

Gatifloxacin 400 mg PO:

Safety data at the 400 mg oral dose level were derived from 14 clinical studies (AI420-001, -002, -003, -004, -005, -006, -007, -008, -010, -011, -012, -020, -031, and -038). The duration of dosing ranged from 1 day (Studies AI420-010 and -012) to 14 days in four pneumonia trials (Studies AI420-002, -003, -006, and -038). In the randomized studies, data for five comparators were pooled (3 quinolones: levofloxacin, ciprofloxacin, ofloxacin; [redacted] clarithromycin; and [redacted] cefuroxime axetil). The 400 mg PO dose level was investigated in all seven indications included in this application.

Of those patients treated with the 400 mg dose strength of gatifloxacin, just over half (54%) experienced adverse clinical events; the most frequent of these were nausea and headache (ten and nine percent of gatifloxacin-treated patients, respectively). The safety profiles for gatifloxacin-treated patients were comparable for the non-comparative and comparative studies. Additionally, in the comparative trials, the gatifloxacin data were comparable to those of the pooled comparator agents. The overall incidence of adverse clinical events among gatifloxacin-treated patients did not vary by geographic region: 54% in North America, 56% in other countries.

Selected Frequent Adverse Clinical Events All Cause: Gatifloxacin 400 mg PO				
No. (%) Patients				
Adverse Event	Non-Comparative Trials Gatifloxacin N=769	Comparative Trials Gatifloxacin N=2252	Comparator N=2111	TOTAL GATIFLOXACIN N=3021
Headache	76 (10)	186 (8)	204 (10)	262 (9)
Nausea	61 (8)	241 (11)	171 (8)	302 (10)
Dizziness	32 (4)	93 (4)	63 (3)	125 (4)
Diarrhea	32 (4)	118 (5)	143 (7)	150 (5)
Vaginitis	40 (9)	91 (7)	54 (4)	131 (7)
Insomnia	11 (1)	39 (2)	47 (2)	50 (2)
Rash	11 (2)	34 (2)	30 (1)	48 (2)

For these most frequently occurring events the differences appear to be similar between gatifloxacin and the comparator groups. This was slightly more nausea and dizziness in the gatifloxacin group; however, when one examines the individual comparators within the various studies (see indication reviews) it is noted that the rates of nausea are higher in the clarithromycin group, and the dizziness is seen to the same extent as the levofloxacin group.

Syncope was reviewed across studies and found to have occurred in < 1% in the gatifloxacin and comparator arms. There were 6/3021 patients in the gatifloxacin group who reported syncope and 3/2111 patients in the comparator group. None of these cases were felt to be related to the study drug by the investigators. Three were considered to grade III in severity (1 clarithromycin treated patient, 2 gatifloxacin treated patients). Only one patient had their medication discontinued because of this adverse event

(comparator arm). One patient in each group died, and death was felt not to be related to this event.

Selected Adverse Events of All Cause by Severity, Gatifloxacin 400 mg PO				
No. (%) Patients N=3021				
Adverse Event	Mild N=.694 (23%)	Moderate N=693 (23%)	Severe N=232 (8%)	TOTAL N= 1625 (54%)
Nausea	199 (7)	79 (3)	23 (<1)	302 (10)
Headache	127 (4)	107 (4)	28 (<1)	262 (9)
Diarrhea	95 (3)	48 (2)	7 (<1)	150 (5)
Vaginitis	76 (4)	50 (3)	4 (<1)	131 (7)
Dizziness	85 (3)	31 (1)	8 (<1)	125 (4)
Pain Abdomen	58 (2)	31 (1)	6 (<1)	95 (3)
Vomiting	38 (1)	32 (1)	14 (<1)	85 (3)
Insomnia	28 (<1)	16 (<1)	4 (<1)	50 (2)
Rash	31 (1)	13 (<1)	3 (<1)	48 (2)

Again most of the adverse clinical events were reported to be of the mild to moderate nature. Of the eight percent of patients reported to have severe events, they were scattered throughout the adverse event classifications with all categories being reported at less than 1% in frequency.

85 patients were reported to have serious adverse events in the gatifloxacin group. Problems of a respiratory or cardiovascular nature accounted for over half of these events. Overall, these events were similar to the comparator arms. In the gatifloxacin treatment group there were 16 serious adverse events related to the central nervous system: most of them were not considered related to drug by the investigator in particular the four episodes of seizure. There was one seizure reported in the comparator group, that patient received ciprofloxacin.

