duration of Treatment: 12 weeks

Primary Efficacy Endpoint – Number of Incontinence Episodes per week. The data were collected using electronic patient diaries. In Studies A1371002 and A1371001, patients were requested to complete the diary daily during the entire medication free/placebo run-in period (baseline) and daily for the 2 weeks prior to visits at the end of Weeks 2, 6 and 12. In Study A1371041 diary data was collected 1 week prior to the baseline and Weeks 2, 6 and 12 visits.

> ***Comments:*** *It is noted that number of diaries used to calculate the mean value of incontinence episode per week (primary efficacy endpoint) differed among the three studies. In Study 1041, efficacy assessment was based the diaries collected during a one-week period. In Study 1001 and 1002, on a two-week period. The impact of this variation will be carefully reviewed since a longer assessment period will reduce both inter and intra-subjects variation.*

Secondary Efficacy Endpoints: The following secondary endpoints were also recorded in the bladder diary.

- **Number of micturitions per day;**
- **Number of episodes of urgency per day**
- **Volume of urine passed per void**
- **Severity of urgency per day**
- **Number of nocturnal awakening due to OAB per week**
- **Number of incontinence episode per week resulting in a change of clothing or pad**
- **Maximum volume void**

In addition, the sponsor also prospectively defined treatment responders as those who achieved a 50% or greater reduction from baseline in the number of incontinence episodes per week (incontinence responder), or those who achieved a "normal" frequency of micturition (< 8 micturitions per day – micturition responder).

> ***Comments:*** *Number of micturitions per day and number of episodes of urgency per day were the only two secondary endpoints that were included in this review . In the opinion of this reviewer, these two variables play a "critical role" for determining the drug's efficacy for the treatment of OAB.*
>
> *Since there is no perfect way to define a treatment or clinical responder, it was appropriate to have the cut-off points prospectively defined. The sponsor's definition also appeared to be appropriate.*

Statistical Analysis Plan (SAP): The highlights of the statistical analysis plan are as follows:

? All SAP were finalized prior to unblinding the treatment assignment;
? The efficacy determination was based on full analysis set (FAS), including all subjects who were randomized, took at least 1 dose of medication and had some bladder diary data;
? The analysis was based on ITT principle;
? The primary time point for the efficacy analysis was changes from baseline to Week 12. Last-observation-carried-forward (LOCF) approach was used to handle any missing data at Week 12;
? Non-parametric approach (Wilcoxon rank-sum test) was employed for much of the efficacy data had a skewed distribution across study participants;
? For the clinical responder analysis, logistical regression approach was employed;
? Multiplicity was handled by a step down testing procedures;
? No interim analyses were planned and none were performed.

In addition, a post-hoc meta-analysis was performed to study:

? dose and response relationship;
? the impact of the following factors on the efficacy:
  ? age (<65 and ? 65) and (18-44, 45-64, 65-74 and ? 75),
  ? gender
  ? race
  ? concomitant medication (inhibitors and inducers of CYP3A4 and CYP2D6 inhibitors)
  ? baseline severity of incontinence.

Comments: *This reviewer does not accept a statistical association established from a meta-analysis of pivotal studies as the basis for determining drug's efficacy for the treatment of OAB. Only the evidence presented in each of the three pivotal studies (1001, 1002, and 1041) can be used for fulfilling the regulatory requirements in determining a drug's efficacy.*

After the efficacy is demonstrated, however, a pooled analysis from the studies can be used to provide (1) a more reliable estimate for the magnitude of the effect; and (2) statistical power to conduct a subgroup analysis.

Though three pivotal studies were almost identical, there was some dissimilarities that may affect the interpretation of the data (Table VI-C-3.2)

Table VI-C-3.2 The key differences among three pivotal trials (Study 1001, 1002, and 1041)

	Study 1001	Study 1002	Study 1041
Study Sites in the US	Yes	No	No
Darifenacin 7.5mg Group	No	Yes	Yes
Active Comparator	Yes	No	No
Placebo Used in Run-in Period	No	Yes	Yes
Number of diaries used in efficacy endpoint calculation	Two weeks	Two weeks	One week

4. What are the demographic and baseline characteristics in the three Phase 3 pivotal clinical trials?

Table VI-C-4.1 shows demographic and baseline characteristics by treatment group among subjects in three pivotal studies (1001, 1002, and 1041). The majority of subjects in these three studies was female. The percentage of female subjects in the placebo group of Study 1001 is significantly higher than that in darifenacin 15mg group (90% vs. 79%). The mean ages were similar across treatment groups in all three studies (ranged from 55-60 for darifenacin-treated groups vs. 54-59 for placebo-treated groups). While racial/ethnic distribution was similar across treatment groups, non-white populations were underrepresented because approximately 100%, 95% and 90% of subjects in Study 1002, 1041 and 1001 were white, respectively. Study 1001 was the only pivotal study that included subjects in the US though Study 1047 also was conducted in the US.

All subjects had a primary diagnosis of OAB and cardinal symptoms indicative of OAB for at least 6 months. The mean duration of OAB symptoms was between 8-9 years and was similar across treatment groups in all three studies (data not shown). The percent of subjects with prior OAB treatment (drugs or bladder training) was similar across the treatment groups in each study. In Study 1001, the percent of subjects with prior treatment was lower than that in the other two studies. In addition, less than 5% subjects had a prior surgery of lower urinary tract, including operations on female genital system, male genital system and urinary system in these three studies.

Table VI-C-4.1 Demographics in the three Phase 3 pivotal studies (Study 1001, 1002 and 1041)

	Study 1002		
	Darifenacin 7.5mg (n=108)	**Darifenacin 15mg (n=107)**	**Placebo (n=109)**
% Female	87%	86%	83%
% White	100%	99%	100%
Mean Age (range)	56 (23-88)	55 (24-82)	54 (21-85)
Prior Treatment (Drug or bladder training)	41%	51%	44%
	Study 1041		
	Darifenacin 7.5mg (n=229)	**Darifenacin 15mg (n=115)**	**Placebo (n=164)**
% Female	85%	87%	84%
% White	94%	96%	95%
Mean Age (range)	58 (22-88)	57 (24-81)	57 (19-81)
Prior Treatment (Drug or bladder training)	45%	51%	47%
	Study 1001		
	Darifenacin 7.5mg	**Darifenacin 15mg (n=112)**	**Placebo (n=115)**
% Female	---	79%	90%
% White	---	93%	88%
Mean Age	---	60 (32-85)	59 (21-88)
Prior Treatment (Drug or bladder training)	---	34%	30%

Source data: Table 6, 8 of 2.7.3 Summary of Clinical Efficacy. and Table 2.1.1 and 5.6.5 of Individual study reports

Comments: *In summary, data suggest that the randomization worked well and percent distribution across treatment groups were similar. However the percent distribution for some variables, such as prior OAB treatment, differed among the studies which may affect the magnitude of treatment effect of each study. The non-white population was underrepresented in all three pivotal studies though there is no evidence to suggest that non-white subjects would have responded to the drug differently. In the opinion of this reviewer, this deficiency can be corrected by having the sponsor conduct a Phase 4 study in non-white patients.*

5. What is the patient disposition in the three Phase 3 pivotal clinical trials?

Table VI-C-5.1 shows that a total of 337, 334 and 388 subjects were randomized into darifenacin 7.5mg, darifenacin 15mg and placebo groups in the three pivotal studies, respectively. The percent of subjects who completed the study was similar between placebo and darifenacin 7.5mg groups (90%-96%), but was lower in darifenacin 15mg groups (82%-92%). Less than 2% of subjects discontinued from the study due to the lack of efficacy. Despite the study discontinuation from

some subjects, more than 99% (between 97% an 100%) of the originally randomized subjects were included in the efficacy analysis because they had at least one efficacy assessment before the withdrawal from the study.

Table VI-C-5.1 Subject disposition in the three Phase 3 pivotal studies (Study 1001, 1002 and 1041)

	Study 1002		
	Darifenacin 7.5mg	**Darifenacin 15mg**	**Placebo**
Randomized	108	107	109
Completed	99 (92%)	93 (87%)	101 (93%)
FAS	108 (100%)	106 (99%)	108 (99%)
	Study 1041		
	Darifenacin 7.5mg	**Darifenacin 15mg**	**Placebo**
Randomized	229	15	164
Completed	219 (96%)	106 (92%)	152 (93%)
FAS	229 (100%)	115 (100%)	164 (100%)
	Study 1001		
	Darifenacin 7.5mg	**Darifenacin 15mg**	**Placebo**
Randomized	--	112	115
Completed	--	92 (82%)	104 (90%)
FAS	--	109 (97%)	114 (99%)

Source data: Table 4 of 2.7.3 Summary of Clinical Efficacy
Completed: Subject with Efficacy Assessment at Week 12
FAS: Full Analysis Set, including subjects who discontinued but had a valid efficacy assessment prior to Week 12.

Comments: *The sponsor made a reasonable effort to ensure that every subjects would have at least one post-randomization efficacy assessment. As a result, almost all originally randomized patients were included in the efficacy analysis. In Study 1001, a significantly lower percent of subjects (82%) completed the study in darifenacin 15mg group, compared to that (90%) in the placebo group. Therefore more subjects would have to use an efficacy assessment of a prior visit at Week 2 or Week 6 by using LOCF procedures. This small imbalance in LOCF replacement may affect the efficacy result in that trial.*

6. What is the evidence to support the efficacy of darifenacin 7.5mg and 15mg in reducing incontinence episodes – the primary endpoint?

The primary efficacy endpoint of the studies was change in the average number of incontinence episodes per week from baseline to endpoint, as computed by [endpoint – baseline]. The average number of incontinence episode per week was calculated based on subject-recorded count of the number of incontinence episodes obtained from the subject diaries prior to each visit at baseline and at Week 2, 6 and 12 post-baseline.

The sponsor employed last observation carried forward (LOCF) approaches to handle the missing data. Endpoint assessment was the last non-missing value obtained at Week 2, 6 or 12.

Table VI-C-6.1 shows the changes in number of incontinence episodes per week from baseline to Week 12 in three pivotal Phase 3 studies (1001, 1002, and 1041). In Study 1002 and 1041, the subjects in darifenacin 15mg groups 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 groups (p-values <0.001 and =0.02 for Study 1002 and 1041, respectively). In the Study 1001, the median reduction in the number of incontinence episodes in darifenacin and placebo groups were 11.4 and 9.0 episodes, respectively. The p-value for that comparison was 0.049. This is not considered statistically significant because the statistical significant level for this study was set at p=0.025, not 0.05 because this trial employed a different statistical testing procedures to handle multiple comparison issue, compared to the one used in another two pivotal studies.

The subjects in darifenacin 7.5mg groups of the two pivotal studies (Study 1002 and 1041) experienced a statistically significant median reduction of 8.1 and 9.0 in the number of incontinence episode per week from baseline, compared to that of 5.9 to 7.6 in placebo groups. The p-values were 0.007 and 0.01, respectively. Darifenacin 7.5mg was not studied in Study 1001.

> ***Comments:*** *In two pivotal trials (Study 1002 and 1041), subjects in darifenacin 7.5mg and 15mg groups showed a statistically significant improvement in number of incontinence episode per week over the placebo in a 12-week period.*
>
> *In Study 1001, darifenacin 7.5mg was not studied. While predefined level of statistical significance was not achieved in Study 1001, this reviewer noted that p-value was small (0.049). Compared to the results of other two studies, this reviewer believes that the main reason for Study 1001's failure to achieve a pre-defined level of statistical significance was a high placebo response rather than a lower treatment response. This may have been a consequence of a no-treatment run-in in this trial rather than a placebo run-in.*

Table VI-C-6.1 Change in number of incontinence episodes per week from baseline to Week 12 in the three Phase 3 pivotal studies (Study 1001, 1002 and 1041), LOCF, FAS

Incontinence Episode Per Week	Study 1002		
	Darifenacin 7.5mg (N=108)	Darifenacin 15mg (N=106)	Placebo (N=108)
Median Baseline	14.0	17.3	16.1
Median Change from Baseline	-8.1	-10.4	-5.9
Median Difference from Placebo	-2.8	-4.3	--
P value	0.007	<0.001	--
	Study 1041		
	Darifenacin 7.5mg (N=228)	Darifenacin 15mg (N=115)	Placebo (N=163)
Median Baseline	16.3	17.0	16.6
Median Change from Baseline	-9.0	-10.4	-7.6
Median Difference from Placebo	-1.5	-2.1	--
P value	0.01	0.02	--
	Study 1001		
	Darifenacin 7.5mg	Darifenacin 15mg (N=109)	Placebo (N=113)
Median Baseline	--	16.2	15.5
Median Change from Baseline	--	-11.4	-9.0
Median Difference from Placebo	--	-2.4	--
P value	--	0.049	--

Source data: Table 11 of 2.7.3 Summary of Clinical Efficacy or Table 5.1.3 of Individual Study Report
N: number of subjects included in the analysis
LOCF: Last observation carry forward
FAS: Full Analytical Set

7. Are the efficacy results of darifenacin 7.5mg and 15mg in reducing average number of daily micturitions and average number of daily episodes of urgency consistent with the results from primary endpoint?

Frequency of micturition and urgency are two important symptoms of OAB. Urgency is defined as the complaint of a sudden compelling desire to pass urine, which is difficult to defer. All patients enrolled into the darifenacin Phase 3 program were required to have at least 8 micturitions and 1 episode of urgency per day at baseline.

The change of the number of micturitions and number of episode of urgency from baseline to endpoint was prospectively defined as two of the secondary endpoints, as computed by [endpoint – baseline]. They were calculated based on subject-recorded count during a one-week (Study 1041) and two-week (Study 1001 and 1002) period obtained from the subject diaries prior to each visit at baseline and at Week 2, 6 and 12 post-baseline.

The sponsor employed last observation carried forward (LOCF) approaches to handle the missing data. Endpoint assessment was the last non-missing value obtained at Week 2, 6 or 12.

Table VI-C-7.1 and 7.2 show the changes in the number of micturitions per day and the number of episodes of urgency per day, respectively, from baseline to Week 12 in three pivotal Phase 3 studies (1001, 1002, and 1041). The results indicate:

? Darifenacin 15mg is associated with a statistically significant improvement in both micturition and urgency outcomes in two pivotal studies (Study 1002 and 1041);

? Darifenacin 7.5mg is associated with a statistically significant improvement in both micturition and urgency outcomes in one of two pivotal studies (Study 1041);

Table VI-C-7.1 Change in average number of daily micturitions from baseline to Week 12 in the three Phase 3 pivotal studies (Study 1001, 1002 and 1041), LOCF, FAS

Number of Micturitions Per Day	Study 1002		
	Darifenacin 7.5mg (N=107)	Darifenacin 15mg (N=106)	Placebo (N=108)
Median Baseline	10.3	11.0	10.1
Median Change from Baseline	-1.7	-1.9	-1.1
Median Difference from Placebo	-0.5	-0.7	--
P value	0.066	0.033	--
	Study 1041		
	Darifenacin 7.5mg (N=228)	Darifenacin 15mg (N=115)	Placebo (N=163)
Median Baseline	10.1	10.1	10.1
Median Change from Baseline	-1.6	-1.7	-0.8
Median Difference from Placebo	-0.8	-0.9	--
P value	<0.001	<0.001	--
	Study 1001		
	Darifenacin 7.5mg	Darifenacin 15mg (N=109)	Placebo (N=114)
Median Baseline	--	10.5	10.4
Median Change from Baseline	--	-1.9	-1.2
Median Difference from Placebo	--	-0.5	--
P value	--	0.076	--

Source data: Table 20 of 2.7.3 Summary of Clinical Efficacy or Table 5.2.3 of Individual Study Reports
N: number of subjects included in the analysis
LOCF: Last observation carry forward
FAS: Full Analytical Set

Table VI-C-7.2 Change in average number of daily episodes of urgency from baseline to Week 12 in the three Phase 3 pivotal studies (Study 1001, 1002 and 1041), LOCF, FAS

Number of Episodes of Urgency Per Day	Study 1002		
	Darifenacin 7.5mg (N=107)	Darifenacin 15mg (N=106)	Placebo (N=108)
Median Baseline	8.5	8.6	8.1
Median Change from Baseline	-1.8	-2.3	-1.2
Median Difference from Placebo	-0.5	-1.1	--
P value	0.196	0.013	--
	Study 1041		
	Darifenacin 7.5mg (N=228)	Darifenacin 15mg (N=115)	Placebo (N=163)
Median Baseline	7.7	8.0	8.3
Median Change from Baseline	-2.0	-2.0	-0.9
Median Difference from Placebo	-0.9	-0.9	--
P value	0.001	0.005	--
	Study 1001		
	Darifenacin 7.5mg	Darifenacin 15mg (N=109)	Placebo (N=113)
Median Baseline	--	8.6	8.5
Median Change from Baseline	--	-2.6	-1.9
Median Difference from Placebo	--	-0.7	--
P value	--	0.061	--

Source data: Table 30 of 2.7.3 Summary of Clinical Efficacy or Table 5.2.5 of Individual Study Reports
N: number of subjects included in the analysis
LOCF: Last observation carry forward
FAS: Full Analytical Set
ND: Not done due to step down testing procedure

Comments: *In two pivotal trials (Study 1002 and 1041), subjects in darifenacin 15mg groups showed a statistically significant improvement in average number of daily micturition and average number of daily episodes of urgency over the placebo in a 12-week period.*

Though darifenacin 7.5mg only showed a statistically significant improvement in number of micturition and number of episodes of urgency in one of the two pivotal studies (Study1041), this reviewer believes that direction of symptom improvement in the second study (Study 1002) is consistent with the result of Study 1041. For the micturition outcome, the p-value for Study 1002 was 0.06 which is very close to the predefined level of statistical significance i.e., p=0.05.

After taking into consideration the totality of the evidence, including relative importance of three symptoms outcomes, the strength of statistical evidence, and direction of treatment effect, this reviewer concludes that the evidence from three adequate and well controlled studies supports the effectiveness of darifenacin (7.5mg and 15mg qd) for the treatment of

overactive bladder. The magnitude of effect, generalizibility of this conclusion and risk and benefit of the drug, however, will be addressed under different sections.

8. What is the magnitude of effect of darifenacin 7.5mg and 15mg for the treatment of overactive bladder and how consistent is the treatment effect in different subgroups of OAB patients?