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Most Frequent Serious Adverse Events; Gatifloxacin 400 mg PO				
No. (%) Patients				
Body System	Non-Comparative Trials Gatifloxacin N=769	Comparative Trials Gatifloxacin N=2252	Comparator N=2111	TOTAL GATIFLOXACIN N=3021
Any Body System	20 (3)	65 (3)	40 (2)	85 (3)
Body as A Whole	5 (<1)	13 (<1)	6 (<1)	18 (<1)
Cardiovascular	6 (<1)	14 (<1)	4 (<1)	20 (<1)
Congestive Heart Failure	1 (<1)	4 (<1)	2 (<1)	5 (<1)
Myocardial Infarction	2 (<1)	4 (<1)	--	6 (<1)
Digestive	2 (<1)	9 (<1)	6 (<1)	11 (<1)
Endocrine	--	1 (<1)	--	1 (<1)
Metabolic/Nutritional	--	2 (<1)	4 (<1)	2 (<1)
Musculoskeletal	--	3 (<1)	5 (<1)	3 (<1)
Nervous	3 (<1)	13 (<1)	4 (<1)	16 (<1)
Respiratory	13 (2)	18 (<1)	17 (<1)	31 (1)
Dyspnea	3 (<1)	2 (<1)	2 (<1)	5 (<1)
Pneumonia	7 (<1)	7 (<1)	8 (<1)	14 (<1)
Skin/Appendages	--	1 (<1)	--	1 (<1)
Urogenital	--	4 (<1)	4 (<1)	4 (<1)

Discontinuation of therapy was due to an adverse event in 128/3021 (4%) gatifloxacin-treated patients and 86/2111 (4%) patients treated with the comparator agents. Treatment discontinuation was associated with drug-related adverse events in 169 (3%) patients, equally distributed between the treated groups.

Of those gatifloxacin-treated patients that stopped treatment because of adverse events or laboratory abnormalities (see table below), gastrointestinal side effects, such as nausea, vomiting, abdominal pain, and diarrhea were among the most frequent reasons for discontinuation. In the comparative studies, the overall numbers of gatifloxacin- and comparator-treated patients discontinuing for adverse events were comparable. There were some minor differences with respect to the individual adverse events that prompted discontinuation; headache and abdominal pain tended to be more common among the comparator agents, while vomiting and dyspepsia were more common among gatifloxacin-treated patients.

There were 11 discontinuations of therapy due to laboratory abnormalities (7 gatifloxacin and 4 comparator). For 10 patients, these abnormalities were documented in the pre-treatment assessment and treatment was disrupted when the laboratory report became available. The last patient (gatifloxacin group) was treated for 5 days and experienced a transient increase in liver enzyme (see laboratory section for further discussion)

Discontinuation Due to Selected Adverse Events; Gatifloxacin 400 mg PO				
No. (%) Patients				
Adverse Event	Non-Comparative Trials Gatifloxacin N=769	Comparative Trials Gatifloxacin N=2252	Comparator N=2111	TOTAL GATIFLOXACIN N=3021
Headache	3 (3)	1 (1)	2 (2)	4 (4)
Nausea	1 (1)	8 (8)	10 (9)	9 (9)
Dizziness	2 (2)	10 (8)	8 (8)	12 (10)
Tremor	--	8 (8)	2 (2)	8 (8)
Insomnia	1 (1)	5 (5)	5 (4)	6 (6)
Nervousness	2 (1)	4 (2)	4 (4)	6 (3)
Diarrhea	3 (3)	11 (11)	11 (11)	14 (14)
Vaginitis				
Vomiting	3 (2)	22 (21)	15 (15)	25 (23)
Allergic Reaction	3 (3)	1 (1)	2 (2)	4 (4)
Rash	2 (2)	5 (5)	6 (6)	7 (7)

It is of interest to view this population of events across studies as some of the events are specific to the underlying disease in which gatifloxacin is being studied. The following table displays this information for selected events. Overall, the events were similar in character between the North American Countries and Other Countries. The symptoms related to upper respiratory tract infections were more commonly seen in the pneumonia, bronchitis and sinusitis studies. Nausea and Dizziness were more frequently seen in the complicated urinary tract infection study. Independent review of these events in Dr. Roca's review did not reveal any specific underlying cause for these events other than the infection being treated. It is not uncommon to see nausea in complicated urinary tract infections. Vaginitis was highest in the sinusitis and gonorrhea studies. Insomnia was seen at a low frequency across all studies and occurred more frequently in the CAP studies where it might be expected if the patient were having difficulty breathing.

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Adverse Events of All Cause by Diagnosis, Gatifloxacin 400 mg PO