The magnitude of the treatment effect was estimated from two separated pooled analyses, comparing darifenacin 7.5mg or 15mg with placebo in three pivotal studies (Table VI-C-8.1). The results show:

? Subjects treated with darifenacin 15mg were associated with a higher median reduction in average number of incontinence episodes per week, compared to that of subjects treated with darifenacin 7.5mg (an improvement of 3.2 vs. 2.0 episode per week, respectively);\

? Treatment effects, as measured by the reduction in average number of daily micturitions and average number of daily episodes of urgency, were similar for the subjects treated with darifenacin 7.5mg and 15mg (an improvement of approximately 0.8-0.9 episode per day for both outcomes across two treatment group);

Table VI-C-8.2 and 8.3 show the impact of age, gender and baseline severity on number of incontinence episodes per week for darifenacin 7.5mg and 15mg, respectively. The results indicate:

? Subjects of 65 years of age or older appear to have a greater improvement in number of incontinence episode per week across both dosing groups;

? Female subjects appear to have a greater improvement in the number of incontinence episode per week across both dosing groups;

? For subjects treated with darifenacin 7.5mg, the improvement in incontinence outcome does not appear to be affected by the incontinence severity at baseline;

? For subjects treated with darifenacin 15mg, the improvement in incontinence outcome does appear to be affected by the incontinence severity at baseline;

Comments: *The sponsor also showed treatment effect by race/ethnic group in the subgroup analysis. The results are not presented here because this reviewer believes that no meaningful conclusions could be made because the percent of non-white subjects was less than 5% of the total population used in the pooled analysis.*

The direction of treatment effect for male subjects in darifenacin 7.5mg groups was inconsistent with treatment effects observed in other subgroups. This reviewer will have no major concern about this inconsistency if both darifenacin 7.5mg and 15mg are to be approved because male subjects will have an option to increase the dose to 15mg if they fail to respond to darifenacin 7.5mg. However, if due to any safety reason, darifenacin 15mg

Table VI-C-8.1 Treatment effect of Darifenacin 7.5mg and 15mg in average number of incontinence episode per week, average number of micturition per day, and number of episodes of urgency per day (Study 1001, 1002 and 1041)

Darifenacin	Number of Subjects		Median Change from baseline		
	Darifenacin	Placebo	Darifenacin	Placebo	Difference*
Number of Incontinence Episodes Per Week					
7.5 mg	335	271	-8.8	-7.0	-2.0
15 mg	330	384	-10.6	-7.5	-3.2
Number of Micturitions Per Day					
7.5 mg	335	271	-1.6	-0.9	-0.8
15 mg	330	385	-1.9	-1.0	-0.8
Number of Episodes of urgency Per Day					
7.5 mg	335	271	-2.0	-1.0	-0.8
15 mg	330	384	-2.3	-1.2	-0.9

Source data: Table 12, 21, and 31 of 2.7.3 Summary of Clinical Efficacy
* Difference was a statistically adjusted difference of median change from baseline between darifenacin and placebo group.

Table VI-C-8.2 Subgroup analysis of treatment effect of darifenacin 7.5mg in average number of incontinence episodes per week by age, gender and baseline severity (Study 1002 and 1041)

Subgroups	Number of Subjects		Median Change from baseline		
	Darifenacin 7.5mg	Placebo	Darifenacin 7.5mg	Placebo	Difference*
AGE					
< 65	238	199	-7.6	-7.6	-1.0
≥ 65	97	72	-11.2	-4.8	-5.9
Gender					
Female	286	226	-9.0	-6.6	-2.7
Male	49	45	-6.9	-7.9	1.0
Baseline Severity – Number of Incontinence Episodes per Week at Baseline					
< 21	214	172	-7.0	-5.7	-2.0
> 21	121	99	-15	-11	-2.2

Source data: Table 43, 46 and 50 of 2.7.3 Summary of Clinical Efficacy
* Difference was a statistically adjusted difference of median change from baseline between darifenacin and placebo group.

Table VI-C-8.3 Subgroup analysis of treatment effect of darifenacin 15mg in average number of incontinence episodes per week by age, gender and baseline severity (Study 1001, 1002, and 1041)

Subgroups	Number of Subjects		Median Change from baseline		
	Darifenacin 15mg	Placebo	Darifenacin 15mg	Placebo	Difference*
AGE					
< 65	221	276	-10.5	-7.8	-2.8
≥ 65	109	108	-10.8	-6.8	-4.1
Gender					
Female	279	327	-10.9	-7.5	-3.7
Male	51	57	-8.6	-7.6	-1.3
Baseline Severity – Number of Incontinence Episodes per Week at Baseline					
< 21	199	243	-8.1	-6.0	-2.1
> 21	131	141	-18.5	-13.5	-4.6

Source data: Table 12, 43, 46 and 50 of 2.7.3 Summary of Clinical Efficacy

* Difference was an statistically adjusted difference of median change from baseline between darifenacin and placebo group.

9. What is the magnitude of the treatment effect of darifenacin 7.5mg and 15mg in terms of number needed to treat (NNT)?

For a practicing physician, it may be difficult to interpret a treatment effect expressed as median reduction in number of incontinence episode per week. Therefore this reviewer attempts to employ the concept of the number needed to treat (NNT) in order to present the treatment effect in a clinically meaningful manner.

In this analysis, this reviewer used the following criteria to define a clinical responder: ≥ 50% improvement in number of incontinence episodes per week from baseline to Week 12, which was prospectively defined by the sponsor in SAP.

Table VI-C-9.1 shows that over a 12-week period, 66% and 52% of subjects in darifenacin 7.5mg and placebo groups, respectively, achieved a 50% improvement or more in number of incontinence episodes from baseline. The net treatment effect therefore was 14%, which indicated that for every 100 similar OAB patients treated with darifenacin 7.5mg for 12 weeks, approximately 14 subjects would have achieved a clinically significant improvement in number of incontinence episodes per week because of darifenacin. In other words, the number needed to treat (NNT) is 7 (100/14), i.e., it requires treatment of 7 patients for 12 weeks to produce one clinical responder.

Table VI-C-9.1 Treatment effect of darifenacin 7.5mg and 15mg expressed as number needed to treat (NNT) – a pooled analysis of Study 1001, 1002 and 1041

	Study 1002 and 1041		Study 1001, 1002 and 1041	
	Darifenacin 7.5mg	Placebo	Darifenacin 15mg	Placebo
Number of subjects treated	335	270	330	383
Number of clinical responder	220	141	231	216
Percent of clinical responder	66%	52%	70%	56%
Percent difference	14%	--	14%	--
Number needed to treat (NNT)	7	--	7	--

Source data: Table 18 and 28 of 2.7.3 Summary of Clinical Efficacy

Comments: *Though subjects treated with dariferacin 15mg were associated with a higher median improvement in the number of incontinence episodes per week than 7.5mg group, there was no difference in terms of NNT for both dose groups.*

10. When is the earliest time point at which the treatment effect was observed?

Table VI-C-10.1 presents the change in the number of incontinence episodes per week from baseline to Week 2. Data appear to suggest that the treatment effect started as early as at Week 2 for both darifenacin 7.5mg and 15mg groups.

Comments: *It is noted that subjects treated with darifenacin 15mg in Study 1001 showed statistically significant improvement over placebo in the number of incontinence episodes per week at Week 2 (p=0.006). As demonstrated earlier, the treatment effect became less significant at Week 12.*

Table VI-C-10.1 Change in average number of incontinence episodes per week from baseline to Week 2 in Study 1001, 1002 and 1041, FAS

Incontinence Episode Per Week	Study 1002		
	Darifenacin 7.5mg (N=107)	Darifenacin 15mg (N=106)	Placebo (N=108)
Median Baseline	14.0	17.3	16.1
Median Change from Baseline	-5.4	-7.6	-3.8
Median Difference from Placebo	-2.1	-3.8	--
P value	0.015	<0.001	--
	Study 1041		
	Darifenacin 7.5mg (N=228)	Darifenacin 15mg (N=115)	Placebo (N=162)
Median Baseline	16.3	17.0	16.6
Median Change from Baseline	-5.6	-8.4	-4.0
Median Difference from Placebo	-2.0	-4.0	--
P value	0.003	<0.001	--
	Study 1001		
	Darifenacin 7.5mg	Darifenacin 15mg (N=109)	Placebo (N=113)
Median Baseline	--	16.2	15.5
Median Change from Baseline	--	-8.9	-5.9
Median Difference from Placebo	--	-2.6	--
P value	--	0.006	--

Source data: Table 13 of 2.7.3 Summary of Clinical Efficacy or Table 5.7.1 and 5.5.1 of Individual Study Reports
N: number of subjects included in the analysis
FAS: Full Analytical Set

11. What is the treatment effect of darifenacin for the treatment of overactive bladder in a dose lower than 7.5mg or higher than 15mg ?

As stated in Table VI-C-3.1, darifenacin 3.75mg was tested in Study 1041 and darifenacin 30mg was tested in Study 1001 and 1002. Table VI-C-11.1 shows the efficacy results for these two dosages.

Table VI-C-11.1 Change in number of incontinence episodes per week from baseline to Week 12 for darifenacin 3.75mg and 30mg in the three Phase 3 pivotal studies (Study 1001, 1002 and 1041), LOCF, FAS

Incontinence Episode Per Week	Study 1041	Study 1002	Study 1001
	Darifenacin 3.75mg (N=53)	Darifenacin 30mg (N=114)	Darifenacin 30mg (N=225)
Median Baseline	16.0	19.1	18.5
Median Change from Baseline	-8.6	-11.4	-12.6
Median Difference from Placebo	-0.7	-6.3	-4.2
P value	ND	0.001	<0.001

Source Data: Table 11 of 2.7.3 Summary of Clinical Efficacy

Comments: *As demonstrated earlier, median improvement in number of incontinence episodes per week were 2.0 and 3.2 for darifenacin 7.5mg and 15mg, respectively. Darifenacin 30mg appears to have the largest treatment effect with a median improvement between 4.2 and 6.3 episodes per week and the treatment effects were statistically significant at $p<0.001$ level. Darifenacin 3.75mg was associated with a median treatment effect of 0.7 episode per week. While statistical testing was not conducted due to restriction of stepdown procedure, the difference between 3.75mg and placebo group was unlikely to be statistically significant.*

It appears that the sponsor has made a reasonable effort to find the minimally effective dose for the treatment of overactive bladder.

12. Are the efficacy results applicable to US population?

Key evidence to support the efficacy of darifenacin 7.5mg and 15mg for the treatment of overactive bladder comes from two pivotal studies (Study 1002 and 1041) that were conducted outside of the United States. In the third pivotal study (Study 1001), darifenacin 7.5mg was not tested and the treatment effect of darifenacin 15mg was not statistically significant at a predefined p level of 0.025. There is an additional supportive study (1047) conducted in the US but employing a dose-titration design. The question has been raised regarding the applicability of efficacy results from Study 1002 and 1041 to the US population.

Comments: *While US Study 1001 failed to achieve a predefined level ($p=0.025$) of statistical significance for darifenacin 15mg group, the p-value of that study was small ($p=0.049$) and treatment effect was consistent with that observed in the other two pivotal studies. Recently the sponsor has submitted a final study report of Study 1047 – a multicenter, double-blind, randomized, placebo-controlled, parallel group study of darifenacin (flexible dosing) for the treatment of OAB in the US and Canada. In Study A1371047, all darifenacin-treated subjects started on 7.5mg daily with an upward option to 15 mg daily after 2 weeks of treatment. A total of 269 and 129 subjects were enrolled into darifenacin 7.5/15mg and placebo groups, respectively. The demographic and baseline characteristics of the subjects and efficacy assessment of this study were similar to that in Study 1001.*

The results show that darifenacin 7.5mg/15mg was associated with a median improvement of 1.4 episodes per week in number of incontinence episodes per week and the treatment effect was statistically significant at $p=0.035$ level. This result was verified by FDA's statistical reviewer in the statistical review of this NDA.

Since it was shown that darifenacin's treatment effect was dose dependent, there is no reason to believe that darifenacin 15mg would not have worked for the treatment of OAB in the US population if darifenacin 7.5mg/15mg

(flexible dosing) was shown to be effective for the treatment of this condition. Further, the dose-titration design is similar to that proposed for use in the label.

After taking all these factors into consideration, this reviewer believes that darifenacin 15mg is effective for the treatment of OAB in the US population. With the evidence that darifenacin 15mg was efficacious for both US and non-US population, and darifenacin 7.5mg was efficacious from two non-US studies, this reviewer believe that lack of direct evidence of efficacy for darifenacin 7.5mg from US study should not preclude this dose from approval in the US.

D. Efficacy Conclusions

The sponsor has conducted three adequate and well controlled clinical studies in support of proposed treatment indication in this NDA. The primary endpoint of the studies was thought to be appropriate and clinically meaningful. The studies have provided substantial evidence in support of the effectiveness of darifenacin 7.5mg and 15mg once daily (orally) for the treatment of overactive bladder in men and women 18 years of age or older in the US, based on darifenacin's ability in reducing average number of weekly incontinence episodes, average number of daily micturitions and average number of daily episodes of urgency.

The main efficacy conclusions are as follows:

? Over a 12-week treatment period, darifenacin 7.5mg and 15mg were associated with a median reduction of 2.0 and 3.2 incontinence episodes per week, respectively, from baseline. Statistical significance was achieved in two of three pivotal clinical studies at a predefined level. In the third trial, the p-value was 0.049.

? If a 50% improvement in incontinence episodes from baseline was used to define a clinical responder, the number needed to treat (NNT) was seven. In other words, seven OAB patients need to be treated for 12 weeks in order to produce one clinical responder. Despite the fact that darifenacin 15mg was associated with a greater treatment effect, expressed as a median reduction in number of incontinence episodes from baseline, the number needed to treat for both darifenacin 7.5mg and 15mg dosages was the same;

? The treatment effect was observed as early as at Week 2. At this time, no controlled data are available to support the long-term effectiveness of the darifenacin 7.5mg and 15mg for the treatment of overactive bladder.

? For subjects treated with darifenacin 7.5mg or 15mg, the magnitude of the treatment effect was higher in female subjects and in older subjects (> 65 years of age or older). For subjects treated with darifenacin 15mg, the magnitude of treatment effect appeared to be greater for those who had more severe incontinence symptoms (> 21 incontinence episodes per week) at

baseline. The difference was not observed for subjects treated with darifenacin 7.5mg.

? In addition to the reduction in the number of incontinence episodes, darifenacin 7.5mg and 15mg were also associated with the reductions in average number of daily micturitions and average number of daily episodes of urgency. The treatment effect was approximately 0.8 episode per day for both outcomes and did not appear to be dose dependent;

? There was reasonable evidence to suggest that darifenacin 7.5mg is the minimally effective dose for the treatment of OAB from a clinical perspective.

The majority of study participants were white (varying from 95% to 100% for three pivotal studies). While there is little reason to suspect that non-white population would have responded differently to darifenacin treatment, eventually such a statement needs to be confirmed by evidence presented in an adequate and well controlled clinical study.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Adverse event profile of darifenacin appears to be similar to that of other anticholinergic drugs. Dry mouth, constipation and dyspepsia were the most frequently reported adverse events over a 12-week treatment period. Most adverse events occurred in the first two weeks of the treatment and were dose-dependent. For darifenacin 7.5mg, the AE-related dropout rate was similar to that in placebo groups. Darifenacin does not appears to be associated with an increase in liver enzymes, but may increase the incidence of urinary tract infection (UTI). Two adverse events that require special attention in the product labeling are constipation and urinary retention.

There is a difference between darifenacin and placebo in incidence of bone fractures requiring hospitalization. The reason for this is unclear. Additional Phase 4 study appears to be necessary.

Pre-clinical suggests that darifenacin has the potential to cause a QT prolongation. While QT safety data was available in human, these were not adequate to rule out the possibility of a clinically important QT prolongation in the target population at a range of plasma concentrations that is clinically relevant.

B. Description of Patient Exposure

As of 11 October 2002, the cut off date for this NDA submission, the sponsor had completed 94 Phase 1, 2 and 3 clinical studies in the US and worldwide in which a total of 6,655 subjects had been exposed to at least one dose of darifenacin up to 60mg once daily.

Depending on type of safety issues, different combinations of clinical studies may be used in the integrated review of safety. Table VII-B-1 defines those combinations, including number of subjects and duration of exposures.

? *OAB fixed dose Phase 3 studies:* a combination of data from three pivotal Phase 3 studies of 12-week duration in patients with overactive bladder (OAB);

? *OAB placebo-controlled studies:* a combination of data from all placebo controlled studies of a 2-week duration or longer in OAB patients;

? *Phase 2/3 OAB/IBS studies:* a combination of Phase 2 and 3 studies of all doses, formulations and indications (including overactive bladder and irritable bowel syndrome);

? *Long-term studies:* a combination of three uncontrolled open label studies in OAB and IBS patients. Studies 137-311, a 52 week open study in OAB subjects, A1371014, a 40 week open extension of Study A1371001 in OAB subjects and Study 137-359, a six month study in subjects with irritable bowel syndrome (IBS).

Table VII-B-1. Level of darifenacin exposure by different combinations of clinical studies

Type of Studies	Number of Subjects Treated with	Cumulative person-year of exposure	Study ID
OAB fixed dose Phase 3 studies	1,069	228	1001, 1002, 1041
OAB placebo-controlled studies	1,833	356	315 1001, 1002, 1011, 1012, 1013, 1041
Phase 2/3 OAB/IBS studies	5,398	1,412	101. 103, 301, 302, 303, 304, 305, 305A, 307, 308, 310, 311, 312, 313, 315. 316, 317, 350, 351, 352, 353. 356, 359, 360, 666, 676, 684, 1001, 1002, 1011, 1012, 1013, 1014, 1018, 1019, 1026, 1027, 1041
Long-term studies	1,002	371	311. 359. 1014

Source data: Table 3, 17.1, 17.2, 17.4 and 17.5.8 of Summary of Clinical Safety (page 823 and 4375)

Of those 6,655 subjects, 5,398 had enrolled into darifenacin groups of 38 Phase 2 and 3 clinical studies of all formulations, dosage and indications, including 601 and 363 subjects who were exposed to darifenacin for at least 6 months and 12 months, respectively. In addition, 792 subjects were treated with an active comparator and 1,910 with placebo (Table VII-B-2).

Table VII-B-2 Number of subjects tested with the exposure duration by treatment group – a pooled analysis of Phase 2 and 3 OAB/IBS studies

Treatment group	Number of Subjects Treated	Number of subjects treated > 6 months	Number of subjects treated > 12 months	Cumulative person-year of exposure	Average treatment duration per subject (years)
Darifenacin	5398	601	363	1,415	0.26
Active Comparator	792	0	0	120	0.15
Placebo	1910	8	4	322	0.17

Source data: Table 38 of Summary of Clinical Safety (page 74)

In OAB fixed dose Phase 3 studies, 337 and 334 patients had been exposed to 7.5mg and 15mg darifenacin for a 12-week period. Table VII-B-3 shows demographic characteristics of these patients. Approximately 84% were females and 96% white with a mean age of 58 (ranged from 22-88).

Comments: *Amount of darifenacin exposure meets the ICH guidance. The average treatment duration (years) per person differed between darifenacin and placebo groups (0.26 vs. 0.17 – Table VII-B-2) in Phase 2/3 OAB/IBS studies . Appropriate time adjustment may be needed for incidence rate calculation and adverse events comparisons between the two groups.*

Table VII-B-3 Demographic characteristics of patients enrolled in OAB fixed dose Phase 3 studies – a pooled analysis of three pivotal studies (1001, 1002 and 1041)

Demographics	Darifenacin 7.5mg N=337 (PYE*=77)	Darifenacin 15mg N=334 (PYE*=73)	Placebo N=338 (PYE*=87)
Mean age (range)	57 (22-88)	58 (24-85)	56 (19-88)
% Female	85.5%	84.1%	85.3%
% White	96.1%	95.8%	94.3%

Source data: Table 41 of Summary of Clinical Safety (page 76)
* PYE = Person-year exposure

C. Methods and Specific Findings of Safety Review

1. Method of Integrated Safety Review:

1.1 What is the guiding principles for the integrated safety review?

This review is guided by the FDA Draft Guidance – conducting a clinical safety review of a new product application and preparing a report on the review. The key considerations are summarized as fellows:

? The safety review is carried out in the following order regarding the safety outcomes:
  ? Death
  ? Serious adverse events
  ? Adverse events that resulted in dropout

- ? Common adverse events
- ? Less common adverse events
- ? Vital signs
- ? Laboratory findings
- ? QT safety
- ? Hepatic safety
- ? Other safety outcomes of special interest

? The review primarily focuses on OAB fixed dose Phase 3 studies (Study 1001, 1002 and 1041);

? Other studies are used for (1) searching for death cases; (2) screening for clinically significant adverse events that might not be reported in OAB fixed dose Phase 3 studies; (3) reconfirming any safety signal detected in OAB fixed dose Phase 3 studies;

? In addition to reviewing the safety results compiled by the sponsor, an independent safety analysis is conducted based on the original safety databases submitted in the NDA

? Auditing source materials is conducted to insure the accuracy and consistency of AE coding in the database

1.2 What is the sponsor's approach to eliciting adverse events or serious adverse events?

In darifenacin clinical development program, the adverse events were typically collected at baseline and at each follow-up visit. The sponsor provided each study site with a standard open-ended AE collection form which was filled out for each study subject. Data elements included description of event, onset and stop dates, severity and seriousness of the event and the relationship to the study drug as judged by the study investigator.

Adverse events in this discussion refer to treatment emergent adverse events, *i.e.* those events which occurred up to 14 days after treatment which were either first reported during the study or which worsened relative to severity at baseline. The analysis includes all reported events regardless of whether the events were considered to be treatment-related by the principal investigator.

For all events reported prior to 6 April 1998, serious adverse events were defined as those that were fatal, life threatening, resulted in permanent disability, required inpatient hospitalisation or prolongation of a hospital stay or involved a congenital abnormality, cancer or drug overdose. From 6 April 1998 onwards, cancer and drug overdose were taken out from the list and disability was redefined as those that were resulted in a persistent or significant disability/incapacity. In addition, important medical events that may not result in death, be life threatening or require hospitalization were to be considered serious adverse events if, based on appropriate sound medical judgement, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

The serious adverse event tables and listings are derived from a separate, centralized adverse event monitoring (AEM) database that is based on rapidly communicated reports from the investigators to the sponsor or to monitors approved by the sponsor.

1.3 Is adverse event categorized appropriately?

The sponsor has provided in this submission databases (SAS format) that contain all adverse events recorded in the adverse events collection form from all subjects in three pivotal Phase 3 OAB trials. The original description of the adverse event (terms used by investigator and patients) was receded by using the standard dictionary.

> ***Comment:*** *To ensure the quality of AE data, this reviewer randomly selected 10 subjects who discontinued from one of the three controlled studies and compared the AE events contained in the database with the ones recorded in CFR. All As recorded in the AE collection sheet were correctly transferred and categorized in the AE database.*
>
> *To ensure that the AE terms are not too narrowly defined, resulting in an underestimation of the true incidence for a particular event, this reviewer first identified all adverse events that occurred at least in 1% of darifenacin-treated groups. These event terms were then compared with all AE terms reported in the trials for the similarities to determine whether regrouping is necessary.*
>
> *In addition, AE were grouped by organ system to enhance safety signal identification, particularly those events related to cardiovascular, nervous and urogenital systems.*

2. Death

As of 11 October 2002, death was reported in three darifenacin treated patients due to suicide, adenocarcinoma and hepatic failure, respectively (Table VII-C-2). One placebo subject died of cancer (Subject 02900152 in Study 315). The incidence rate adjusted for exposure was 2 and 3 per 1,000 person-years of exposure for darifenacin and placebo-treated subjects. None of these deaths were assessed to be related to study drug by either the investigator or the sponsor.

Table VII-C-2 List of three darifenacin-treated subjects who died during darifenacin clinical development program

ID	Protocol #	Age/Sex Country	Dose /Length	Cause of death and relationship of initial event to treatment
51347137	137-1017	74/M Japan	15mg/6 months	Depression related suicide – during treatment
06050032	137-666	77/F USA	30mg/13 days	Adenocarcinoma of unknown origin – during treatment
0443-13	137-1005	46/F Germany	15mg/1 dose	Liver failure - 5 months after treatment

Source Data: page 914 of Summary of Clinical Safety

Comments: *Subject 0443-13 had liver failure 5 months after a single dose administration of 15mg darifenacin and Subject 06050032 was diagnosed to have a cancer 13 days after the initiation of treatment. It was highly unlikely that these two cases were drug related.*

Subject 513473, a 74-year old Japanese male, discontinued treatment due to severe depression after being treated with darifenacin 15mg qd for 6 months. 23 days after the drug was stopped, he committed suicide. This was a confounded case because the patient had 20 years of psychiatric history and was hospitalized many times due to this condition. At this time, it appears that it is more likely that the depression episode that led to patient's death was associated with his psychiatric history, though the role of darifenacin cannot be completely excluded.

3. Serious Adverse Events (SAE):

For the 6,655 unique subjects treated with darifenacin in all completed Phase 1,2 and 3 clinical studies, 189 subjects experienced at least one serious adverse events. Table VII-C-3.1 shows the overall incidence rates of the serious adverse events in darifenacin and placebo treated groups.

Comments: *While the number of subjects with serious adverse events is similar between two groups after adjusting for the length of treatment, it appears that the number of serious events reported per 100 person years is slightly higher in darifenacin groups than placebo groups (18.4 Vs. 16.4). Table VII-C-3.2 identifies serious events that require further analysis. These events were either closely related to a body system that is the target of darifenacin's potential pharmacological effect or occurred in a much higher rate in darifenacin groups.*

Table VII-C-3.1 Incidence of serious adverse events by treatment group in darifenacin clinical development program – a pooled analysis of all completed clinical studies

	Darifenacin	Placebo
Total number of subjects	6,655	2,216
Total person years of exposure	1462	329
Total number of subjects with serious events	189	40
Total number of subjects with serious events per 100 person years	12.9	12.1
Total number of serious events reported	269	54
Total number of serious events reported per 100 person years	18.4	16.4

Source Data: Table 34.4.3 of 2.7.4 Summary of Clinical Safety

Table VII-C-3.2 Incidence of serious adverse events by treatment group in darifenacin clinical development program – a pooled analysis of all completed clinical studies

	Darifenacin (N=6655, PYE*=1462)		Placebo (N=2216, PYE*=329)	
	Number	Rate (Per 100 PYE)	Number	Rate (Per 100 PYE)
Events That Are Directly Related to the Drug's Pharmacological Effects				
Constipation	5	0.34	1	0.30
Urinary retention	7	0.48	0	0
Events That May Be Indirectly Related to the Drug's Pharmacological Effects				
Acute renal failure	1	0.07	0	0
Intestinal Obstruction	2	0.14	0	0
Events of GI System				
Appendicitis	6	0.41	0	0
Cholecystitis	5	0.34	0	0
Events with Unusually High Rates				
Bone fracture	15	1.03	0	0

Source Data: Table 34.4.1 of 2.7.4 Summary of Clinical Safety
* PYE = person-year exposure

A. Constipation and Urinary Retention:

Since the subjects under these two categories represents those with more severe clinical presentations, they will be discussed in Sections 5.2 and 6.

B. Renal Failure:

Subject 51267126 (Study A1371017): A 83-year-old Asian female in Japan received darifenacin in this long-term safety study following participation in the dose-response study, A1371012 where she received darifenacin 7.5mg per day for approximately 40 days. After ten months of darifenacin treatment (30mg qd), she reported general malaise and urination difficulty for one week and then was found

dehydrated with a decreased level of consciousness. She was hospitalized and catheterized, at which time 1400ml of urine was collected. She was diagnosed with urinary retention, bilateral hydronephrosis, and post-renal failure. The study drug was permanently discontinued. The patient's urinary retention was resolved at 16th day after the hospitalization and was discharged one week later. In the investigator's opinion, the urinary retention was due to study drug. The investigator believed that the events bilateral hydronephrosis and post-renal failure were due to urinary retention. In the sponsor's opinion, bilateral hydronephrosis and post-renal failure were most likely due to urinary retention or other illness, and were not a direct effect of study drug.

Comments: *This case clearly demonstrates that the severe clinical consequence can occur if urinary retention is not discovered early and treated appropriately. Aging, high dose of darifenacin and possible delay in the treatment all contributed to the development of acute renal failure. While the sponsor did not request 30mg dose to be approved in this NDA, the product labeling should clearly state* [redacted] *urinary retention and*

C. Appendicitis (with or without concomitant intestinal obstruction):

A total of six subjects in darifenacin groups and none in placebo group reported appendicitis as serious adverse events. All subjects were hospitalized. Five subjects developed appendicitis while being treated with darifenacin and one subject developed appendicitis 21 days post last dose Table VII-C-3.3 shows demographic and clinical characteristics of these six subjects. Three subjects reported perforated appendix and two bowel obstruction.

Table VII-C-3.3 List of subjects with a diagnosis of appendicitis in darifenacin clinical development

ID	Protocol # (137-X)	Age/Sex Country	Dose /Onset	Clinical Presentation
Controlled Studies				
00450403	305	72/M Finland	30mg/6 days	Appendicitis and Perforated Appendix
01160187	351	25/F Finland	5mg/6 days	Acute Appendicitis
00280022	224	45/M Belgium	7.5mg/42 days	Acute Appendicitis (21 days post treatment)
Uncontrolled long-term Studies				
50600891	1014	55/F US	30mg/250 days	Appendicitis, Perforated Appendix, Bowel obstruction
04230226	359	42/F Australia	7.5mg/63 days	Acute Appendicitis
51537594	1017	65/F Japan	30mg/107 days	Appendicitis, Peritonitis and Bowel obstruction

Source Data: Table 34.2.1 of 2.7.4 Summary of Clinical Safety

Comments: *Of five appendicitis cases that occurred while the patients were being treated with darifenacin, only two occurred during treatment in placebo controlled studies. The following is a brief summary of these two cases:*

Subject 00450403 (Study 305): A 72 year old white male with a history of detrusor instability from Finland participated in this multicenter, double blind, placebo controlled trial of a 12-week duration on [redacted]. *He was treated with Ditropan before study enrollment and was assigned to receive darifenacin 30mg daily (10mg tid). On the 6th day after the initiation of darifenacin treatment, patient developed acute appendicitis. The drug was temporarily stopped and PI considered this event was moderate in severity. In SAE table, "perforated appendix" was mentioned. However, this reviewer could not find this description in CRF. The event was resolved one week later and patient continued the treatment without withdrawal from the study. PI did not consider that this event was drug-related.*

Subject 01160187 (Study 351): A 25 year old white female with a history of irritable bowel syndrome from Finland participated in this multicenter, double blind, placebo controlled trial of a 12-week duration on 15 December 1994. According to SAE table, she was assigned to receive darifenacin 5mg daily. However, this trial did not have 5mg qd group. Most likely this patient received darifenacin 5mg tid for a total daily dose of 15mg. Three days after the initiation of darifenacin treatment, the patient complained about diarrhea and developed severe abdominal pain two days later. She was diagnosed to have "acute appendicitis" and underwent appendectomy. The event was resolved one week later and the study drug was permanently discontinued. PI did not consider that this event was drug-related.

While it is biologically possible that darifenacin contributed to the development of appendicitis by its pharmacological effect on GI system, there is no reasonable evidence to support this hypothesis at this time. None of these two patients had severe constipation prior to the events and they occurred with darifenacin immediate release formulation which now has been discontinued.

Since the person years of exposure in darifenacin group were at least three times higher than that in the placebo groups, there is little statistical evidence to suggest an association between the drug and acute appendicitis. There is also little evidence to suggest that incidence rate in the open label groups is higher than that of the background rate.

Nevertheless, it would appear prudent to request the actual pathology and surgical reports in order to confirm the diagnosis of appendicitis in these

cases. Further, it is comforting that bowel obstruction was not reported outside the context of an acute appendicitis episode.

D. Cholecystitis:

Cholecystitis was identified as one of the safety concerns at FDA 74-day filing meeting. The sponsor provided a written response to address FDA's concern on 16 April 2003.

In the written response, the sponsor identified three additional cases of cholecystitis reported as serious adverse events since the original submission of NDA. Of these eight cases, two were reported in the randomized, controlled studies but only one was acute cholecystitis. The other was found by incidental cholecystectomy performed during elective hiatal hernia repair. Of six cases that occurred in darifenacin open label studies, only three were acute cholecystitis. All subjects had at least one risk factors for cholecystitis, including gallbladder stone, overweight/obesity, and hypercholesterolemia.

Table VII-C-3.3 List of subjects with a diagnosis of cholecystitis in darifenacin clinical development

ID	Protocol # (137-X)	Age/Sex Country	Dose /Onset	Clinical Diagnosis
Controlled Study				
06050095	666	85/F USA	15mg/ 13day	Cholecystitis and cancer of gallbladder
11550068	1047	69/F Canada	15mg/ 28 days	Acute Cholecystitis
Uncontrolled Long-Term Studies				
00350286	311	40/M Norway	30mg-15mg/ 64 days	Acute cholecystitis and gall bladder stone
50260068	1014	75/F USA	30mg/ 150 days	Acute cholecystitis and biliary colic
50270705	1014	69/F USA	30mg/ 75 days	Acute cholecystitis and cholelithiasis
50520854	1014	72/F USA	30mg 303 days	Chronic cholecystitis and appendiceal carcinoma
10840112	1042	72/F Unknown	3.75-15mg 211 days	Cholesystitis
11100422	1042	53/F Unknown	15mg 223 days	Cholecystitis

Source Data: Table 17 of Response to FDA request for information dated 16 April 2003

Comments: *At this time, this reviewer identified only one acute cholecystitis from controlled clinical trials. With 969 and 357 person years of exposure in darifenacin and placebo groups, respectively, there is little statistical evidence suggesting an association between acute cholecystitis and the drug. All open label cases have risk factors for cholecystitis. The incidence rate of acute cholesystitis in open label studies was 0.42 per 100 person years (3/722 person years), which is consistent with literature data, where the rate of*

hospitalization for cholecystitis has been estimated as being between 0.38 and 0.86 per 100 person-years.

E. Bone Fractures:

Table VII-C-3.4 shows 16 darifenacin-treated subjects who had a bone fracture that required hospitalization and was being reported as serious events. 9 cases occurred in controlled clinical trials and 7 from uncontrolled long-term studies. The bone fractures were related to a fall or a road traffic accident or accident in the majority of cases (14) except for Subject #0461481 in Study 1041 (unknown) and Subject #00550108 in Study 305 (possible osteoporosis). According to principle investigator's assessment, causality was not assigned to study drug for any of these events.

None of subjects in the placebo group and one subject in the active control group had bone fracture that required hospitalization. Subject 1106-115, a 68 years old of female from a controlled OAB Study 1011, had a humerus fracture 87 days after starting tolterodine 2mg. The fracture was said to be related to an accident but the nature of the accident is unknown.

Comments: *In addition to 15 events in Table VII-C-3.2, this reviewer identified one more bone fracture event (Subject # 00550108 in Study 305).*

The reviewer noted that 14 out of 16 cases were related to fall (10), road traffic accident (3) or other accident (1). The reasons for the fracture were unknown for one subject and were claimed to be related to osteoporosis in an another subject.

The reasons for fall were absent in four subjects. In another six subjects where the reasons for fall were stated, the submitted data did not provide an adequate assurance that the drug did not play a role in the fall except for Subject # 1126128 in Study 1041 who had a fall due to a dog attack.

For three subjects who were involved in road accident, only one was reported not to have had dizziness or blurred vision. In addition, one subject had a fracture due to an accident of unknown origin.

This reviewer also noted an uneven distribution of the "serious" bone fracture cases – all in darifenacin-treated group and none in placebo groups. This reviewer acknowledges that some of these cases had occurred in uncontrolled long-term trials and combining data from controlled and uncontrolled trial may be problematic.

Clinical Review Section

Table VII-C-3.4 List of subjects with a diagnosis of bone fractures in darifenacin clinical development

ID	Protocol #	Age/Sex Country	Dose /Onset	Clinical Presentation (PI Assessment)
OAB Phase 2/3 Controlled Studies				
5060839	1001	89/F USA	30mg/ 8 days	Fracture of right ankle (Fall – slipped on a wet floor)
04560810	1002	44/F Sweden	15mg/ 54 days	Fractured 12th thoracic vertebra (Fall - horse riding)
1059341	1013	70/M Norway	30mg/ 75 days	Right Femur Fracture (Fall - due to alcohol use)
0461481	1041	68/M Denmark	7.5mg/ 54 days	Fractured right distal radius (Unknown)
1126128	1041	55/F Australia	3.75mg/ 11 days	Broken left leg (Fall - attacked by dog)
Other Controlled Studies				
00550108	305	73/F Sweden	7.5mg/ 80 days	Fracture of lumbar spine (Unknown - possible osteoporosis)
1145066	305A	28/M France	15mg/ 218 days	Compression fracture lumbar spine (Road traffic accident)
3110245	356	25/F	3.75mg/ 53 days	Neck injury and nose fracture (Road traffic accident)
10280002	1010	32/M Spain	30mg/ 8 days	Fracture of hip (Road traffic accident - Denied dizziness or blurred vision)
Uncontrolled Long-Term Study				
0260016	311	55/F UK	15mg/ 61 days	Broken wrist (Fall - slipped on ice)
3010192	311	46/F UK	30mg/ 40 days	Accidental pelvic fracture (Fall – weakness from multiple sclerosis)
51327127	1017	83/F Japan	15mg/ 12 days	Right leg fracture (Fall - Unknown)
50777016	1017	65/F Japan	15mg/ 39 days	Compression Fracture (Fall - Unknown)
50817068	1017	70/M Japan	7.5mg/ 107 days	Fracture of right hip (Fall – Alcohol use)
11404102 23	1042	68/F Poland	7.5mg 70 days	Fractured Hip (Fall - Unknown)
11414101 93	1042	46/M Poland	7.5mg Unknown	Right leg fracture (Accident – unknown)

Source Data: Table 34.2.1 of 2.7.4 Summary of Clinical Safety and response to request for information dated 12 September 2003.

It is noted that 9 out of 16 cases occurred in placebo-controlled trials (see table). In particular, each of the three pivotal trials had a case in darifenacin-treated group but not in placebo groups. However, this reviewer also noted that number of subjects taking darifenacin in three pivotal trials was approximately three times higher that that in the placebo group.

The lack of detailed event description, uneven distribution of the subjects who were exposed to darifenacin and placebo, and relative small number of events from the controlled trials do not allow this reviewer to draw any final conclusions regarding the relationship between darifenacin and bone fracture as a result of fall or accident. The pattern observed in darifenacin clinical development program, however, is a concern. It appears that it is reasonable to request that the sponsor conduct a Phase 4 large simple safety study to fully resolve this issue. A discussion of such a trial design can be found under Section X.

4. Adverse Events Associated with Dropouts:

In three OAB fixed dose Phase 3 studies (1001, 1002, and 1041), 5.6% and 12.9% patients prematurely discontinued from the studies in 7.5mg and 15mg groups respectively, compared to that of 8.0% in the placebo groups. The overall incidence of discontinuation due to adverse events was significantly greater in darifenacin 15mg group (5.1%) than that of the placebo group (2.6%). Constipation was the leading cause for AE-related study discontinuation (0.6% and 1.2% for 7.5mg and 15mg groups respectively) (Table VII-C-4).