No. (%) Patients

	North America							Other Countries		
	Pneumonia N=461	AECB N=494	Sinusitis N=468	SSTI N=202	CUTI N=359	UUTI N=436	Gonorrhea N=295	Pneumonia N=136	Bronchitis N=64	Sinusitis N=106
Abnormal Breath Sounds	75 (16)	29 (6)	3 (<1)	--	1 (<1)	1 (<1)	1 (<1)	15 (11)	10 (16)	1 (<1)
Nausea	52 (11)	46 (9)	52 (11)	17 (8)	54 (15)	33 (8)	25 (8)	12 (9)	5 (8)	5 (5)
Coughing	47 (10)	39 (8)	39 (8)	--	3 (<1)	--	1 (<1)	11 (8)	9 (14)	8 (8)
Increased Sputum	47 (10)	34 (7)	--	--	--	--	--	10 (7)	8 (13)	--
Headache	44 (10)	35 (7)	51 (11)	14 (7)	22 (6)	53 (12)	17 (6)	15 (11)	3 (5)	8 (8)
Chest Pain	32 (7)	31 (6)	1 (<1)	1 (<1)	2 (<1)	1 (<1)	1 (<1)	5 (4)	6 (9)	--
Diarrhea	31 (7)	31 (6)	29 (6)	13 (6)	18 (5)	13 (3)	6 (2)	7 (5)	1 (2)	1 (<1)
Pharyngitis	28 (6)	20 (4)	29 (6)	5 (2)	16 (4)	10 (2)	2 (<1)	2 (1)	4 (6)	6 (6)
Vomiting	28 (6)	17 (3)	7 (1)	4 (2)	14 (4)	7 (2)	2 (<1)	6 (4)	--	--
Pain	21 (5)	8 (2)	48 (10)	8 (4)	11 (3)	15 (3)	1 (<1)	8 (6)	--	4 (4)
Insomnia	19 (4)	8 (2)	7 (1)	2 (<1)	7 (2)	--	1 (<1)	4 (3)	1 (2)	1 (<1)
Dizziness	17 (4)	23 (5)	17 (4)	10 (5)	28 (8)	12 (3)	6 (2)	3 (2)	5 (8)	4 (4)
Vaginitis	16 (7)	14 (6)	35 (12)	10 (9)	12 (6)	11 (3)	24 (16)	5 (7)	3 (14)	1 (2)
Abdomen Pain	16 (3)	10 (2)	17 (4)	9 (4)	14 (4)	17 (4)	2 (<1)	9 (7)	--	1 (<1)
Rash	16 (3)	3 (<1)	8 (2)	6 (3)	5 (1)	4 (<1)	1 (<1)	5 (4)	--	--
Dry Mouth	9 (2)	9 (2)	7 (1)	--	11 (3)	1 (<1)	--	6 (4)	2 (3)	2 (2)

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400 mg IV-PO Dose Regimen in Efficacy Trials:

Safety data at this dose level were derived from two studies (AI420-037 and -038) in community-acquired pneumonia where patient treatment was initiated with IV gatifloxacin and switched to oral gatifloxacin (both at the 400 mg dose level). Both studies were conducted in North America; the duration of therapy was 7-14 days. Data from the two comparator arms (levofloxacin in -038 and ceftriaxone ± erythromycin followed by clarithromycin in -037) were pooled by the applicant.

In those patients who began therapy with the 400 mg IV dose of gatifloxacin and then switched to PO therapy, three of the four most common adverse clinical events, abnormal breath sounds, increased sputum, and chest pain, were related to the infection under study. With a few exceptions, the safety profile of gatifloxacin was comparable to that of the pooled comparators.

There were 67 injection site reactions, 34 (21%) in the gatifloxacin group and 33 (20%) in the comparator group. They mostly consisted of signs or symptoms such as infiltration, pain, or discomfort at the injection site. There were 16 cases, 8 (5%) in each group, of redness. For gatifloxacin-treated patients, these represented the characteristic local intolerance described in the Phase I study in volunteers.

The majority of adverse clinical events occurring in patients treated with gatifloxacin 400 mg IV-PO were mild or moderate in severity. Severe adverse events were uncommon.

There were 21 discontinuations due to adverse events, 13 of which were felt to be drug-related. These discontinuations occurred more often in the comparator group; the responsible adverse events consisted mostly of gastrointestinal intolerance and worsening signs and symptoms of pneumonia. There were 6 discontinuations due to CNS events, three in the gatifloxacin and comparator groups. Of note, one gatifloxacin patient discontinued due to a rash which was related to an allergic reaction, not phototoxicity.

Overall, the safety profile of this regimen was similar to that of the 400 mg PO dose reported in the previous section.

200 mg PO Dose in Efficacy Trials:

Safety data at this dose level were derived from 443 patients accrued in one treatment arm of a single study (AI420-010) in women with uncomplicated UTI. The study was conducted entirely in North America and the duration of therapy was 3 days. The comparator was ciprofloxacin given at a dose of 100 mg BID for 3 days.

In the single study that used the 200 mg dose of gatifloxacin, the incidence of adverse clinical events was 51% in gatifloxacin-treated patients and 45% comparator-treated patients. Headache and nausea were the most frequent adverse events in both treatment arms. Headache was noted in 10% of the gatifloxacin patients compared to 15% in the ciprofloxacin group while vaginitis was reported in 7% of gatifloxacin-treated patients compared to 3% with ciprofloxacin.

The majority of adverse clinical events were either mild or moderate in severity. Seven percent of patients treated with the 200 mg gatifloxacin dose experienced what were categorized as severe/very severe adverse events by the Investigator. They consisted mainly of headache, nausea and abdominal pain. The two very severe events were migraine headache and cholecystitis.

There were nine discontinuations due to adverse events, two in the gatifloxacin group and seven in the comparator (ciprofloxacin) group. All but one of these patients had at least one event that was drug-related. The most frequent adverse events leading to discontinuation were related to gastrointestinal intolerance. In some instances (e.g., urinary tract infection), the assessment of relatedness was questionable.

Overall, the safety profile of this regimen was similar in types of events to that of the 400 mg PO dose reported in the previous section.