Table VII-C-4 Study discontinuation in three OAB fixed dose phase 3 studies – a pooled analysis of Study 1001, 1002, and 1041

Adverse Events	Darifenacin 7.5mg N=337 (PYE*=77)	Darifenacin 15mg N=334 (PYE*=73)	Placebo N=338 PYE*=87
Discontinued (All causes)	19 (5.6%)	43 (12.9%)	31 (8.0%)
Discontinued due to AE	5 (1.5%)	17 (5.1%)	10 (2.6%)
Constipation	2 (0.6%)	4 (1.2%)	1 (0.3%)
Dry mouth	0 (0%)	3 (0.9%)	0 (0%)
Dyspepsia	0 (0%)	3 (0.9%)	0 (0%)
Cardiovascular system	1 (0.3%)	1 (0.3%)	1 (0.3%)
Nervous system	0 (0%)	2 (0.6%)	3 (0.8%)
Urogenital system	0 (%)	0 (0%)	2 (0.5%)

Source data: Table 13.1 and 19.1 of 2.7.4 Summary of Clinical Safety
PYE = person-year exposure

***Comment:** Adverse events accounted for less than 50% of all study discontinuation in the three Phase 3 pivotal studies. The AE-related dropout rate provided a reasonable indicator of the drug's tolerability. It appears that 7.5mg was well tolerated as the incidence of AE-related discontinuation rate (1.5%) was not greater than that in the placebo group*

(2.6%). However, the discontinuation rate in 15mg groups is slightly higher(5.1%).

A second reason for conducting a dropout analysis is to screen for any clinically significant adverse events that might have not been reported as serious events. This reviewer examined the original Table 13.1 in the NDA submission which showed a list of dropout-related adverse events. No consistent pattern suggests any additional potential safety concerns than what had been suggested by the analyses of the subjects with death and serious adverse events.

5. Common Adverse Events:

5.1 What are the common adverse events and their frequencies in subjects taking the proposed dose regimens (7.5mg or 15mg qd)?

Based on a pooled analysis of three pivotal Phase 3 studies (1001, 1002 and 1041), 54% and 66% of subjects in darifenacin 7.5mg and 15mg groups, respectively, reported one or more adverse events (AE) during a 12-week period, compared to that of 49% in placebo groups (Table VII-C-5.1.1). The percentage of subjects in whom the AE was rated as severe is comparable between darifenacin 7.5mg and placebo groups (7%), but is a slightly higher in darifenacin 15mg group (11%).

Table VII-C-5.1.1 Incidence of adverse events and their severity – a pooled analysis of three pivotal phase 3 studies (1001, 1002 and 1041)

Treatment group	Number of Subject Enrolled	Subject with Adverse Events			
		Total	Mild	Moderate	Severe
Darifenacin 7.5mg	337	182 (54%)	133 (40%)	84 (25%)	24 (7%)
Darifinacin 15mg	334	219 (66%)	168 (50%)	113 (34%)	37 (11%)
Placebo	388	189 (49%)	124 (32%)	3112 (29%)	27 (7%)

Source data: Table 43 of Summary of Clinical Safety (page 82)

Table VII-C-5.1.2 summarizes the adverse events by body system. Data suggest that the GI, urogenital and special senses were the systems that were most frequently affected by the drug in a dose-dependant fashion. It appears that the drug may have little effect on cardiovascular system and little evidence suggests an association between nervous system and the drug.

Table VII-C.5.1.2 Summary of adverse events by body system – a pooled analysis of three pivotal phase 3 studies (1001, 1002 and 1041)

Adverse Events	Darifenacin 7.5mg N=337 (PYE*=77)	Darifenacin 15mg N=334 (PYE*=73)	Placebo N=338 PYE*=87
Digestive	121 (35.9%)	167 (50.0%)	80 (20.6%)
Body as a whole	47 (13.9%)	59 (17.7%)	70 (18.0%)
Respiratory	29 (8.6%)	41 (12.3%)	52 (13.4%)
Urogenital	24 (7.1%)	37 (11.1%)	22 (5.7%)
Nervous	12 (3.6%)	25 (7.5%)	28 (7.2%)
Special senses	9 (2.7%)	19 (5.7%)	6 (1.5%)
Skin and appendages	14 (4.2%)	16 (4.8%)	22 (5.7%)
Metabolic and nutritional	10 (3.0%)	13 (3.9%)	17 (4.4%)
Cardiovascular	21 (6.2%)	12 (3.6%)	9 (2.3%)
Musculoskeletal	11 (3.3%)	11 (3.3%)	14 (3.6%)
Hemic and lymphatic	2 (0.6%)	4 (1.2%)	6 (1.5%)
Endocrine	0	0	2 (0.5%)

Source data: Table 12.1 of Summary of Clinical Safety

Table VII-C-5.1.3 shows the selected adverse events that occurred in more than 1% subjects in darifenacin 15mg group and at a greater frequency compared with the subjects in placebo group. The most common events were dry mouth, constipation and dyspepsia. The majority of the common adverse events appears to be dose dependent.

Table VII-C.5.1.3 Incidence of adverse events occurring at > 1% in darifenacin 15mg group by treatment group – a pooled analysis of three pivotal Phase 3 studies (1001, 1002 and 1041)

Adverse Events	Darifenacin 7.5mg N=337 (PYE*=77)	Darifenacin 15mg N=334 (PYE*=73)	Placebo N=338 PYE*=87
Dry mouth	68 (20.2%)	118 (35.3)	32 (8.2%)
Constipation	50 (14.8%)	71 (21.3%)	24 (6.2%)
Dyspepsia	9 (2.7%)	28 (8.4%)	10 (2.6%)
Urinary tract infection	16 (4.7%)	15 (4.5%)	10 (2.6%)
Abdominal pain	8 (2.4%)	13 (3.9%)	2 (0.5%)
Asthenia	5 (1.5%)	9 (2.7%)	5 (1.3%)
Dizziness	3 (0.9%)	7 (2.1%)	5 (1.3%)
Dry eyes	5 (1.5%)	7 (2.1%)	2 (0.5%)
Rhinitis	2 (0.6%)	6 (1.8%)	5 (1.3%)
Dry skin	0	6 (1.8%)	2 (0.5%)
Nausea	9 (2.7%)	5 (1.5%)	6 (1.5%)
Abnormal vision	2 (0.6%)	5 (1.5%)	1 (0.3%)
Accidental injury	4 (1.2%)	4 (1.2%)	2 (0.5%)
Arthralgia	2 (0.6%)	4 (1.2%)	3 (0.8%)

Source data: Table 45 of 2.7.4 Summary of Clinical Safety (page 84)

Comments: *It is apparent that the most common special sense-related adverse events were abnormal vision and dry eyes, which are expected based on the anticholinergic effect of the drug. No further analysis will be conducted. In some sense, however, this finding suggest that M3 selectivity does not mean*

urologic selectivity. The three most common adverse events will be discussed in the next section (Section 5.2) and the cardiovascular effect will be discussed in Section 6.

It is noted that a higher percent of subjects developed UTI in darifenacin groups (4.5% - 4.7%), compared to that (2.6%) in the placebo group. Table VII-C-5.1.4 shows the percent of subjects who reported UTI in each of the three pivotal studies (1001, 1002 and 1041). The evidence presented in three studies consistently suggests that darifenacin may be associated with UTI and this effect was not dose-dependent. Of 31 UTI subjects in two treatment groups, only one subject was rated as severe. None of the subjects discontinued from the studies due to UTI. In addition, 68 (3.7%) of 1833 darifenacin-treated subjects in OAB Phase 2/3 controlled studies developed UTI, compared to that of 15 (2.1%) in placebo-treated subjects (N=703). The reason for this association is unclear, but may be related to increased post-void residual urine retention. Risk of UTI should be adequately stated in the product labeling.

Table VII-C.5.1.4 Incidence of UTI by treatment group in each of three pivotal phase 3 studies (1001, 1002 and 1041)

Adverse Events	Darifenacin 7.5mg	Darifenacin 15mg	Placebo
Study 1001	----	(N=112)	(N=115)
	----	7 (6.3%)	5 (4.3%)
Study 1002	(N=108)	(N=107)	(N =109)
	3 (2.8%)	3 (2.8%)	2 (1.8%)
Study 1041	(N= 229)	(N=115)	(N=164)
	13 (5.7%)	5 (4.3%)	3 (1.8%)

Source Data: Table 6.1.3 of Study Report 1001, 1002, and 1041

5.2 What are characteristics of three most common adverse events?

Table VII-C-5.2.1 shows time of onset, severity and duration of the three most common adverse events. Majority of these events were judged as either mild or moderate in nature and did not lead to discontinuation of treatment.

? **Dry mouth**: It was the most commonly reported adverse event in the darifenacin clinical program and had occurred in 20.2% and 35.3% of subjects treated with darifenacin 7.5mg and 15mg respectively for 12 weeks. 1.4% and 8.5% of the events in the two groups were rated as severe in nature and approximately 60-70% of event occurred in the first week of the treatment.

? **Constipation**: It was the second most commonly reported adverse event in the darifenacin clinical program and had occurred in 14.8% and 21.3% of subjects treated with darifenacin 7.5mg and 15mg respectively for 12 weeks. 2 (4.0%) and 9 (12.6%) of the events in the two groups were rated as severe in nature. Despite anti-constipation treatment, all 2 subjects and 5 out of 9 subjects who developed severe constipation still suffered from constipation at the end of the study (Source data: Table 68 of 2.7.4 Summary of Clinical Safety). More subjects in darifenacin 15mg group had constipation within the first week than that in 7.5mg group (66.2% vs. 38.0%).

? **Dyspepsia:** Dyspepsia is the third most commonly reported adverse event, which encompasses a variety of symptoms including indigestion, heartburn and gastroesophageal reflux. Approximately 50% of the events occurred in the first week of the treatment.

Table VII-C-5.2.1 Time of onset, severity and duration of the three most common adverse events

Adverse Events	Number of Subjects with the Event	% Rated as Severe	% Dropouts	% within first week
Darifenacin 7.5mg				
Dry mouth	68	1.4%	0%	60.3%
Constipation	50	4.0%	4%	38.0%
Dyspepsia	9	33.3%	0%	44.4%
Darifenacin 15mg				
Dry mouth	118	8.5%	3%	66.9%
Constipation	71	12.6%	5.6%	66.2%
Dyspepsia	28	17.8%	10.7%	50.0%

Source Data: Table 15 of 2.5 Clinical Overview and Table 13.1, 22.1, 23.2, 23.7 and 24.1 of 2.7.4 Summary of Clinical Safety

Comment: *The GI side effects listed here are the expected from an muscarinic antagonist. Again, this highlights the fact that darifenacin does not act clinically as a "uro-selective" anti-muscarinic. Darifenacin 7.5mg appears to provide a better safety profile. Compared to darifenacin 15mg, the incidence rates of dry mouth and constipation for the 7.5mg dose over a 12-week period are by 43% and 31% lower, respectively. The incidence rate of dyspepsia in darifenacin 7.5mg group was similar to that of placebo group.*

Among the three GI events, this reviewer is most concerned about constipation because it may lead to serious clinical consequence, such as intestinal obstruction. In OAB fixed dose Phase 3 studies, 7 subjects with severe constipation remained constipated at the end of the study despite anti-constipation treatment. In the darifenacin clinical development program, three of the serious adverse events reported were constipation-related. Table VII-C-5.2.2 shows the characteristics of those three cases. Though none of these subjects required any surgical intervention or suffered serious sequelae of constipation such as sustained intestinal obstruction or perforation, constipation-related sequelae remains as a possibility. The risk of constipation should be emphasized in the product labeling ⊏

⊐ *In addition, the label should emphasize use of the lowest dose sufficient to achieve symptomatic relief.*

Table VII-C-5.2.2 List of three serious constipation-related adverse events in darifenacin clinical program

ID	Protocol # (137-X)	Age/Sex Country	Dose /Onset	Clinical Diagnosis (Actions Taken and Outcomes)
Controlled Study				
00350282	311	36/M Norway	30mg/ 155 days	Constipation (hospitalized and resolved without serious sequelae)
11300088	1015	66/F UK	60mg/ 12 days	Abdominal distension and acute constipation (hospitalized, NG-Tube inserted, the drug stopped, and resolved without serious sequelae)
04410051	1026	76/M France	15mg/ 12 days	Abdominal pain and constipation (hospitalized, drug stopped, and resolved without serious sequelae)

Data source: Table 34.2.1 and Appendix D of 2.7.4 Summary of Clinical Safety

6. Less Common Adverse Events:

Table VII-C-6.1 and Table VII-C-6.2 show the incidence of three adverse events (tachycardia, palpation and urinary retention) that are typically related to antimuscarinic drugs but were not listed under the common AE table due to their low frequency. The analyses were based on (1) three Phase 3 pivotal studies in OAB patients (Table VII-C-6.1), (2) OAB Phase 2/3 controlled studies and (3) Phase 2/3 OAB/IBS studies (Table VII-C-6.2), respectively.

Table VII-C-6.1 Incidence of tachycardia, palpation and urinary retention in three pivotal phase 3 studies (1001, 1002, and 1041)

Adverse Events	Darifenacin 7.5mg N=337 (PYE*=77)	Darifenacin 15mg N=334 (PYE*=73)	Placebo N=338 (PYE*=87)
Tachycardia	2 (0.6%)	0 (0%)	0 (0%)
Palpation	1 (0.3%)	1 (0.3%)	0 (0%)
Urinary retention	1 (0.3%)	0 (0%)	0 (0%)

Source Data: Table 12.1 of 2.7.4 Summary of Clinical Safety

* PYE = person-year exposure

Table VII-C-6.2 Incidence of tachycardia, palpation and urinary retention in (1) OAB Phase 2/3 controlled studies and (2) Phase 2/3 OAB/IBS studies

Adverse Events	OAB phase 2 & 3 controlled studies		Phase 2 & 3 OAB/IBS studies	
	Darifenacin (n=1833) PYE=355*	Placebo (n=703) PYE=144	Darifenacin (n=5398) PYE=1414	Placebo (n=1910) PYE=322
Tachycardia				
N	5	1	54	15
Percent	0.3%	0.1%	1.0%	0.7%
Rate (per 100 person-year)	1.4	0.7	3.8	4.6
Palpitation				
N	9	4	43	21
Percent	0.5%	0.6%	0.8%	1.1%
Rate (per 100 person-year)	2.5	2.8	3.0	6.5
Urinary retention				
N	18	2	43	3
Percent	1.0%	0.3%	0.8%	0.2%
Rate (per 100 person-year)	5.1	1.4	3.0	1.0

Source Data: Table 12.2 and 12.4 of 2.7.4 Summary of Clinical Safety

* PYE = person-year exposure

Comments: *The sponsor claims that as a selective muscarinic M3 receptor antagonist, darifenacin would not be expected to be associated with tachycardia. An analysis of pooled heart rate data in phase 1 PK/PD studies showed that darifenacin did not increase the heart rate at any dose evaluated. While the data presented here from three different combinations of studies did not show a consistent pattern suggestive that darifenacin is associated with tachycardia or palpitation, this reviewer believes that the drug still has the potential to cause tachycardia. However, the risk is relatively low. The conclusion is mainly based on the data from the pooled analysis of OAB Phase 2/3 controlled studies in which the incidence rates of tachycardia were 1.4 and 0.7 per 100 person years for darifenacin and placebo treated subjects, respectively. In the same pooled analysis, a total 450 subjects were treated with an active comparator with approximately 100 person-year exposure. The incidences of tachycardia and palpation were 4 and 5 per 100 person years, respectively.*

Data presented in this review show a consistent pattern that darifenacin is associated with urinary retention. Investigator texts for this term included incomplete bladder emptying, incomplete voiding of the bladder, incomplete urinary voiding, unable to empty bladder, difficulty emptying the bladder, feeling of urine retention, temporary retention of urine, persistent urinary retention and recurrent urinary retention. This review focused on six "urinary retention" cases identified by PI as acute or required catheterization or were classified a serious event in subject taking 7.5mg or 15mg dose. Table VII-C-6.3 shows the characteristics and clinical outcomes of these six subjects. All urinary retention resolved after either intervention or discontinuation of treatment. For some of these patients, the role of

darifenacin in causing urinary retention can not be determined with a great certainty. Labeling must fully describe this risk to prescribing physicians and patients.

It is particularly notable that four of these patients were men, including three older men and are one young man with paraplegia. This is even more notable when one consider that roughly 70% of trial subjects were women. Thus the risk of urinary retention for older men with co-existing urinary outflow obstruction may be much higher. Use of darifenacin in such a patient population requires a careful discussion between patients and their physicians. In the opinion of this reviewer, the drug should not be prescribed to men with severe urinary outflow obstruction.

Table VII-C-6.3 List of five subjects with a clinical significant "urinary retention" while being treated with 7.5mg or 15mg dose

Subject ID	Study ID	Age/Sex	Dose	Time Onset	Intervention	Other Significant Events
01600008	137-310	74/male	5mg tid	3 days	Hospitalized and Catheter	Discontinued from the study
00260013	137-311	41/female	15mg	1 day	Catheter	AUR occurred again at a lower dose
01140305	137-305	24/male	2.5mg tid	65 days	Catheter	Paraplegic patient
04400151	137-1026	76/male	15mg	11 days	None	BPH-related outflow obstruction
00610573	137-1041	80/female	7.5mg	?	Catheter	Post-Operative patient
51290260	137-1012	74/male	15mg	3 days	Catheter	Discontinued from the study

7. Vital Signs:

Table VII-C-7 summarizes median change from baseline to endpoint for vital signs in three OAB fixed dose pivotal studies. There are no differences between the darifenacin and placebo groups in median blood pressure and pulse rate changes during studies.

Table VII-C-6.1 Median changes in vital signs from baseline to study endpoint – a pooled analysis of three OAB fixed dose pivotal studies (1001, 1002, and 1041)

Vital Signs	Baseline Value		Median Change from Baseline	
	Placebo (n=375)	Darifenacin (n=1042)	Placebo (n=375)	Darifenacin (n=1042)
Systolic blood pressure (mmHg)	130	130	0	0
Diastolic blood pressure (mmHg)	80	80	0	0
Heart rate (beats per minute)	72	72	0	0

Source Data: Table 25.1 of 2.7.4 Summary of Clinical Safety

Comments: *220 subjects received an active comparator in one of the pivotal trials. Median pulse rate change from baseline was 2 for this group.*

Table VII-C-6.2 Median changes pulse rate from baseline to study endpoint – a pooled analysis of single or multiple dose studies in healthy volunteers

Pulse Rate (bpm) at Supine position	Baseline Value		Median Change from Baseline	
	Placebo	Darifenacin	Placebo	Darifenacin
Single dose studies	(n=43) 62	(n=131) 63	4	1
Multiple dose studies	(n=66) 65	(n=568) 62	2	4

Source Data: Table 25.3 and 25.4 of 2.7.4 Summary of Clinical Safety

Comments: *In single dose studies, no association between darifenacin and pulse rate was observed. In multiple dose studies, a median change of 2 bpm was observed after adjusting for placebo effect. It is noted that pulse rates for two groups in multiple studies were not the same.*

Since a pooled analysis may produce a false negative result, this reviewer made an effort to examine the drug's potential on heart rate in Study 1015. Study A1371015 was a randomized, placebo controlled, parallel group study in 62 healthy male and female volunteers [56 extensive metabolisers (EM) and 6 poor metabolisers (PM)] aged 50 years or over. Subjects were dosed with either darifenacin 60mg (n = 42), or darifenacin 30mg (n =10) or placebo (n = 10) for 14 days. Pulse rate were taken in supine position at baseline (day 1) and at the end of the study on Day 15 (steady status).

Data were available from 38 and 10 subjects treated with darifenacin 60mg and placebo for 14 days, respectively. The pulse rates at baseline for these two groups were the same (61 bpm). On the last observation at Day 15, the median changes from the baseline were 5.5 and 8.0 bpm for darifenacin and placebo groups, respectively (Source Data: Table 8 of Final Study Report for Study 1015).

Conclusion: *The totality of the evidence suggest that darifenacin, in general, is not associated with the increase in pulse rate. However, the drug may still have the potential to cause tachycardia in a very small group of patients when the drug is used alone or when combined with other factors.*

8. Laboratory Findings:

8.1 What are the routine laboratory tests and schedules?

In three OAB fixed dose pivotal studies, the following laboratory safety tests were performed on samples taken at baseline and the last visit (Visit 6):

- Haematology: haemoglobin (Hb), haematocrit (HCT), red blood cell count (RBC), white blood cell (WBC) and platelet count, lymphocytes, monocytes, neutrophils, basophils and eosinophils.
- Biochemistry: total bilirubin, albumin, total protein, aspartate transaminase (AST or SGOT), alanine transaminase (ALT or SGPT), alkaline phosphatase (AP), non-fasting glucose and electrolytes - sodium and potassium.
- Renal Function: blood urea nitrogen (BUN) and creatinine.
- Urinalysis: by standard dipstick test on midstream specimens for pH, protein, glucose, ketones and blood. A mid stream sample was sent to the central laboratory for microscopy and culture if the stick test was positive.

All laboratory tests were carried out in a central laboratory approved by the sponsor. Data were transferred electronically to the sponsor and a hard copy was sent to the center.

8.2 What are the results of lab tests?

VII-C-8 shows the median change from baseline to the study endpoint for key lab results in three OAB fixed dose pivotal studies. The liver function or enzymes tests results will be discussed later under Section 10 (Liver safety).

> ***Comment:*** *The median changes from baseline to the study endpoint are comparable between darifenacin and placebo groups in three OAB fixed dose studies. In addition, this reviewer employed an outlier analysis which also failed to reveal any safety signals (data not shown).*

Table VII-C-8. Listing of lab test results for subjects with normal baseline in three OAB fixed dose pivotal studies

Laboratory Tests	Placebo			Darifenacin		
	N	Baseline	Median Change	N	Baseline	Median Change
Hemoglobin (F)	320	15.55	-0.07	820	15.47	-0.07
Hemoglobin (M)	52	15.66	-0.07	148	15.37	0
Platelets	347	231.7	-4.3	951	231.7	-1.23
White blood cells	354	5.9	0	967	5.8	-0.08
Glucose	361	81.09	-0.64	986	81.09	0
Potassium	361	4.21	0	986	4.21	0
Sodium	361	140.23	0	986	140.60	0
Creatinine	362	1.15	0	986	1.07	0
Urea	362	32.35	1.09	986	32.89	0

Source data: Table 21.1 of 2.7.4 Summary of Clinical Safety

9. QT Safety:

9.1 What is extent of ECG/QT testing in the darifenacin development program?

QT safety assessments of darifenacin were conducted in both Phases 1 and 3 clinical trials. Data derived from ECG's were digitized and centrally read from five studies, which formed the basis for the analysis and interpretation of the effects of drug treatment on the QT interval (Table VI-C-9.1). The sponsor stated that all other studies included the recording of ECGs at the screening visit and/or the final follow-up visit off treatment, and so these could not be analyzed to assess the effect of drug.

> ***Comment:*** *During the review, the clinical pharmacology reviewer identified one additional study (Study 1035) in which on treatment ECG measurements were taken. In their response to request for information dated 20 August 2003, the sponsor also identified a few more studies in which on-treatment ECG measurements were taken. However, no QT data from those studies were available for the analysis at this time.*
>
> *In a subsequent submission dated 17 September 2003, the sponsor summarized the QT results of 1035. The result will be discussed in a later section of this review.*

Two of five studies were Phase 3 studies and the rest were Phase 1 PK/PD studies. In these five studies, ECG's were recorded several hours (~4-9 hours) following the prescheduled dosing in the morning and immediately prior to a blood sample being taken for PK measurement.

Due to study withdrawal or a dose reduction, not all subjects listed under Table VI-C-9.1 have QT safety data available for the analysis. A total of 1,002 darifenacin treated subjects and 261 placebo treated subjects contributed digitized ECG data from Studies 137-684, A1371002, A1371007, A1371015 and Study A1371005. The doses used in these studies ranged from 3.75mg to 60mg. The highest serum concentrations were achieved when darifenacin 30mg was co-administrated with ketoconazole 400mg for a total of 6 days in subjects in Study A1371007.

Table VII-C-9.1 Characteristics of three phase 1 PK/PD and two phase 3 studies in which ECG assessments were assessed at baseline and on-treatment

Study ID	Type of Subjects (M:F)	Dose Tested	Total Treatment Days	Number of Subjects	Sex (M:F) And Age range	Time of ECG in Relation to Dosing
Phase 3 Studies (Fixed Dose)						
137-684	IBS patients	Placebo 3.75mg 7.5mg 15mg 30mg		155 157 166 156 153	Sex (213:569) Age (18-83)	Any time
A137-1002	OAB patients	Placebo 7.5mg 15mg 30mg		109 108 107 115	Sex (64:375) Age (21-88)	Any time
Phase 1 PK/PD Studies						
A137-1007	Healthy volunteer	Placebo 30mg 30mg+keto	6 days	-- 16 16 (2 phases cross-over)	Sex (16:0) Age (20-52)	Baseline and Hour 4 post dose on Day 6
A137-1015	Health volunteers	Placebo 30mg 60mg	14 days	10 10 42	Sex (17:40) Age (50-78)	Baseline and Hour 4 post dose on Day 14
A137-1005	Healthy volunteers & stable hepatic impairment	Placebo 15mg	Single dose period & 6-day multiple period	-- 41	Sex (28:13) Age (40-65)	Baseline and Hour 4,8,24 post single dose or on Day 6

Source data: Table 3 and 4 – Appendix F of Clinical Summary (2.7), page 1278

9.2 What are the QT safety results from a pooled analysis of four controlled studies?

The sponsor provided the results of a pooled analysis in which a total of 964 darifenacin treated subjects and 261 placebo treated subjects contributed digitized ECG data from Studies 137-684, A1371002, A1371007 and A1371015. Table

VII-C-9.2 summarizes the analysis of ECG parameters expressed by QTcF (Fridericia's correction) in the pooled analysis. The sponsor concluded that:

? There was no evidence that darifenacin is associated with any statistically or clinically relevant increase in the QT interval;

? The percentage of subjects with a maximum individual increase in QTcF from baseline of ? 60msec was the same for darifenacin (0.4%) and placebo (0.4%);

? Neither females nor the elderly showed any additional risk of QT prolongation compared with the overall population;

Table VII-C-9.2. Summary of QTcF statistics by age and gender – sponsor's pooled analysis from four studies (Studies 137-684, A1371002, A1371007 and A1371015)

Measurement	Darifenacin (3.75-60mg qd)	Placebo
Total		
Subject (N)	964	261
Baseline (ms)	395.0	395.5
Mean Change from baseline (ms)	2.2	1.9
Number and percent with QTc change ≥ 30 ms and < 60 ms	69 (7.2%)	15 (5.7%)
Number and percent with QTc change ≥ 60 ms	4 (0.4%)	1 (0.4%)
By Gender		
Male Subject (N)	224	73
Baseline (ms)	382.6	386.5
Mean Change from baseline (ms)	4.6	0.6
Number and percent with QTc change ≥ 30 ms and < 60 ms	17 (7.6%)	4 (5.5%)
Number and percent with QTc change ≥ 60 ms	0 (0%)	0 (0%)
Female Subject (N)	740	188
Baseline (ms)	398.8	399.0
Mean Change from baseline (ms)	1.4	2.4
Number and percent with QTc change ≥ 30 ms and < 60 ms	52 (7.0%)	11 (5.9%)
Number and percent with QTc change ≥ 60 ms	4 (0.5%)	1 (0.5%)
By Age		
<65 Subject (N)	833	221
Baseline (ms)	393.4	393.9
Mean Change from baseline (ms)	3.1	2.1
≥ 65 Subject (N)	131	40
Baseline (ms)	405.4	404.0
Mean Change from baseline (ms)	-0.4	0.4

Source data: Table 5-9 – Appendix F of Clinical Summary (2.7), page 1278-86

Comment: *The sponsor has appropriately employed both central tendency and categorical approaches to search for a potential QT signal in the pooled analysis. In general, this reviewer agrees with the sponsor that the pooled analysis did not reveal an apparent QT signal. However,*

it was noted that both mean change from baseline in male subjects and the percent of subjects with QTcF change from baseline > 30ms and < 60 ms were slightly higher in darifenacin-treated groups of both male and female subjects.

This reviewer believes that pooling data from different studies without examining each study separately may be problematic. Such a pooling strategy may dilute a potential QT signal, especially in a group of patients in whom concomitant use of potent 3A4 inhibitors was precluded.

9.3 What is the QT safety results from an uncontrolled study of patient with liver impairment?

The subjects who received single and multiple doses of darifenacin 15mg in Study A1371005 were presented separately in the sponsor's analysis because the study was not placebo controlled and it was conducted in healthy volunteers and patients with stable hepatic impairment (Table VII-C-9.3).

This was a small open pharmacokinetic study in male and female patients with stable hepatic impairment and healthy volunteers. Among 41 subjects enrolled, 12 health volunteer, and 15 and 12 subjects with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment respectively contributed to QT analysis.

As part of the protocol, ECG's were taken 4, 8 and 24 hours following a single dose of darifenacin 15mg and again on Day 6 of the multiple-dose period. ECG traces were originally analyzed by [redacted] and then later by [redacted]

Table VII-C-9.3.1 and VII-9.3.2 show the results of QT analyses conducted by two independent consultants. The former focused on QTcF change from baseline to Hour 4 post dose and the latter from baseline to the maximum post dose measurement at Hour 4, 8 or 24 post dose. In this uncontrolled study, that administration of a single dose or multiple doses of darifenacin 15 in health volunteers or subjects with mild and moderate liver impairment was associated with a slight increase of QTcF change. Depending on the endpoint selected, mean QTcF changes ranged from –0.9 to 5.3 ms in the first analysis and 4.7 to 11.9 ms in the second analysis. The sponsor concluded that the small sample size and uncontrolled nature of the trial preclude definitive conclusions being reaching.

Comment: *This reviewer agrees with sponsor that uncontrolled nature of the Study A1371005 precludes a definitive conclusion. Nevertheless, a mean QTcF increase of 4.7 to 11.9 ms, in the opinion of this reviewer, could be clinically significant. In the next few sections, this reviewer examines the studies in the previously pooled analysis individually.*

Table VII-C-9.3.1 Summary of QTcF change from baseline to Hour 4 pose dose by status of liver impairment – Study A1371005 (analyzed by [ ]

Measurement	Darifenacin 15mg (Single Dose)	Darifenacin 15mg (Multiple dose)
Health Volunteer		
Subject (N)	12	12
Baseline (ms)	407.7	408.9
Mean Change from baseline (ms) to Hour 4 post dose measurement	5.3	6.7
Child Pugh A		
Subject (N)	14	15
Baseline (ms)	405.9	406.7
Mean Change from baseline (ms) To Hour 4 post dose measurement	5.3	-0.9
Child Pugh B		
Subject (N)	12	12
Baseline (ms)	427.2	428.7
Mean Change from baseline (ms) To Hour 4 post dose measurement	2.3	3.7

Source data: Table 9.1 and 9.2 of Final Study Report of Study A1371005, page 252

Table VII-C-9.3.2 Summary of QTcF change from baseline to maximum post-baseline measurement by status of liver impairment – Study A1371005 (analyzed by [ ]

Measurement	Darifenacin 15mg (Single Dose)	Darifenacin 15mg (Multiple dose)
Health Volunteer		
Subject (N)	12	12
Baseline (ms)	407.7	408.9
Mean Change from baseline (ms)	10.8	11.9
Child Pugh A		
Subject (N)	14	15
Baseline (ms)	405.9	406.9
Mean Change from baseline (ms)	9.9	4.7
Child Pugh B		
Subject (N)	12	12
Baseline (ms)	427.2	428.7
Mean Change from baseline (ms)	7.1	9.3

Source data: Table 11 – Appendix F of Clinical Summary (2.7), page 1292

9.4 What are the QT safety results from the study with the highest darifenacin plasma concentration?

As stated early, metabolism of darifenacin can be inhibited by CPY3A4 or CPY2D6 inhibitors. In the darifenacin clinical development program, the highest darifenacin plasma concentrations were achieved in Study A1371007 when darifenacin 30mg qd was co-administrated with ketoconazole 400 mg qd (a potent CYP3A4 inhibitor) for six days. Study A1371007 is a randomized, placebo-controlled, two-period cross-over study to investigate the effects of ketoconazole

on the steady state pharmacokinetics of darifenacin, and the pharmacodynamic consequences of ketoconazole CYP3A4 inhibition on darifenacin metabolism.

16 healthy male subjects (age range 20 to 52 years) with no medical history were recruited by their CYP2D6 genotype status, 12 extensive metabolisers (EMs), and four poor metabolisers (PMs). Subjects received oral darifenacin tablets (30mg qd) with either ketoconazole (400mg dq) or with placebo in two separate periods of six days each, separated by a washout period of at least seven days. A 12-lead ECG recording was obtained at pre-dose on Day 1 and four hours post-dose on Day 6 for each period. A follow-up ECG was taken at 14 days after the completion of the study.

Table VII-C-9.4 Mean changes from baseline by treatment group – Study A1371007

Measurement	Darifenacin 30mg And Ketoconazole	Darifenacin 30mg And placebo
Fridericia's Correction		
Subject (N)	16	16
Baseline (ms)	353.6	353.6
Change from baseline (ms)		
Mean	12.1	-0.5
S.D.	14.4	11.8
Min and Max	[	]
Bazett's Correction		
Subject (N)	16	16
Baseline (ms)	354.6	364.6
Change from baseline (ms)		
Mean	6.8	-4.3
S.D.	16.7	11.6
Min and Max	[	]

Source data: Table 9.2 of Final Study Report of Study A1371007, Page 115

Comment: *Combined use of darifenacin 30mg and ketoconazole 400mg was associated with a mean 12.1 ms QT prolongation from baseline. Based on the summary statistic provided in the Table (n=16, mean QTcF change = 12.1 msec and a standard deviation of 14.4 msec), this reviewer calculates that the lower and upper limits of 95% CI for subjects taking darifenacin and keto were 4.4 and 19.8 msec. The corresponding plasma concentration (not at Cmax) at the time of ECG (4 hours post dose at day 14) was 103 ng/ml with a range of 25 to 167 ng/ml (based on clinical pharmacology review).*

This finding was discussed with the sponsor during the NDA review and the sponsor argued that that " increase in QTcF in Study 1007 is attributable to the well known effects of ketoconazole itself and dose not provide a clinically meaningful signal" for itself (see Response to Request for Information submitted on 11 September 2003). The sponsor suggested the ketoconazole's QT prolonging effect was about 5-10 ms based on

personnel communication with [redacted]

While it is possible that the QT prolongation observed in this study was due to ketoconazole alone, this reviewer makes the following observations:

(1) No direct evidence (controlled human clinical trial data) has been provided to support ketoconazole's QT prolonging effect;

(2) Without a ketoconazole control group in this study, it cannot be assured that that QT effect observed in the study was due to ketoconazole alone even if ketoconazole was shown to cause QT prolongation in other trials;

(3) While the mean QTcF in darifenacin and keto group was 12.1 ms, the upper limit of 95% CI was approaching 20 msec. Even this upper limit of 95% CI carries some degree of uncertainty due to the lack of placebo-placebo group in this study.

In summary, Study 1007 showed that co-administration of darifenacin 30mg and ketoconazole 400mg for 14 days was associated with a mean 12.1 ms QTcF prolongation from baseline. The true magnitude of effect is uncertain at this time due to the wide range of 95% CI and the lack of placebo-placebo group. While the role of ketoconazole in causing QT prolongation in this study cannot be excluded, darifenacin remains as the primary concern for this reviewer because pre-clinical studies had demonstrated the drug, at a higher concentration, has the potential to cause a measurable QT prolongation.

On 17 September 2003, the sponsor submitted a summary of QT safety results from Study 1035 which was designed to investigate the effects of ketoconazole on the steady state pharmacokinetics, safety and toleration of oral darifenacin controlled release (CR) tablets at doses of 7.5mg and 15mg. Design and the timing for ECG measurements in Study 1035 is identical to that in Study 1007 except the doses of darifenacin used in the study were 7.5mg and 15mg. While 12 male subjects (10 EM and 2 PM) for each dose groups were enrolled, only 8 and 6 subjects for 7.5mg and 15mg dose groups, respectively, were included in the QT analysis.

In summary, the results showed:

? *A mean change of 12 ms in QTcF from baseline was observed when darifenacin 7.5mg and ketoconazole 400mg was administrated to 8 subjects for 6 days, compared to that of 2 ms when darifenacin 7.5mg and placebo was administrated to the same subjects.*

? *A mean change of 10 ms in QTcF from baseline was observed when darifenacin 15mg and ketoconazole 400mg was administrated to 6 subjects for 6 days, compared to that of -3 ms when darifenacin 15mg and placebo was administrated to the same subjects.*

Based on these findings, the sponsor stated "when darifenacin is concomitantly given with the same dose of ketoconazole, namely, 400mg, there is a constant change from baseline in QTcF duration of 10-12 msec irrespective of the extent of darifenacin exposure achieved with the combination (Cmax, 11-130ng/ml). The most plausible explanation for this finding is that the 10-12 msec QTcF effect with ketoconazole and darifenacin is solely due to the well known effect on QTc duration of ketoconazole alone".

This reviewer acknowledges that lack of darifenacin dose-dependent responses in QTcF may provide a reasonable argument for the role of ketoconazole in prolonging the QT in the combination groups of these two studies. However, the primary concern of this reviewer, as stated earlier, is the lack of the adequate controls in the study design, namely a ketoconazole alone group and a placebo-placebo control group. Like Study 1007, Study 1035 has a similar deficiency. Such a deficiency makes it difficult to conclude that QT change observed in two studies (1007 and 1035) was due to ketoconazole alone.

With the uncertainty surrounding the role of ketoconazole in QT prolongation in these two studies, one important clinical question is "Does placebo-controlled study (1015) provide sufficient clinical data to support QT safety at a range of plasma concentration that is clinically relevant?