600 mg PO Dose in Efficacy Trials:

Safety data at this dose level were derived from a single study (AI420-012) conducted in patients with uncomplicated gonococcal urethritis/cervicitis. The study was conducted entirely in North America; the duration of therapy was one day. The comparator was ofloxacin, given as a single 400 mg dose. Comparison between the two gatifloxacin doses (400 mg single dose and 600 mg single dose) was presented in the individual report (Study AI420-012) and are briefly reported here. In general, the events are similar to those reported above.

Selected Frequent Adverse Clinical Events All Cause: Gatifloxacin 600 mg PO			
Adverse Event	Gatifloxacin 400 mg N=295	Gatifloxacin 600 mg N=291	Ofloxacin 400 mg N=142
Headache	17 (6)	9 (3)	8 (6)
Nausea	25 (9)	32 (11)	7 (5)
Dizziness	6 (2)	11 (4)	1 (<1)
Diarrhea	6 (2)	11 (4)	4 (3)
Vaginitis	4 (3)	5 (3)	1 (1)

Most of the events reported were mild or moderate in severity. Only one report in the gatifloxacin group was reported as severe, it was a case of asthenia.

In summary, review of the adverse event reports reveals that the most common adverse events that are related to gatifloxacin include headache and nausea. Dizziness and diarrhea were seen at a lower level (2-4%) and occurred at a rate similar to the comparator. Overall, the events were mild or moderate, with few being reported as severe. Review of potential class effects of the quinolones and those reported for gatifloxacin are described below in section 9.4.

9.1.1 Special Populations (Adverse Events: age, race, gender)

Again this analysis reflects the applicant's strategy for reviewing the dose regimens separately in order to determine if any dose related events could be detected. The following include review of the adverse events by age, race and gender.

Safety In Health Volunteers (phase II):

With respect to the analysis by age, nausea and headache appeared to be somewhat more frequent in patients less than 65 years of age, but the results should be interpreted with caution due to the small number of elderly patients.

Gatifloxacin Selected Adverse Events of All Causes by Age, Studies in Volunteers			
No. (%) Patients			
Adverse Event	Age <65 yrs N=424	Age 65-74 yrs. N=42	Age ≥ 75 yrs. N=9
Headache	62 (15)	3 (7)	--
Nausea	43 (10)	2 (5)	--
Dizziness	29 (7)	4 (9)	1 (11)
Puritus	22 (5)	--	--

Analysis of gatifloxacin adverse clinical events by race did not identify substantial differences between White, Black, and Hispanic volunteers. There was a somewhat higher rate of puritus than for whites; however, the numbers are small to draw specific conclusions regarding this event.

Gatifloxacin Selected Adverse Events of All Causes by Race, Studies in Volunteers					
No. (%) Patients					
Adverse Events	White N=392	Black N=58	Hispanic N=21	Asian N=2	Other N=2
Headache	56 (14)	5 (9)	3 (14)	--	1 (50)
Nausea	36 (9)	5 (9)	4 (19)	--	--
Dizziness	28 (7)	5 (9)	1 (5)	--	--
Puritus	11 (3)	7 (12)	4 (19)	--	--

There were essentially no differences in the analysis by gender. It should be noted, however, that dizziness was somewhat more frequent in females than males.

Gatifloxacin Selected Adverse Events of All Causes by Gender, Studies in Volunteers		
No. (%) Patients		
Adverse Events	Male N=379	Female N=96
Headache	49 (13)	16 (7)
Nausea	29 (8)	16 (7)
Dizziness	21 (5)	13 (14)
Puritus	20 (5)	2 (2)
Pain Abdomen	11 (3)	7 (7)

Gatifloxacin 400 mg PO:

The majority of patients treated with the 400 mg PO dose of gatifloxacin were less than sixty-five years of age; just over half of these patients experienced at least one adverse clinical event. The incidence of adverse clinical events in the elderly population was somewhat higher: sixty percent among patients aged 65 to 74 years, and 65% among patients greater than 75 years of age. These data did not differ by geographic region. When considering individual events, nausea, vomiting, and dizziness each occurred with greater frequency among those ≥ 75 years; this was true in both North America and other countries. Headache was seen in a lower frequency in those ≥ 75 years.

Selected Adverse Events by Age All Cause: Gatifloxacin 400 mg PO			
Adverse Event	<65 years N=2463	65-74 years N=321	≥ 75 years N=237
Nausea	233 (9)	27 (8)	42 (18)
Headache	232 (9)	22 (7)	8 (3)
Diarrhea	121 (5)	17 (5)	12 (5)
Vaginitis	119 (8)	9 (6)	3 (3)
Dizziness	89 (4)	18 (6)	18 (8)
Pain Abdomen	74 (3)	13 (4)	8 (3)
Vomiting	63 (3)	6 (2)	16 (7)
Insomnia	39 (2)	6 (2)	5 (2)
Rash	39 (2)	3 (<1)	6 (3)

The incidence of adverse clinical events by race is presented in the table below; the overall incidence data are remarkably consistent across geographic regions. With the caveat that there were very few Asian patients enrolled, there were no adverse clinical events that occurred with greater frequency in a particular race.

Selected Adverse Events of All Cause by Severity by Race, Gatifloxacin 400 mg PO				
Adverse Event	No. (%) Patients			
	White N=2095	Black N=570	Hispanic N=306	Asian N=31
Nausea	233 (11)	44 (8)	20 (7)	3 (10)
Headache	207 (10)	32 (6)	18 (6)	3 (10)
Diarrhea	117 (6)	21 (4)	11 (4)	1 (3)
Vaginitis	94 (7)	30 (11)	7 (3)	--
Dizziness	89 (4)	16 (3)	14 (5)	4 (13)
Pain Abdomen	75 (4)	7 (1)	9 (3)	2 (6)
Vomiting	71 (3)	6 (1)	7 (2)	--
Insomnia	41 (2)	5 (<1)	3 (<1)	1 (3)
Rash	40 (2)	2 (<1)	5 (2)	--

Fifty-seven percent of females and forty-nine percent of males experienced adverse clinical events; this difference in incidence is largely accounted for by the cases of vaginitis occurring in females. The two most frequent adverse clinical events, nausea and headache, were somewhat more common in females than in males. In most instances, the occurrence of adverse events by gender was very consistent across geographic regions.

Gatifloxacin Selected Adverse Events of All Causes by Gender, Gatifloxacin 400 mg PO		
No. (%) Patients		
Adverse Events	Male N=1221	Female N=1800
Headache	84 (7)	178 (10)
Nausea	74 (6)	228 (13)
Dizziness	55 (5)	70 (4)
Rash	15 (1)	33 (2)
Vaginitis	---	131 (7)
Diarrhea	70 (6)	80 (4)
Vomiting	17 (1)	68 (4)
Pain Abdomen	26 (2)	69 (4)

400 mg IV-PO Dose Regimen in Efficacy Trials:

The overall incidence of adverse clinical events was somewhat higher among patients ≥ 75 years of age. Coughing (7 patients; 15%), constipation (8 patients; 17%), agitation (4 patients; 9%), confusion (5 patients; 11%), and anxiety (patients: 9%) were among the events occurring more frequently in this age group.

An analysis of adverse clinical events by race did not highlight any notable differences; the overwhelming majority of patients treated with this dose and formulation were white, making comparisons difficult.

The incidence of adverse clinical events was higher in females (92%) than males (82%). Constipation, chest pain, and headache were among the events more common in women, while dyspnea, vomiting, and anxiety were noted more often in men.

200 mg PO dose in Efficacy Trials:

This study was conducted in women alone. Analysis by age and race did not reveal any substantial differences.

600 mg PO dose in Efficacy Trials:

All patients enrolled were less than 65 years of age.

In contrast to the demography of other dosage groups, the majority of patients treated with the 600 mg dose of gatifloxacin were Black. There was no difference in the overall incidence of adverse clinical events in Black and White patients. Data from Hispanics and Asians were insufficient to make any conclusions.

The incidence of adverse clinical events was slightly higher in females (38% vs. 31% in males); this difference is accounted for by the cases of vaginitis, dizziness and vomiting.

9.1.2 Additional Safety Experience

4 month Safety Update:

The applicant supplied a 4 month safety update to the FDA on May 6th, 1999. It provided information on safety of the ongoing, blinded Bristol-Myer Squibb studies, and Safety Listings on Kyorin-Sponsored Studies.

Studies by Bristol-Myer Squibb, which were reported as ongoing, were not unblinded. The safety data was reported without knowledge of the treatment assignment. The studies included in this report include several where trovafloacin was the comparator. The list of adverse events provided was similar to the profile seen in the original NDA report. No new, unexpected events were reported.

STUDIES SPONSORED BY [REDACTED]

There were seven Phase III randomized, double-blind trials conducted in six indications: community-acquired pneumonia, acute exacerbation of chronic bronchitis, sinusitis, skin and skin structure infections, uncomplicated and complicated UTI. In most cases, the design of these studies was similar to those sponsored by Bristol-Myers Squibb. There were, however, some notable differences. There were two dose-ranging trials, one in AECB, and one in complicated UTI. In these two trials, daily doses of 200 mg and 400 mg were tested. Shorter duration of dosing was also explored in a number of indications, including community-acquired pneumonia, AECB, complicated UTI, sinusitis, and SSTI. In these indications, treatment courses as short as 5 days were allowed by the protocol, usually as part of a dosing range of either 5-10 or 5-14 days.

These seven efficacy trials accrued a total of 3,894 patients, the majority of whom were treated for urinary tract infections. These studies were multi-national trials, conducted throughout Europe and in South Africa, Australia, and New Zealand.

At the time of this report, all clinical studies were closed for accrual. Safety and efficacy analyses were not yet performed. It is anticipated that these analyses will become available during the first and second quarters of 1999.

A total of 137 serious adverse events were reported in studies sponsored by [REDACTED]: 48 in Study GU5023 (complicated UTI), 29 in Study GU5028 (pneumonia), 22 in Study GU5021 (acute exacerbation of chronic bronchitis), 17 in Study GU5022 (uncomplicated UTI), 10 in Study GU5024 (SSTI), 7 in Study GU7005 (CAP), 3 in Study GU5020 (sinusitis), and 1 in a clinical pharmacology study. The blind was broken in three patients with SAE. They consisted of hepatitis in one amoxicillin-clavulanate treated patient, confusion and hypoglycemia (one gatifloxacin treated patient each). Of the listing provided by the applicant, none of these serious adverse events were related to tourse-de-point.