9.5 What are the QT safety results from the placebo-controlled study (Study 1015)?

Study A1371015 was a randomized, placebo controlled, parallel group study in 62 healthy male and female volunteers [56 extensive metabolisers (EM) and 6 poor metabolisers (PM)] aged 50 years or over. Subjects were dosed with either darifenacin 60mg (n = 42), or darifenacin 30mg (n =10) or placebo (n = 10) for 14 days. ECG measurements were taken at baseline (day 1) and 4 hours post dose on Day 14 (not at Cmax). Table VII-C-9.5 shows mean QTc changes from baseline by treatment groups.

***Comment:** In darifenacin 60mg qd group, the mean QTcF at 4 hours post dose on Day 14 showed a 7.6 msec reduction (not an increase) from baseline, compared to that of 10.4 msec in placebo group. The corresponding mean darifenacin plasma concentration was approximately 45ng/ml (source data: Figure 3.2 of Final Study Report of Study 1015 -- page 162).*

While the QTcF differences between darifenacin 60mg and placebo group were not statistically significant, the design of this trial is not adequate to allow for the conclusion that darifenacin at a plasma concentration of 45ng/ml or less is not associated with a clinically meaningful QT

prolongation due to the lack of a concurrent positive control arm. A positive control arm would assure that the assay was sensitive to detect small changes in the QTc interval. The need to confirm QT safety with assurance for this drug at this concentration is amplified by the following observations: (1) a mean change in QTcF of approximately 12 ms from baseline in darifenacin and ketoconazole studies, and (2) a clear pre-clinical QT signal.

Table VII-C-9.5 Mean changes from baseline to 4 hours pose dose on Day 14 by treatment group – Study A1371015

Measurement	Darifenacin 60mg qd (n=39)	Darifenacin 30mg qd (n=9)	Placebo (n=10)
Fridericia's Correction (QTcF)			
Baseline (ms)	408.1	414.9	407.1
Change from baseline (ms) to Day 14			
Mean	-7.6	-9.4	-10.4
S.D.	15.5	14.9	15.0
Min and Max	[redacted]		
Bazett's Correction (QTcB)			
Baseline (ms)	407.9	416.8	407.4
Change from baseline (ms) to Day 14			
Mean	-4.0	-6.7	-6.8
S.D.	19.7	16.4	19.2
Min and Max	[redacted]		

Source data: Table 10 of Final Study Report of Study A1371015, Page 151

9.6 What are the mean maximum darifenacin plasma concentration (C_{max}) when darifenacin 7.5mg or 15mg was used alone or in combination with ketoconazole?

Table VII-C-9.6.1 shows a mean steady state peak (Cmax) for darifenacin 7.5mg and 15mg CR tablets without any CYP3A4 inhibitions based on a pooled analysis of 20 Phase 1 studies.

Table VII-C-9.6.1 Mean Steady State Peak (Cmax) for darifenacin CR Tablets – a pooled analysis of 20 Phase 1 Studies without CYP3A4 inhibition

Darifenacin Cmax (ng/ml)	Darifenacin 7.5mg	Darifenacin 15mg
EM	1.8 (n=95)	4.8 (n=104)
PM	4.5 (n=6)	9.1 (n=10)

Source Data: Table 5 of 2.5 Clinical Overview (or Table III-A-1 of this review)

PK profiles for subjects taking a CYP3A4 inhibitor were derived from Study A1371035 which was a randomized, placebo controlled, two-period crossover study, designed to investigate the effects of ketoconazole on the steady state pharmacokinetics, safety and tolerability of oral darifenacin tablets at doses of 7.5mg and 15mg.

12 healthy male subjects each (10 EM and 2 PM) were enrolled into 7.5mg and 15mg groups respectively. In each group, subjects who received darifenacin and ketoconazole in Period 1 received darifenacin and placebo in Period 2 and *vice versa*. There was a minimum washout period of seven days before the crossover from ketoconazole to placebo or *vice versa*. The ketoconazole dose used in the study was 400mg qd and treatment duration for each period was 6 days for darifenacin and 8 days for ketoconazole.

Table VII-C-9.6.2 shows Cmax by darifenacin dose and CPY2D6 genotype when ketoconazole was co-administrated. Those subjects who took a reduced dose due to adverse events were not included in the analysis.

Table VII-C-9.6.2 Mean Steady State Peak (Cmax) for darifenacin CR Tablet with ketoconazole (CYP3A4 inhibitor) – Study 1035

Darifenacin Cmax (ng/ml)	Darifenacin 7.5mg	Darifenacin 15mg
EM	11.2 (n=10)	67.6 (n=3)
PM	55.4 (n=1)	58.9 (n=1)

Source data: Page 31 and 32 of Final Study Report of Study A1371035

Comment: *Without CYP3A4 inhibition, the mean Cmax for CYP2D6 poor metabolizers was 4.5mg and 9.1mg for darifenacin 7.5mg and 15mg qd, respectively. In addition to the subjects who participated in Phase 1 studies, the sponsor also provided PK data on some of the subjects who participated in Phase 3 studies. The highest Cmax observed for any individual subject taking 7.5mg and 15mg were* [redacted] *ng/ml, respectively (Table 4 in the response to request for information dated 5 September 2003).*

Due to small sample size, the information on Cmax was limited for the following groups: (1) PM subjects taking darifenacin 7.5mg and ketoconazole 400mg, and (2) subjects taking darifenacin 15mg and Ketoconazole 400mg regardless of PM/EM status. Although limited by few observations, this reviewer believes that darifenacin plasma concentration for subjects in those specific groups would exceed the mean plasma concentration (45ng/ml) seen in Study 1015. Therefore the high dosing arm for any future QT study should be determined in such a way that the proposed dosing regimen would produce a darifenacin plasma concentration which is similar to the darifenacin plasma concentration achieved when ketoconazole 400mg is administrated to PM patients.

9.7 Do clinical events occurred in darifenacin clinical development program suggest darifenacin's potential in prolonging QT?

Sudden Death: None.

Syncope: In the darifenacin clinical development program (excluding phase 1 studies), 11 of 5,398 darifenacin-treated subjects and 5 of 1,910 placebo-treated reported syncope as adverse events regardless of indication, dose or formulation. In 6 of 11 subjects who developed syncope while being treated with darifenacin, the events were rated as severe and one was reported as a serious adverse event. Table VII-C-9.7 shows the frequency and incidence rate of syncope in darifenacin and placebo-treated subjects.

Comment: *The results does not suggest darifenacin is associated with syncope. This reviewer examined this data again by dose range and type of study (controlled vs. uncontrolled). The conclusion remains the same (data not shown).*

This reviewer also examined the clinical presentation for each of the 6 severe syncope cases (including one serious case) and no evidence suggests that these syncope episodes were QT related.

Table VII-C-9.7. Frequency and incidence rate of syncope in darifenacin clinical development program (excluding phase 1 studies)

Measurement	Darifenacin	Placebo
Number of Subjects (N)	5,398	1910
Person years drug exposure	1414	322
Number of subjects with syncope	11	5
Frequency (per subject)	0.2%	2.6%
Incidence rate (per 1,000 person-year)	7.8	15.5

Source data: Table 12.2 of 2.7.4 Summary of Clinical Safety (page 1475)

Arrhythmia: In the darifenacin clinical development program (excluding phase 1 studies), a slightly higher percentage of subjects (8 of 5,398 or 0.15%) who were treated with darifenacin reported arrhythmia as an adverse event, compared to the percentage of 0.10% (2 of 1,910) in placebo-treated subjects regardless of indication, dose or formulation. In addition, one subject each from both groups reported ventricular arrhythmia.

While no detailed nature of arrhythmia were reported, all eight cases of arrhythmia and one ventricular arrhythmia in darifenacin groups were reported as either mild (6) or moderate (3). Only one subject (Subject No 00230258, a 71 years old female taking darifenacin 30mg qd from Study 311) was admitted to hospital as a result of the arrhythmia. This subject had a history of aortic valve replacement and was taking digoxin suggesting a diagnosis of atrial fibrillation.

Comment: *At this time, no data suggests that the few arrhythmias observed in the darifenacin clinical development, even if they were darifenacin-related, represents the type of ventricular arrhythmia that are typically related to QT prolongation.*

9.8 **What are the main findings of pre-clinical studies?**

Darifenacin has been examined in the following *in vitro* and *in vivo* tests designed to identify compounds with the potential to cause increases in QTc. These include:

? HERG by both dofetilite-binding and patch clamp techniques
? Canine isolated Purkinje fibers study;
? In vivo study using anaesthetized and conscious dogs.

The main findings were as follows:

? Darifenacin produced a concentration-related inhibition of the amplitude of the HERG potassium current with IC_{50} values for darifenacin at 32.8ng/ml;
? Darifenacin produced a concentration-related [3H]-dofetilide binding inhibition with IC_{50} values for darifenacin at 469ng/ml;
? At an atrial pacing rate of 150bpm, darifenacin caused a concentration-related increase in monophasic action potential duration (MAPD) at unbound plasma concentrations of 10.7ng/ml (or 357ng/ml total plasma concentration) and above. MAPD was a direct assessment of ventricular repolarization during atrial pacing.

9.9 **What are the preliminary conclusions with regard to darifenacin's potential to cause clinically significant QT prolongation in human?**

Based on the data presented at this time, this reviewer has reached the following preliminary conclusions:

? Pre-clinical suggest that darifenacin has the potential to cause QT prolongation.
? When darifenacin (7.5mg, 15mg or 30mg) was co-administrated with ketoconazole 400mg in two human PK/PD studies, a mean change of 10-12 msec in QTcF from baseline were observed. No final conclusion with regard to the magnitude of QT effect or casualty assessment can be made due to the lack of adequate control groups in study design;
? While some QT safety data was available at the mean darifenacin plasma concentration of 45ng/ml in Study 1015, the design of this trial is not adequate to allow for the conclusion that darifenacin at a plasma concentration of 45ng/ml or less is not associated with a clinically meaningful QT prolongation due to the lack of a concurrent positive control arm;
? The darifenacin plasma concentration is likely to exceed 45ng/ml when (1) darifenacin 15mg is co-administrated with ketoconazole or other potent CYP3A4 inhibitors; and (2) darifenacin 7.5mg is co-administrated with ketoconazole or other potent CYP3A4 inhibitors to PM patients.

10. Liver Safety:

10.1 What is extent of liver enzyme monitoring in darifenacin development program?

For OAB indication, hepatic analytes were collected at baseline and then at each of the last follow-up visits.

10.2 Is there any evidence suggesting a relationship between darifenacin and abnormal liver enzymes or total bilirubinemia?

Table VII-C-10.2.1 shows the percentages of the subjects with a predefined cut-off points for an abnormal ALT, AST or total bilirubin in three Phase 3 clinical trials on OAB patients (1001, 1002 and 1041). No subjects in darifenacin treated group developed an abnormal ALT or AST > 3 times upper limit of normal (ULN).

> ***Comment:*** *This reviewer focused the analysis on the percentage of subjects with > 3X ULN for ALT and AST, and >1.5 ULN for total bilirubin because they have greater clinical significance. With the size of data base presented here, it is unlikely that this type of analysis would miss a liver toxicity signal while the drug is actually associated with a liver enzyme elevation.*
>
> *Data from OAB Phase 3 trials shows no signal of liver toxicity. To support this observation, this reviewer also examined liver enzyme and total bilirubin data from 34 phase 2 and 3 clinical trials of both OAB and IBS patients. The results are displayed in Table VII-10.2.2. Only subjects with a normal baseline were included in the analysis.*
>
> *From the table, it first appeared that a slightly higher percentage of darifenacin-treated subjects experienced the pre-defined levels of liver enzymes or total bilirubin abnormality. It needs to be pointed out, however, that the denominator for the percentage calculations was number of subjects not person-years of drug exposure. On average, each subject in darifenacin-treated groups stayed on the treatment for 0.28 year (1395 person years /5048 subjects), compared to that of 0.18 year in placebo-treated subjects. After adjusting for this 56% (0.28/0.18) increase in average length of treatment, the incidence rate of those three events (ALT > 3 times ULN, AST > 3 times ULN and total bilirubin > 1.5 ULN) is comparable in two groups.*
>
> *By using cut-off points that are both sensitive and clinically meaningful, there is little evidence suggesting that use of darifenacin is associated with abnormal ALT, AST or total bilirubin in both male and female population.*

Table VII-C-10.2.1 Percent of subjects with a pre-defined level of abnormality in ALT or AST or total bilirubin – a pooled analysis of three Phase 3 pivotal OAB studies (1001, 1002 and 1041)

Criteria for an abnormal ALT or AST	Placebo (total = 366)			Darifenacin (total=996)		
	N	n	%	N	n	%
ALT > 3X ULN	336	0	0	939	0	0
AST > 3X ULN	349	1	0.3	971	0	0
Total Bilirubin > 1.5 ULN	358	1	0.3	979	0	0

Source data: Table 20.1.1 of Summary of Clinical Safety (page 3745)
N = number of subjects tested; n=number of subjects with an predefined level of abnormality

Table VII-C-10.2.2 Percent of subjects with a pre-defined level of abnormality in ALT or AST or total bilirubin – A pooled analysis of 34 phase 2 and 3 OAB/IBS studies

Criteria for an abnormal ALT or AST or total bilirubin	Placebo (total = 1754) (person-years: 315)			Darifenacin (total=5048) (person-years:1395)		
	N	n	%	N	n	%
ALT > 3X ULN	1643	2	0.12	4826	13	0.27
AST > 3X ULN	1706	2	0.12	4978	8	0.16
Total Bilirubin > 1.5 ULN	1728	2	0.12	5006	10	0.20

Source data: Table 21.4, 21.5 and 21.6 of Summary of Clinical Safety (page 3874)
Total=number of subjects enrolled; N = number of subjects tested; n=number of subjects with an predefined level of abnormality
Protocols included are 101, 301, 302, 303, 304, 305, 305A, 307, 308, 310, 311, 312, 313, 315, 316, 350, 351, 352, 353, 356, 359, 360, 666, 676, 684, 1001, 1002, 1011, 1012, 1013, 1014, 1019, 1027 and 1041

10.3 Is there any evidence suggesting a relationship between darifenacin and severe liver injury?

Among 13 darifenacin-treated subjects who developed > 3X ALT in Table VII-C-10.2.2, two had ALT > 10 times ULN (one had ALT > 15 times ULN and the other > 30 times ULN). Clinical presentations of these two cases are as follows:

Subject 06380767, Study 137-684: This 26-year-old Hispanic male in the United States received 15mg *od* darifenacin for the treatment of IBS. On [ ] approximately 100 days after starting treatment, a routine blood chemistry indicated elevated AST and ALT values of 103u/L (normal range = 15-46u/L) and 174u/L (normal range 0-56u/L), respectively. A serum chemistry sample obtained on three days later on [ ] again indicated elevated AST (180u/L) and ALT (299u/L) values, and serology was positive for Hepatitis B. The subject completed the study on 16 March 1998 at which time AST and ALT values increased further to 671u/L and 1224u/L respectively and alkaline phosphatase was slightly elevated at 104 u/L. Serology was positive for HbS-Ag and reactive to anti-HbC. Post-study serum chemistries continued to indicate acute hepatitis with AST (1594u/L), ALT (2412u/L), total bilirubin (8.4mg/dl) and direct bilirubin (5.4mg/dl) all elevated on [ ] In the opinion of the investigator, this event was due to acute hepatitis B (HBV) and was not related to study drug toxicity.

Subject 00060036, Study 137-305: This 72 year old white male in the United Kingdom was randomized to received darifenacin 5mg *tid*, for the treatment of OAB. On 14 September 1994, 112 days after starting treatment, routine blood chemistries collected at the end of study indicated elevated AST, ALT, alkaline phosphatase, and GGT values of 634u/L, 697 u/L, 340u/L and 134u/L, respectively. Previous laboratory values during the study were within normal limits. The subject had been receiving concurrent mefloquine treatment (250mg each week) from 05 June 1994 to 21 August 1994. Darifenacin treatment ended on 14 September 1994. Following discontinuation of both darifenacin and mefloquine, liver function tests remained abnormal on [ ] (AST = 149u/L, ALT = 545u/L, alkaline phosphatase = 441u/L, GGT = 189u/L), but had returned to normal by [ ] In the opinion of the investigator, this event was due to study drug. Review by the sponsor could not exclude causality associated with either mefloquine or darifenacin.

Comment: *Causality assessment for individual cases is always difficult because the role of one agent can never be completely eliminated even when an agent known to cause liver injury exits. With the data presented at this time, however, the role of darifenacin in the case #1 (Subject 06380767) can be reasonably excluded. This reviewer agrees that the viral hepatitis was the most probable cause for the severe liver injury in this case.*

In case #2 (Subject 00060036), it appears that the subject had asymptomatic ALT/ASL elevations with no hyperbilirubinemia. With no additional information regarding tests for other causes of liver injury, no specific information regarding the patient's history of concomitant medication use, and the overall lack of population-based evidence that darifenacin can cause liver injury, it is difficult to associate this case to darifenacin with great certainty. However, darifenacin's role, alone or in combination with other factors, can not be totally excluded in this case.

It needs to be pointed out, even though the possibility remains, the severity of liver injury in this case dose not represent the typical clinical presentation that would signal the risk of acute liver failure.

At this time, the totality of evidence does not suggest that darifenacin can cause liver injury. However, with less than 3,000 person years of drug exposure, it can never be assured that darifenacin is not capable of causing idiosyncratic acute liver failure in very small group of patients after the drug is marketed.

D. Adequacy of Safety Testing

The amount of darifenacin exposure, in term of both number of subjects exposed to the drug and exposure duration, presented in this NDA meets the ICH guidance. While the sponsor has conducted QT safety assessments in both Phase 1 and 3 studies with over 900 darifenacin-treated subjects, the study results were unable to confirm QT safety with a high degree of assurance due to limitations in study design.

The current database is not designed to detect rare adverse events, such as drug-induced acute liver failure. The detection of such a rare event would be the task of good post-marketing surveillance program.

E. Summary of Critical Safety Findings and Limitations of Data

Pre-clinical data suggest that darifenacin has the potential to cause a QT prolongation. In two human studies, co-administration of darifenacin and ketoconazole was associated with a mean increase of 10-12 ms in QTcF from baseline, compared to that of the administration of darifenacin alone. Due to limitations in study design, particularly the lack of appropriate control groups, the role of darifenacin alone cannot be reasonable excluded and the true magnitude of potential darifenacin-related QT prolonging effect cannot be determined at this time. Uncertainty also remains at this time regarding what would be the lowest darifenacin plasma concentration, if any, at which darifenacin is not associated with a clinically significant QT prolongation.

Other important safety-related findings are as follows:

- Dry mouth, constipation and dyspepsia were the three most frequently reported adverse events and they occurred in 20%, 15% and 3% of subjects treated with darifenacin 7.5mg for 12 weeks in three OAB pivotal trials;
- The majority of adverse events typically occurred in the first two weeks of treatment and they were dose-dependent. For subjects treated with darifenacin 15mg for 12 weeks, the incidence of the three most frequent adverse events increased to 35%, 21% and 8%, respectively;
- While the majority of adverse events were mild to moderate at onset, some adverse events had a significant percentage rated as severe (such as 17-33% of patients with dyspepsia rated the symptoms as severe);
- While the median duration for the majority of adverse event episodes was relatively short, some can last a long time. Despite anti-constipation treatment, 7 out of 11 subjects who developed severe constipation still suffered from the event at the end of the study;
- In three OAB pivotal studies, 5.6% and 12.9% of patients prematurely discontinued from the studies due to an adverse event in the darifenacin 7.5mg and 15mg groups, respectively, compared to that of 8.0% in the placebo groups;

- ? Darifenacin appears to be associated with UTI though none of the subjects discontinued from the study or were hospitalized due to UTI. In three OAB pivotal studies, the incidence of UTI was 4.5-4.7% for the subjects treated with darifenacin 7.5 or 15mg, respectively, compared to that of 2.6% in the placebo groups;
- ? Darifenacin appears to be associated with the occurrence of urinary retention. Though the incidence of urinary retention was low (0.2%) in subjects treated with darifenacin in three OAB pivotal trials, one female subject in darifenacin clinical development program developed acute renal failure as a consequence of urinary retention 40 days after the initiation of darifenacin 7.5mg treatment, and six patients developed acute urinary retention requiring medical interventions;
- ? Of 6,655 darifenacin-treated subjects (1462 person years) in darifenacin clinical development program, 16 had a bone fracture requiring hospitalization but none of those events were assessed by PI as drug- related. Many of these were reported during open-label studies. No such a report was received in 2,216 subjects received placebo (329 person years);
- ? Darifenacin does not appear to be associated with an clinically significant increase in liver enzymes. One subject in the darifenacin clinical development program had ALT > 10 times ULN without hyperbilirubinemia.

VIII. Dosing, Regimen, and Administration Issues

The sponsor proposes a starting dose of darifenacin 7.5mg once daily orally without regard to meals. The sponsor also stated that "for those patients starting on 7.5 mg daily and requiring greater symptom relief, the dose may be increased to 15 mg daily, as early as two weeks after starting therapy, based on individual response".

From an efficacy perspective, both darifenacin 7.5mg and 15mg once daily are efficacious for the treatment of OAB. Darifenacin 15mg appears to be associated with a greater reduction in number of incontinence episodes per week, compared to that of darifenacin 7.5mg (a reduction of 3.2 v.s 2.0 episodes per week from baseline, respectively). Such a dose-related improvement, however, was not noted for micturition and urgency endpoints.

It is possible that subjects who fail to respond to darifenacin 7.5mg may respond to darifenacin 15mg. It has not been demonstrated. however, that the subjects who respond to darifenacin 7.5mg would get greater symptom relief if they increase the dose to 15mg.

Common adverse events, such as dry mouth, constipation, dyspepsia appear to be dose related. Though the adverse event profile of darifenacin 7.5mg appears to be superior to that of darifenacin 15mg, availability of darifenacin 15mg to US market would not, in the opinion of this reviewer, significantly change the benefit

and risk ratio of this product at this time. Unless a dose restriction is required due to a future safety concern, this reviewer recommends that both darifenacin 7.5mg and 15mg be made available to the US market.

This reviewer proposes the following statement for this section of the product labeling: *Patients should start with darifenacin 7.5mg once daily orally without regard to meals. Based on the individual response, including adverse events experienced, the dose may be increased to 15 mg daily after two weeks of therapy, after a discussion between patients and their physicians.*

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

As demonstrated in the early analysis, approximately 85% subjects participated in three Phase 3 pivotal studies were female. The sponsor believes that this reflects the demographics of the patients who seek treatment for OAB.

The subgroup analysis shows that the median reductions in number of incontinence episode per week from baseline was 2.7 and 3.7 for female subjects treatment with darifenacin 7.5mg and 15mg, respectively. For male subjects treated with darifenacin 15mg, median reduction was 1.3. For male subjects treated with darifenacin 7.5mg, however, an median increase of 1 episode per week was observed (Table VI-C-8.1 and 8.2 of this review).

The sponsor explained that there was a high degree of overlap of the 95% confidence intervals for the reduction in incontinence episodes per week seen in men and women. Efficacy in men is also suggested by the fact that there appears to be a dose response improvement not only for the primary endpoint, but also for the endpoint of average volume of urine passed per void. In summary, there is similar improvement seen with the administration of darifenacin in both men and women.

> ***Comment:*** *Subgroup analysis is not intended to provide a definitive conclusion with regard to efficacy differences among the subgroups of the patient population. But differences observed in the subgroup analysis should not be totally ignored because these may suggest the need for a future study.*
>
> *This reviewer does not agree with sponsor's interpretation and conclusion in regard to the gender analysis and believes that preliminary data appear to suggest that female subjects may respond to treatment better that their male counterparts. This result may reflect inappropriate patient selection in the male population. This potential gender difference, however, does*

not significantly changed this reviewer's assessment of benefit and risk ratio for darifenacin.

Still this reviewer has a concern over the potential lack of efficacy of darifenacin 7.5mg in the male subgroup, especially if darifenacin 15mg cannot approved due to a future safety concern. With the availability of darifenacin 15mg, those male subjects who fail to respond to darifenacin 7.5mg will always have an option to increase the dose to darifenacin 15mg.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

1. Race or Ethnicity Effects:

The sponsor acknowledged that the majority of patients in the development program were white, making the assessment of efficacy by racial groups difficult . As a result, no meaningful conclusions may be drawn regarding efficacy in different racial groups.

Comment: *As demonstrated in an earlier analysis, more than 95% of subjects in three pivotal studies were white. The reviewer agrees with the sponsor's assessment and believes that insufficient number of non-white subjects makes the race or ethnicity-based efficacy and safety analysis meaningless. While there is no reason to believe that darifenacin would perform differently in a non-white population, it is reasonable to ask the sponsor to address the effectiveness and safety issues in a non-white population as a Phase 4 commitment by conducting a adequate and well controlled clinical trial.*

2. Age:

Approximately one third of subjects in three pivotal studies were 65 years of age or older. For subjects treated with darifenacin 7.5mg, subgroup analysis shows that the median reduction from baseline in average number of incontinence episodes per week was 1.0 and 5.9 for subjects of less than 65 years of age and subjects of 65 years of age or older, respectively. For subjects treated with darifenacin 15mg, the median reductions were 2.8 and 4.1, respectively (Table VI-C-8.1 and 8.2 of this review).

The sponsor stated that "small differences were seen in the median point estimates of the primary endpoint between the two groups (<65 years and =65 years) only for the darifenacin 7.5mg dose, which is attributed to the lower baseline in the younger age group". The sponsor believed that there is no evidence of a difference in efficacy based on age.

Comments: *This reviewer again disagrees with the sponsor's statements. In an early analysis (Table VI-C-8.1), this reviewer showed that the treatment effect was not affected by the baseline OAB severity and the*

sponsor appeared to be in agreement with this conclusion. If this is true, difference in the treatment effect between the higher and lower age groups could not be reasonably explained by the lower baseline in younger age group, as suggested by the sponsor.

This reviewer believes that there is preliminary evidence suggesting that older age may be associated with better symptom improvement. Since the efficacy endpoint improvement for all sub-groups were in the same direction, this reviewer does not recommend any additional studies in this regard.

C. Evaluation of Pediatric Program

The sponsor stated that they remain committed to conducting the pediatric studies proposed in August 30, 2002 letter and hoped that the Division would eventually issue a Written Request for these studies.

D. Comments on Data Available or Needed in Other Populations

1. Pregnancy and Nursing Mothers: Women who were pregnant or breast-feeding and women of childbearing potential who were not using a medically accepted means of contraception were excluded from participating in all darifenacin clinical trials. As a result, information on darifenacin-exposed pregnancy is limited. Of 6,655 subjects exposed to at least one dose of darifenacin, only two women known to be pregnant while being treated with darifenacin. No pregnancy-related outcomes were reported.

Darifenacin is excreted into the milk of lactating rats. Excretion of darifenacin into human milk has not been studied and breast-feeding while being treated with darifenacin is not recommended.

2. Renal Insufficiency: A study of subjects with varying degrees of renal impairment (creatinine clearance between 10 and 136ml/min) given darifenacin 15 mg once daily to steady-state demonstrated no relationship between renal function and darifenacin clearance.

Comments: *The sponsor proposed that* [redacted]*. Our clinical pharmacologist agreed with this statement. This reviewer has no objection to this statement, given that only a small fraction of darifenacin is excreted through kidney unchanged.*

3. Hepatic Insufficiency: Darifenacin pharmacokinetics were investigated in subjects with mild (Child Pugh A) or moderate (Child Pugh B) impairment of hepatic function given darifenacin 15 mg once daily to steady-state. Mild hepatic impairment had no effect on the pharmacokinetics of darifenacin. After adjusting for plasma protein binding, unbound darifenacin exposure was estimated to be 4.7-fold higher in subjects with moderate hepatic impairment than subjects with

normal hepatic function. Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Comments: *The sponsor proposed* [

]

While the sponsor's proposal appears reasonable based on exposure, this reviewer's final recommendation for the use of darifenacin in subjects with hepatic impairment is deferred until data from a prospectively designed QT study with a positive control agent is available.

X. Conclusions and Recommendations

A. Conclusions

From a clinical standpoint, the evidence presented in this NDA submission is substantial and adequate in support of the effectiveness of darifenacin 7.5mg and 15mg for the treatment of overactive bladder in men and women of 18 years of age or older in the US. The adverse events profile of darifenacin appears to be similar to that of other marketed drugs in the same drug class. While the safety evaluation, in general, meets ICH guidance in terms of the number of subjects exposed to darifenacin and the exposure duration, ECG data presented in this NDA does not allow this reviewer to confirm QT safety with assurance for a range of plasma concentrations that is clinically relevant. The need for such assurance is supported by the drug's QT prolonging potential identified in pre-clinical studies and the possibility of a drug-associated QT prolongation identified in two human PK/PD studies (Study 1007 and 1035). This issue should be resolved prior to the approval of this drug product.

Other clinical efficacy and safety issues that require further discussion with sponsor include:

- ? lack of direct clinical data to support the effectiveness of darifenacin 7.5mg and 15mg for the treatment of overactive bladder in the non-white population;
- ? a higher incidence of bone fracture requiring hospitalization in darifenacin-treated subjects, compared to placebo-controlled subjects, and
- ? the drug's potential to cause severe constipation and acute urinary retention, and labeling and risk management plans to prevent serious sequalae of these adverse events.

In the opinion of this reviewer, these issues can be resolved through a combination of a Phase 4 study commitment, appropriate risk assessment and management program, and adequate product labeling.

B. Recommendations

From a clinical perspective, this reviewer recommends that darifenacin for the treatment of overactive bladder indication receive an **approvable action**. The primary deficiency is lack of QT safety data from an adequate and well controlled clinical PK/PD study to rule out a clinically important QT prolongation at a range of plasma concentration that is clinically relevant. This is particularly true for those subjects who may take darifenacin and a potent CPY3A4 inhibitor together. This deficiency can be corrected by the sponsor's conducting an adequate, prospectively designed positive-controlled QT safety study prior to the approval.

While the detailed study protocol can be discussed and finalized later, here are some suggestions for design and conduct of such a study:

- A randomized and double-blind design with both active and placebo control arms;
- A prospectively designed study using QTcF change from baseline to Hour 7 at Day 6 as the primary endpoint;
- Female subjects, preferably OAB female subjects, with a mean age that is consistent with the age distribution of OAB patients in the community ;
- 40-50 subjects per group appears to be a reasonable number to rule out a clinically important mean QTcF prolongation;
- In addition to active and placebo control groups, two darifenacin-treated groups (one high and one standard dose groups) are recommended. The high dose group should be able to address QT safety issue for those PM subjects who may be co-administrated with darifenacin 15mg and ketoconazole 400mg.
- Multiple ECGs measurements at baseline and ECG at Hour 7 post dose.

In addition, this reviewer recommends:

A. The sponsor should conduct the following two clinical studies as part of Phase 4 commitments:
   - An adequate and well controlled clinical investigation to confirm the effectiveness of darifenacin for the treatment of overactive bladder in an appropriate non-white population;
   - A large simple safety trial to investigate the relationship between darifenacin and bone fracture. This reviewer would suggest a multi-center, randomized, double blind, placebo-controlled clinical study with a predefined safety endpoint. The primary endpoint could be all-cause bone fracture. The reason for bone fracture should be clearly documented and the cause-specific bone fracture could be analyzed as a secondary endpoint. Accidental fall that requires a physician or ER

visit could be another secondary endpoint. The study endpoints should be collected actively with an adequately designed questionnaire administrated at an appropriate time interval. It is preferred that the study enroll a large number of subjects and study the potential association to the drug for a relatively short of period, such as three months, rather than to enroll a smaller number of subjects and study it for a longer period.

B. The sponsor should submit an adequate risk management plan, addressing the Agency's concern for the following adverse events. The plan should focus on the strategies for preventing serious clinical sequelae of these adverse events.
   - ? Constipation
   - ? Acute urinary retention
   - ? Urinary tract infection

C. The sponsor should submit a copy of surgical and pathology reports (in English) for the following five subjects who underwent an appendectomy while being treated with darifenacin:
   - ? Subject 00450403 in Study 305
   - ? Subject 01160187 in Study 351
   - ? Subject 50600891 in Study 1014
   - ? Subject 04230226 in Study 359
   - ? Subject 51537594 in Study 1017

XI. Appendix

Appendix A. Pivotal Study Inclusion and Exclusion Criteria

A. Study 1001:

Inclusion Criteria

1. Subjects were male or female, aged 18 years and older.
2. Subjects had symptoms of OAB (UUI) for at least six months.
3. Subjects exhibited all of the following symptoms of OAB (UUI) during the 14 day run-in period (this information was collected using an electronic diary):
   - ? Incontinence - at least ten, but no more than 100, incontinent episodes over 14 days
   - ? Frequency of micturition - at least eight times per 24 hours on average, over 14 days
   - ? Urgency (strong desire to void) - at least once per 24 hours, on average, over 14 days
4. All women of child-bearing potential were to use adequate contraception (hormonal contraception, intrauterine device, or barrier methods with spermicide) throughout and four weeks after completion of the study. The pre-study pregnancy test was to be negative. Women who had been surgically sterilised or were at least two years postmenopausal could be enrolled and did not need to use birth control.
5. Subjects had to be capable of independently completing the diary.
6. Subjects were to give informed consent by signing and dating an informed consent form prior to study entry.
7. Subjects had to be capable of independent toileting.

Exclusion Criteria

1. Pregnant or lactating women.
2. Subjects who had evidence of clinically significant hepatic disease or other clinically significant abnormalities in screening laboratory tests which in the judgement of the investigator and/or sponsor clinician would interfere with the subject's participation in the study.
3. The following medications were discontinued as appropriate at Visit 1 (at least 14 days prior to the treatment free run-in) and were not to be used during the study:
   - ? anticholinergic/antispasmodic drugs (such as oxybutynin, tolterodine, hyoscyamine, propantheline, methantheline or flavoxate)
   - ? other drugs with significant anticholinergic effects (such as tricyclic antidepressants)
   - ? drugs that inhibit cytochrome P450 3A4
   - ? opioids and other drugs that could cause significant constipation

   Subjects treated with finasteride for benign prostatic hypertrophy must have been on a stable dose for six months.

   Subjects on long term stable-dose treatment with diuretics (including loop diuretics), alpha antagonists and calcium channel antagonists for hypertension, hormone replacement therapy, benzodiazepines or antihistamines were not excluded as long as the treatment regimen remained stable during the study.
4. Subjects in whom the use of anticholinergic drugs was contraindicated, eg those with uncontrolled narrow-angle glaucoma, urinary retention or gastric retention.

5. Subjects who had clinically significant stress incontinence (SI), eg subjects who reported more than one episode of SI per week.
6. Subjects who had clinically significant bladder outlet obstruction and/or subjects who had a post-void residual (PVR) volume of urine greater than 200ml at Visit 2.
7. Subjects who had a clinically significant pelvic prolapse, eg cystocele (Grades 3 or 4).
8. Subjects who had undergone urogenital surgery such as prostatectomy or hysterectomy less than six months prior to Visit 2. Subjects who had undergone bladder biopsy less than 30 days prior to Visit 2.
9. Subjects who had local pathology that might lead to urinary symptoms. Examples of such local pathology included interstitial cystitis, bladder stones, fecal impaction/severe constipation (fewer than three bowel movements per week) and a history of chronic intermittent urinary tract infection (UTI; three or more UTIs per year over the preceding two years). However, if present at screening, acute UTI or constipation was to be resolved prior to the start of the medication free run-in period.
10. Subjects who had other clinically significant systemic disease which, in the judgement of the investigator or sponsor, would interfere with the subject's participation in the trial.
11. Subjects who intended to start a bladder training program while in the study. Subjects on such a program at study entry had to have been on a stable regimen and were not to modify or discontinue their bladder training during the course of the study.
12. Subjects who had an indwelling catheter and subjects who practiced intermittent self catheterisation.
13. Subjects who had an allergy, hypersensitivity, or other medical contraindication to administration of darifenacin or other anticholinergic drugs.
14. Subjects who had received any investigational drug during the preceding 30 days or five times the plasma half life (if known), whichever was longer, or who had previously participated in this trial or any other darifenacin trial.
15. Subjects who, in the opinion of the investigator or sponsor, were unable and/or unlikely to comprehend and follow the study procedures and instructions.
16. Subjects who were abusers of alcohol and/or other drugs.
17. Subjects who intended to donate blood or blood products during the study or within one month following the completion of the study.

B. Study 1002:

Inclusion Criteria

1. Subjects were male or female, aged 18 years and older.
2. Subjects had symptoms of overactive bladder (UUI) for at least six months.
3. Subjects exhibited all of the following symptoms of overactive bladder (UUI) during the 14 day run-in period (this information was collected using an electronic diary):
   - ? Incontinence - at least 10, but no more than 100, incontinent episodes over 14 days
   - ? Frequency of micturition - at least eight times per 24 hours on average, over 14 days
   - ? Urgency (strong desire to void) - at least once per 24 hours, on average, over 14 days
4. All women of child-bearing potential were to use adequate contraception (hormonal contraception, intrauterine device, or barrier methods with spermicide) throughout and four weeks after completion of the study or were to be celibate or their partner must have had vasectomy. The pre-study pregnancy test was to be negative. Women who had been

surgically sterilised or were at least two years post-menopausal could be enrolled and did not need to use birth control.

5. Subjects had to be capable of independently completing the diary.
6. Subjects were to give informed consent by signing and dating an informed consent form prior to study entry.
7. Subjects had to be capable of independent toileting.

Exclusion Criteria

1. Pregnant or lactating women.
2. Subjects who had evidence of hepatic disease [aspartate transaminase (AST, SGOT), or alanine transaminase (ALT, SGPT), or total bilirubin >1.5 x upper limit of normal, or alkaline phosphatase >1.2 x upper limit of normal]; or other abnormalities in screening laboratory tests which in the judgment of the investigator and/or sponsor clinician would interfere with the subject's participation in the study.
3. The following medications were discontinued as appropriate at Visit 1 (at least 14 days prior to the single blind run-in) and were not to be used during the study:
   - ? anticholinergic/antispasmodic drugs (such as oxybutynin, tolterodine, hyoscyamine, propantheline, trospium or flavoxate)
   - ? other drugs with significant anticholinergic effects (such as imipramine and most other tricyclic antidepressants; however mianserin and trazadone were permitted), drugs that significantly inhibited CYP2D6 (such as cimetidine, fluoxetine and paroxetine but not other selective serotonin reuptake inhibitors (SSRIs))
   - ? estrogens if taken for less than two months
   - ? opioids and other drugs that could cause significant constipation and, added in the second protocol amendment: the potent cytochrome P450 3A4 inhibitors (administered orally or parenterally) ketoconazole, itraconazole, miconazole, troleandomycin and nefazodone.