No other safety data are available at this time; they will be provided as clinical trials are unblinded and final analyses performed. This has not been supplied during this NDA review period.

STUDIES SPONSORED BY KYORIN PHARMACEUTICAL

Kyorin Pharmaceutical conducted a total of 48 studies, 24 clinical pharmacology trials and 24 efficacy trials. Four hundred seven patients were enrolled in the clinical pharmacology studies. Studies T101 to T111 included pharmacokinetic studies, as well as drug interaction studies. All other studies (T202 to T317) were actually associated with efficacy trials and consisted of measurement of tissue penetration, and pharmacodynamics. The database was completed and analysis was performed on 78 patients.

There were 24 efficacy trials which accrued a total of 3235 patients. These studies were mostly open-label, randomized trials comparing two or more doses/schedules of gatifloxacin. There were only three studies using an active comparator (levofloxacin 100 mg TID). A large number of indications was studied, with doses ranging from 100 mg once a day to 200 mg twice a day. At the time this analysis was performed (cut-off of June 30, 1998), most trials were undergoing quality assurance. Data from three trials were available for safety assessment. It is anticipated that final analysis will be performed in early 1999 and all safety data from Kyorin monitored trials will be presented in the safety updates.

Studies in Volunteers

Seventy-eight volunteers received a total of 108 treatments as single- or multiple-dose at a daily dose ranging from <200 mg to 600 mg. No adverse events were reported.

Laboratory parameters including hematology, renal and hepatic function tests, electrolytes and glucose were assessed. A single abnormality (increase in ALT) was detected in patients who had normal values at baseline. Very few patients had abnormal baseline values and worsening was not documented for any of the parameters.

Efficacy trials

Safety data are available on 323 gatifloxacin-treated patients and 218 patients treated with levofloxacin. The gatifloxacin doses were 200 mg per day or less and 400 mg per day. Adverse events were reported by 12.7% of the gatifloxacin-treated patients and 11% of those treated with levofloxacin. The most common adverse clinical events were diarrhea, nausea, abdominal pain and headache. There were very few reports of CNS adverse events, in particular, dizziness. In general, the incidence of adverse events in the Japanese trial was lower than in the studies sponsored by Bristol-Myers Squibb. Drug-related adverse events were also rare, with an incidence of 8.4% in gatifloxacin-treated patients and 6.9% in levofloxacin-treated patients (Table 14.7). The most frequent drug-related adverse events were diarrhea, nausea, abdominal pain, vomiting, and headache. All other drug-related adverse events occurred in only one or two patients.

Laboratory abnormalities in patients with normal baseline values were infrequent. They consisted mainly of increased ALT, which occurred in 8% of gatifloxacin-treated patients and in 9% of those treated with levofloxacin. Other laboratory changes were infrequent

and no difference was seen between gatifloxacin and levofloxacin. No clinically relevant laboratory abnormalities were detected. There were few patients with abnormal baseline values. In these patients, worsening laboratory abnormalities were uncommon and consisted mainly of worsening of ALT, neutropenia, or leukopenia.

There were 25 premature treatment discontinuations due to adverse events or laboratory abnormalities, 15 in the gatifloxacin group and 10 in the levofloxacin group, for an overall incidence of 4.6% in both treatment options. The most frequent adverse events leading to discontinuation were related to either gastrointestinal intolerance or to CNS side effects.

There were two deaths in the Kyorin sponsored trials; one death in a patient with chronic bronchitis who was treated with levofloxacin, 100 mg TID for 11 days. This death was attributed to acute respiratory insufficiency. There were no other serious adverse events reported in the clinical trials sponsored by Kyorin and there were no documented pregnancies. The other patient received gatifloxacin 200 mg for 3 days and death was attributed to the underlying disease.

The applicant did provide additional safety data on the patients in this database in the 4 month safety update. This report was of the data as it was in February, 1999. The safety profile reported is similar to the description provided above. No new or unexpected events were reported within this update. The majority of events were nausea and headache.

9.2 Deaths

There were 29 deaths, 16 among gatifloxacin-treated patients and 13 in the comparator groups which occurred at any time (see table below). More than half of the deaths occurred in patients treated for pneumonia. In the 12 gatifloxacin cases which occurred less than 30 days after therapy was initiated the causes of death included cardiovascular events (acute myocardial infarction, congestive heart failure or cardiac arrest) in 5 patients, underlying respiratory condition (4 patients), cerebrovascular accident (1 patient), underlying carcinoma (2 patients). The causes of death were similar between both groups. The timing of the deaths was somewhat earlier in the gatifloxacin group where 9 patients died within 10 days of initiating therapy. Review of these deaths revealed the cause of death was probably unrelated to gatifloxacin, and more likely due to the serious nature of the underlying disease of these patients (descriptions of these patients follow). Most patients were more than 60 years of age. The average age in the gatifloxacin group was 76.2 years and 71.8 years for the comparator group. Only one patient in the gatifloxacin group who died was under 60 years of age; a 43 year old female with a history of psychotic problems who committed suicide 43 days after therapy.

Note: the following table lists Death Day, as provided in the applicant's SAS transport files, as the number of days from entry into the study (Study Day).

STUDY:PID	Age	Drug	Sex	Race	Death Day	Cause
CAP:00008 00008	71	CEFTRX (CLARITH)	Female	White	8	Pneumonia; Cardiopulmonary Arrest
CAP:00011 00260	69	CEFTRX (CLARITH)	Female	White	15	Multisystem organ failure
CAP:00043 00343	83	CEFTRX (CLARITH)	Female	White	67	Myocardial infarct
CAP:00048 00116	89	CEFTRX(CLARITH)	Male	White	25	Severe hypotensive episode, unresponsive to iv fluids
CAP:00057 00379	56	CEFTRX(CLARITH)	Female	White	54	GVH disease, AML, Atrial flutter, renal failure, ARDS
CAP:00064 00103	51	CEFTRX(CLARITH)	Male	White	28	Chronic ETOH abuse, aspiration pneumonia, sepsis
CAP:00078 00339	90	CEFTRX(CLARITH)	Female	White	28	CHF
UTic:00004 00263	74	CIPROFL	Female	Black	61	Recurrent bladder cancer
UTic:00007 00017	85	CIPROFL	Female	White	45	CVA, progressive dementia
CAP:00046 00543	88	CLARITH	Female	White	59	Cardiac arrest, CAD, recent MI with 3rd degree heart block
CAP:00051 00527	81	CLARITH	Male	White	28	CHF
CAP:00052 00530	48	CLARITH	Female	White	119	Lung cancer
CAP:00092 00441	48	CLARITH	Male	White	96	Respiratory Arrest
CAP:00041 00002	87	GAT_400	Female	Hispanic/Latino	23	MI, nosocomial pneumonia
ACEB:00015 00013	72	GAT_400	Male	White	34	CAD, acute MI
SKIN:00021 00055	43	GAT_400	Female	Hispanic/Latino	43	Psychotic problems, hx of depression: Suicide
UTic:00004 00257	78	GAT_400	Male	White	10	Hypertension, stroke
ACEB:00027 00355	76	GAT_400	Male	White	18	Severe COPD, pulmonary emphysema
ACEB:00069 00495	82	GAT_400	Male	White	6	Acute MI with rupture
CAP:00011 00368	82	GAT_400(GAT_400)	Female	White	6	AML
CAP:00033 00176	65	GAT_400(GAT_400)	Male	White	81	Metastatic renal cell carcinoma
CAP:00037 00025	78	GAT_400(GAT_400)	Male	White	8	COPD, CAD
CAP:00038 00178	90	GAT_400(GAT_400)	Female	White	4	CHF, MI
CAP:00053 00298	92	GAT_400(GAT_400)	Female	White	9	Preexisting atrial fibrillation, HTN, DM, ventilatory failure
CAP:00071 00195	62	GAT_400(GAT_400)	Female	White	2	Severe pneumonia, COPD
CAP:00071 00489	69	GAT_400(GAT_400)	Male	White	7	COPD
CAP:00071 00534	79	GAT_400(GAT_400)	Female	White	17	Rib-fracture exacerbating COPD
CAP:00010 00090	81	GAT_400	Female	White	45	MI, CAD
CAP:00047 00668	83	GAT_400	Female	White	4	Respiratory failure - morphine drip, metastatic SQ cell CA

Summaries of patients who died within 30 days after the completion of therapy are listed below.

STUDY 002: CAP

There was one death within 30 days of end of treatment in this study. It occurred in an 81 year old male (051-527) with a history of COPD, arrhythmias and congestive heart failure (CHF). The patient presented with signs and symptoms of pneumonia, bilateral pulmonary infiltrates and was randomized to the clarithromycin arm. Sputum culture grew *Klebsiella oxytoca* (clarithromycin MIC >32 • g/ml) and blood cultures were negative. He failed a 6 day course of clarithromycin and on Day +1, was hospitalized for pneumonia and CHF and treated with a 10 day course of intravenous levofloxacin. He was discharged on Day +11. The patient was readmitted and died on Day +22 due to congestive heart failure. This was felt to be unrelated to study drug, pneumonia or new infection.

STUDY 037: CAP 12 Deaths:

011-368: An 82 year-old white female with signs and symptoms of pneumonia was enrolled on 20MAR98. Pre-treatment pleural fluid and sputum specimens were both positive for penicillin-sensitive *S. pneumoniae* (susceptibility results for the pleural fluid isolate were not provided, but the sputum specimen was sensitive to gatifloxacin, ceftriaxone and clarithromycin). The patient was intubated on 20Mar98 and received 100% FiO₂. After six doses (25MAR98), gatifloxacin was discontinued and the patient was diagnosed with acute myelomonocytic leukemia. The patient expired on 25MAR 98 from pneumonia in the setting of acute myelomonocytic leukemia. The investigator considered the death to be unlikely related to study drug.