   Subjects treated with finasteride for benign prostatic hypertrophy must have been on a stable dose for 6 months.

   Subjects on long term stable-dose treatment with diuretics (including loop diuretics), alpha antagonists and calcium channel antagonists for hypertension, benzodiazepines or antihistamines were not excluded as long as treatment remained stable during the study.
4. Subjects in whom the use of anticholinergic drugs was contraindicated, eg those with uncontrolled narrow-angle glaucoma, urinary retention, gastric retention.
5. Subjects who had clinically significant stress incontinence (SI), ie subjects who reported more than one episode of SI per week.
6. Subjects who had clinically significant bladder outlet obstruction and/or subjects who had a post void residual (PVR) volume of urine greater than 200ml at Visit 2.
7. Subjects who had cystocele beyond the hymen and subjects who had repaired uterine prolapse.
8. Subjects who had undergone urogenital surgery such as prostatectomy or hysterectomy less than six months prior to Visit 2. Subjects who had undergone bladder biopsy or cystoscopy less than 30 days prior to Visit 2.
9. Subjects who had local pathology that might lead to urinary symptoms. Examples of such local pathology included interstitial cystitis, bladder stones, severe constipation (fewer than three bowel movements per week) and a history of chronic intermittent urinary tract infection

(UTIs; three or more UTIs per year over the preceding two years). Evidence at screening of UTI, or unexplained haematuria excluded a subject from entering the study.

10. Subjects who had other clinically significant systemic disease.
11. Subjects who intended to start a bladder training programme while in the study. Subjects on such a programme at study entry were not to modify or discontinue their bladder training during the course of the study.
12. Subjects who had an indwelling catheter and subjects who practiced intermittent selfcatheterisation.
13. Subjects who had received any investigational drug during the preceding 30 days or five times the plasma half life (if known), whichever was longer, or who had previously participated in this trial or any other darifenacin trial.
14. Subjects who, in the opinion of the investigator or sponsor, were unable and/or unlikely to comprehend and follow the study procedures and instructions.
15. Subjects who were abusers of alcohol and/or other drugs.
16. Subjects who intended to donate blood or blood products during the study or within one month following the completion of the study.
17. Subjects who had allergy, hypersensitivity or other medical contra-indications to darifenacin.

C. Study 1041:

Inclusion Criteria

1. Males or females aged 18 years and over.
2. Subjects who had had symptoms of OAB for at least six months.
3. Subjects who exhibited all of the following symptoms of OAB during the seven days preceding randomisation. (This information was collected using a electronic patient diary).
   - ? Incontinence – at least five, but no more than 50, incontinent episodes (on average) over seven days.
   - ? Frequency of micturition – at least eight times per 24 hours (on average) over seven days.
   - ? Urgency (strong desire to void) – at least one per 24 hours (on average) over seven days.
4. All women of child-bearing potential were to use adequate contraception (hormonal contraception, intrauterine device, or barrier methods with spermicide) throughout and for four weeks after completion of the study or were to be celibate or their partner must have had a vasectomy. The pre-study pregnancy test was to be negative. Women who had been surgically sterilised or were at least two years post-menopausal could be enrolled and did not need to use birth control.
5. Subjects had to be capable of independently completing the diary.
6. Subjects were to give informed consent by signing and dating an informed consent form prior to study entry.
7. Subjects had to be capable of independent toileting.

Exclusion Criteria:

1. Pregnant or lactating women.
2. Subjects who had evidence of hepatic disease (eg would fit the Pugh Child C classification) or other abnormalities in screening laboratory tests which in the judgment of the investigator and/or sponsor clinician would interfere with the subject's participation in the study.
3. The following medications were to be discontinued as appropriate at Visit 1 (at least 14 days prior to the run-in period) and were not to be used during the study:

- ? anticholinergic/antispasmodic drugs (such as oxybutynin, tolterodine, hyoscyamine, propantheline, trospium or flavoxate)
- ? other drugs with significant anticholinergic effects (such as imipramine and most other tricyclic antidepressants; however mianserin and trazadone were permitted)
- ? hormone replacement therapy if taken for less than two months
- ? opioids and other drugs that could cause significant constipation
- ? the potent cytochrome P450 3A4 inhibitors (administered orally or parenterally) ketoconazole, itraconazole, miconazole, troleandomycin and nefazodone

Subjects treated with finasteride for benign prostatic hypertrophy must have been on a stable dose for 6 months.

Subjects on long term stable-dose treatment with diuretics (including loop diuretics), alpha antagonists and calcium channel antagonists for hypertension, benzodiazepines or antihistamines were not excluded as long as treatment remained stable during the study.

4. Subjects in whom the use of anticholinergic drugs was contraindicated, *eg* those with uncontrolled narrow-angle glaucoma, urinary retention, gastric retention.
5. Subjects who had clinically significant stress incontinence (SI), *ie* subjects who reported more than one episode of SI per week.
6. Subjects who had clinically significant bladder outlet obstruction and/or subjects who had a PVR volume of urine greater than 200ml at Visit 2.
7. Subjects who had cystocele or other clinically significant pelvic prolapse beyond the hymen.
8. Subjects who had undergone urogenital surgery such as prostatectomy or hysterectomy less than six months prior to Visit 2. Subjects who had undergone bladder biopsy or cystoscopy less than 30 days prior to Visit 2.
9. Subjects with chronic persistent local pathology that may lead to urinary symptoms eg interstitial cystitis, bladder stones, severe constipation (fewer than three bowel movements per week), unexplained haematuria or an intermittent urinary tract infection (UTI), (three or more UTIs per year over the preceding two years). Subjects with evidence at screening of an acute UTI, acute constipation or unexplained haematuria were to be excluded from the study until the condition had clinically resolved.
10. Subjects who had other clinically significant systemic disease.
11. Subjects who intended to start a bladder training programme while in the study.
12. Subjects on such a programme at study entry were not to modify or discontinue their bladder training during the course of the study.
13. Subjects who had an indwelling catheter and subjects who practised intermittent self-catheterisation.
14. Subjects who had received any investigational drug during the preceding 30 days or five times the plasma half life (if known), whichever was longer. Subjects who had suffered drug related serious adverse events during the 30 day period following their last dose of the previous investigational drug, during the last six months were also excluded.
15. Subjects who, in the opinion of the investigator or sponsor's clinician, were unable and/or unlikely to comprehend and follow the study procedures and instructions.
16. Subjects who were abusers of alcohol and/or other drugs.
17. Subjects who intended to donate blood or blood products during the study or within one month following the completion of the study.
18. Subjects who had an allergy, hypersensitivity or other medical contra-indications to darifenacin.

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/s/

Zili Li
9/26/03 02:55:34 PM
MEDICAL OFFICER

Mark S. Hirsch
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I concur.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-513 (Darifenacin)

Sponsor: Novartis

Request: Consult request from the Division of Reproductive and Urologic Drug Products for consultative review of annotated ECGs in study DAR328A2302.

Review date: 14 October 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This is a brief review of annotated ECG findings for NDA 21-513 (darifenacin), study DAR328A2302, entitled "A double blind, parallel group, placebo and active controlled, multiple-dose study to evaluate the effects of darifenacin on cardiac safety in poor and extensive CYP2D6 substrate metabolizers."

The review was conducted using the XMLFDA viewer application version 4.0.0beta.

A dozen randomly selected aECG files were examined for high frequency noise, low-frequency noise (baseline wander), and placement of interval markers. The majority of records had three successive beats annotated in Lead II. A few had annotations in Lead V2. The quality of the records is generally quite satisfactory.

A particularly challenging example, not typical, is shown in Figure 1 below.

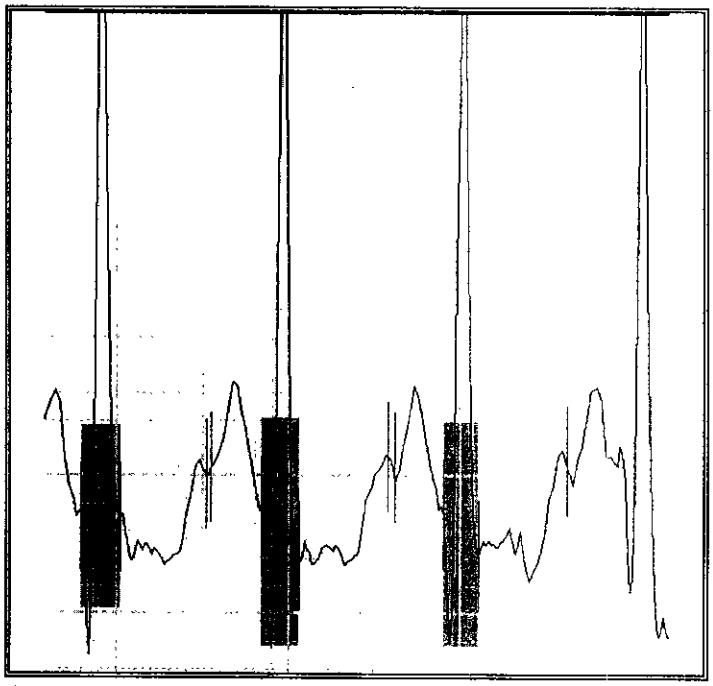

Figure 1. Sample annotated ECG from Study DAR328A2302.

The quality of the records is generally quite satisfactory. In general, the ends of the T wave were marked close to where most observers would likely have placed them.

The samples examined did not have derived waveform data.

In the absence of a clinical review, the sponsor's study report was examined for reports of outliers for QTcF or QTcI. One subject is said to have QTcI > 480 ms on day 6 of darifenacin 75 mg, but the study report does not have a listing of QTcI for each subject (data listing) and the datasets are not with the study report (only the aECG files are in the CRT folder).

Figure 5.5 of the sponsor's study report, reproduced below, shows the time course of QTcI measurements as a function of time for each group at baseline (Day -1) and on treatment (Day 6). The distribution of values on Day 6 in this group does not look different from the distribution at baseline. As a result, I am not particularly concerned about reviewing the aECGs for any "outliers" in this dataset, but I would be happy to do so, if someone were to name a candidate subject ID.

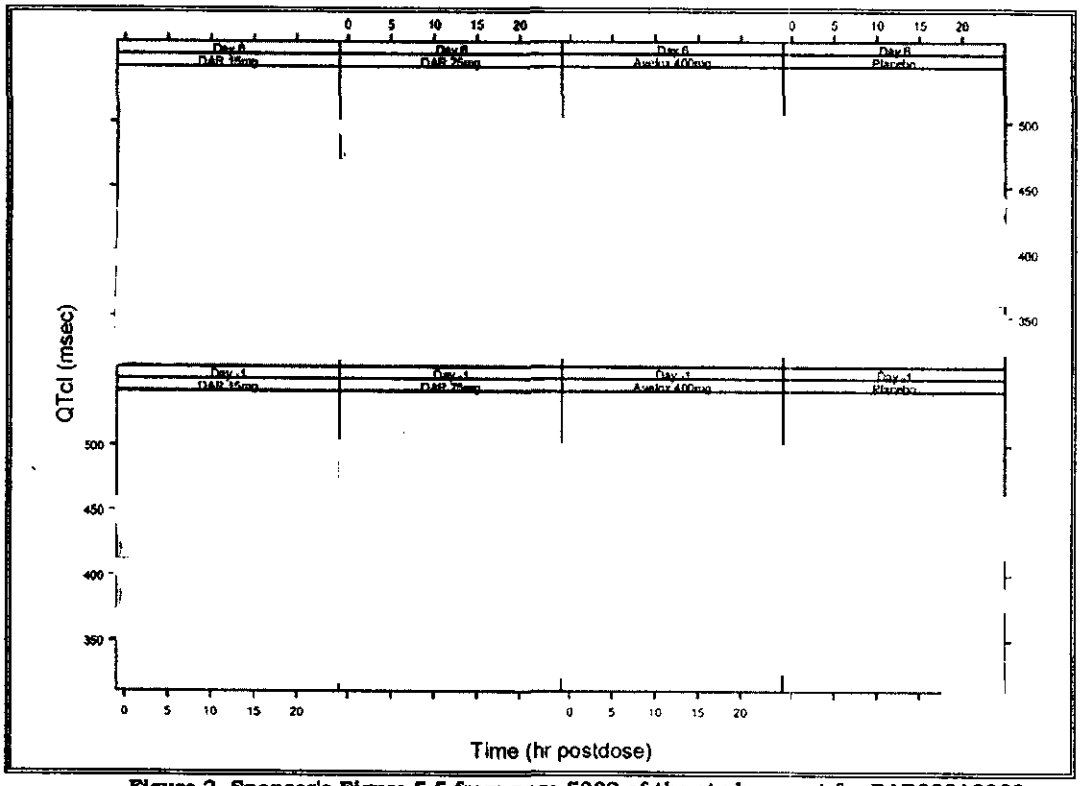

Figure 2. Sponsor's Figure 5.5 from page 5382 of the study report for DAR328A2302.

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/s/

Norman Stockbridge
10/14/04 07:46:42 AM
MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Joint Clinical Review

NDA: 21-513

Sponsor: Novartis

Submission: "Key information" compiled by HFD-580 reviewers, the sponsor's integrated summary of QT data (16 November 2002) and responses to the review division's specific inquiries (4 September 2003).

Review date: 15 September 2003

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Concurrence: Douglas C. Throckmorton, M.D., Director, HFD-110

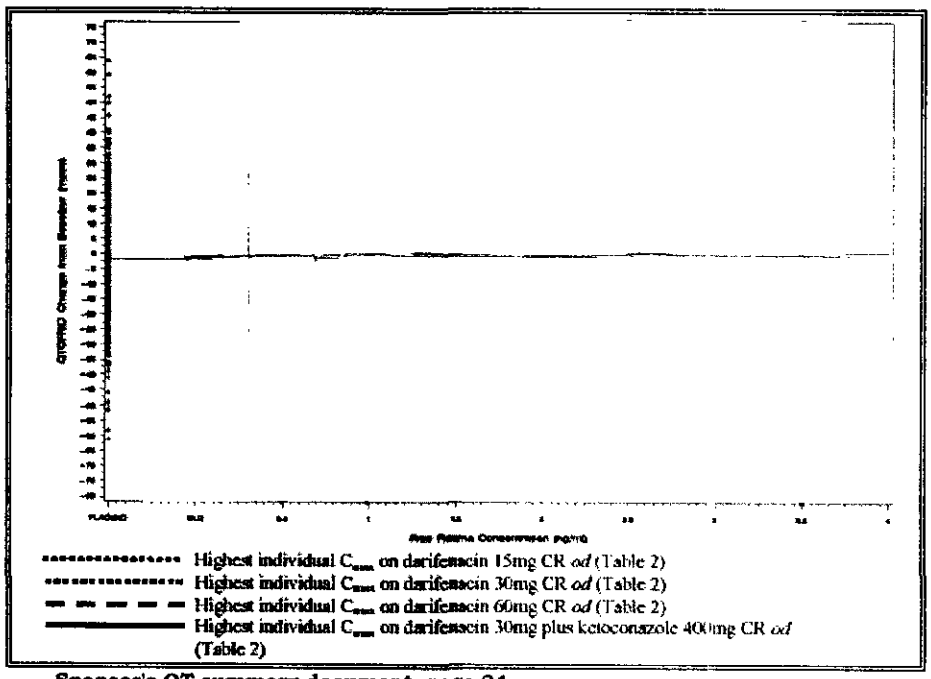
Darifenacin is a selective muscarinc receptor antagonist currently under NDA review for use as a treatment for overactive bladder at doses of 7.5 to 15 mg QD. There are no known merits that would distinguish this agent from previously approved ones. The Division of Cardio-Renal Drug Products has been asked (1) whether study 1015 rules out a clinically relevant QT effect at 60 mg QD, and (2) whether the effect on QT seen with darifenacin 30 mg plus ketoconazole 400 mg in study 1007 is clinically significant.

Darifenacin inhibits HERG with a sub-micromolar IC50, competes for dofetilide binding sites, and increases action potential duration in some cardiac preparation.

Plasma levels of darifenacin peak 7 hours after dosing and reach steady-state after about 6 days. Plasma levels increase more than linearly with dose (about 3-fold per dose-doubling). Metabolism involves 2D6 and 3A4, the former manifesting a 2-fold increase in Cmax in poor metabolizers and the latter producing up to 5-fold increase in plasma levels with ketoconazole.

The safety database of over 6000 subjects is said to contain no evidence of syncope, ventricular arrhythmia, or sudden death. No "thorough" QT study, with a positive control, has been performed.

Darifenacin appears to have no effect on heart rate. An integrated review of change in QTcF as a function of plasma levels of parent reveals no sign of a positive slope nor evident trend for outliers, but there are few data with these higher plasma concentrations.



Sponsor's QT summary document, page 24.

Study 1015[1] was a parallel study in which 62 healthy volunteers over age 50 were randomized to placebo (n=10) or darifenacin 30 (n=10) or 60 mg (n=42) QD for 14 days. Twelve-lead ECGs were obtained 4 hours after dosing on days 1 and 14. The nominal mean change from baseline and placebo in QTcF was 3 ms with a standard error of the mean of about 3 ms.

Study 1007[2] was a crossover study in which 16 normal adult males received, in random order, 6-day courses of darifenacin 30 mg alone or with ketoconazole 400 mg. Continuous Holter recording (leads?) was conducted from 15 minutes prior to dosing to 6 hours after dosing on day 6 only. The nominal increase in QTcF with ketoconazole (there being no placebo reference) was about 12 ms with SEM about 3 ms[3].

If one could prevent drug exposure above 15 mg, use in poor 2D6 metabolizers, and 3A4 inhibition, then the apparently shallow relationship to QT at these relatively high plasma levels might be relatively comforting. In practice, none of these can be prevented. Nor can one determine post hoc what the assay sensitivity was in either study, so one cannot determine what magnitude of mean QT effect has been excluded. In other words, "assay validation" also serves to calibrate the observed effects against a known reference. In addition, ECGs in both studies appear to have been collected prior to attainment of peak plasma levels following a dose.

The ambiguities can be resolved only through a "thorough" QT evaluation with a positive control agent. It is recommended that such a study use as high a dose as can be tolerated during a 6-day exposure. Use of a metabolic inhibitor would necessitate an inhibitor-alone arm or crossover period. The sponsor might wish to consider inclusion of an approved agent for overactive bladder, preferably of the same class as darifenacin.

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[1] *Study report at \\Cdsesub1\N21513\N_000\2002-12-03\hpbio\hupharm\1015.pdf*

[2] *Study report at \\Cdsesub1\N21513\N_000\2002-12-03\hpbio\hupharm\pk\1007.pdf*

[3] *Sponsor's study report, page 115.*

The sponsor should plan to submit annotated waveforms resulting from any "thorough" study.

The Division of Cardio-Renal Drug Products appreciates the opportunity to review these data. The Division would be happy to discuss these matters further with the consulting division.

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/s/

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9/16/03 09:49:38 AM
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Doug Throckmorton
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NDA 21-513 Enablex Extended Release Tablets
Darifenacin hydrobromide, 7.5 and 15 mg

Safety Update Review

See Integrated Review of Safety, pages 46-91 of the Medical Officer Review.

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9/25/03