037-025: A 78 year-old white male with signs and symptoms of pneumonia and a history of COPD and angina was enrolled on 18MAT98. Albuterol, [redacted] isosorbide, metoprolol, ipratropium, methylprednisolone, furosemide and prednisone were concomitant medications. After seven doses (25MAR98) gatifloxacin was discontinued due to cardiac arrest and the patient was treated with atropine, beryllium, epinephrine, heparin and lidocaine to no avail. As recorded on the death summary, the investigator considered the death to be unlikely related to study drug with a probable and possible relationship to COPD and cardiac disease, respectively.

038-178: A 90 year-old white female with signs and symptoms of pneumonia and a history of CHF, coronary artery disease (CAD) and permanent pace maker was enrolled on 03MAR98. [redacted] methylprednisolone, nitroglycerine (topical) [redacted] verapamil and captopril were concomitant medications. The patient received three doses of IV gatifloxacin. On 06MAR98 the patient died after cardiac arrest. The investigator considered the death to be unlikely related to study drug.

053-298: A 92 year-old white female with signs and symptoms of pneumonia and a history of hypertension, cardiomegaly, atherosclerosis, azotemia, chronic renal insufficiency, NIDDM, hyperuricemia and sepsis was enrolled 23JAN98. Albuterol, [redacted] and insulin were concomitant medications. The patient received 7 days of IV gatifloxacin. The patient died on 31JAN98 and the investigator considered the cause of death to be "natural causes" due to many underlying diseases, and unrelated to study drug.

071-195: A 62-year-old white female with signs and symptoms of pneumonia and a history of HTN was enrolled on 02JAN98. After receiving one dose of gatifloxacin (02JAN98) the patient experienced cardiac arrest and study drug was discontinued. The patient was treated with azithromycin, vancomycin, atropine, epinephrine, furosemide, and expired on the same day. The investigator considered the death unrelated to study drug.

071-489: A 69 year-old male with signs and symptoms of pneumonia and a history of HTN and COPD was enrolled on 16MAR98. Albuterol, ipratropium, methylprednisolone and potassium were concomitant medications. The pre-treatment sputum specimen was positive for *M. catarrhalis* and *S. pneumoniae*. After 4 doses of gatifloxacin (20MAT98), the patient refused to continue study therapy or take additional

antibiotics. The patient expired on 22MAR98 from apnea which was considered by the investigator to be unrelated to study drug.

071-534: A 79 year-old white female with signs and symptoms of pneumoniae and an history of adrenal insufficiency, chronic anemia and hypertension was enrolled on 08APR98. Concomitant medications were isosorbide mononitrate, prednisone, theophylline and verapamil. The pre-treatment sputum was positive for *K. pneumoniae* (susceptible to gatifloxacin and ceftriaxone) and *S. aureus* (MS) (susceptible to gatifloxacin, ceftriaxone and resistant to clarithromycin). The patient completed a 14 day course of gatifloxacin, and was discharged on 12APR98 in good condition. The patient fell on 20APR98 resulting in multiple rib fractures. According to the investigator, the fractures resulted in readmission to the hospital on 21APR98 due to an exacerbation of COPD. The patients died from COPD on 24APR98. The investigator considered the death unlikely related to study drug.

008-008: A 71 year-old white female with signs and symptoms of pneumonia and a history of hyperthyroidism was enrolled on 01MAR98. The patient received 6 days of study medications (3 doses ceftriaxone followed by three doses clarithromycin). The patient experienced cardiac arrest on 04MAR98, was intubated on 06MAR98, and again arrested on 08MAR98, which resulted in death. Metoprolol (04MAR98), captopril, and digoxin (06MAR98) were prescribed. The death certificate noted cardiopulmonary arrest and pneumonia as the cause of death. The investigator considered the death to be unrelated to study drug.

011-260: A 69 year-old white female with signs and symptoms of pneumonia and a history of CHF, chronic hepatitis C, adrenal insufficiency and sepsis was enrolled on 17JAN98. No pathogens were isolated pre-treatment. The patient received eight days of study medication (1 dose of ceftriaxone per day and 3 or 4 doses of erythromycin per day) and was intubated on 18JAN98. Furosemide, metolazone, nitroglycerin, digoxin, verapamil, adenosine and hydrocortisone were concomitant medications. The patient experienced heart failure on 20JAN98. On 24JAN98, *C. albicans* (from urine and bronchial aspirate) and *S. coagulase negative* (from bronchial aspirate) were isolated and the patient was treated with fluconazole for possible disseminated candidiasis. The patient experienced multisystem organ failure and expired on 31JAN98. The investigator considered the death unlikely related to study drug.

048-116: A 89 year-old white male with signs and symptoms of pneumonia and a history of CHF, hypertension, CAD and permanent pacemaker was enrolled on 21JAN98. Quinapril, isosorbide and furosemide were concomitant medications. The patient received 2 days of study drug (One day of ceftriaxone and two days of erythromycin). An error in dosing resulted in study discontinuation (study drug was not given on 22JAN98). IV ceftriaxone and oral clarithromycin were prescribed. The patient experienced CHF on 25JAN98 and received morphine. The patient experienced hypotension in addition to continued CHF on 14FEB98 and expired. The investigator considered the death unrelated to study drug.

064-103: a 51 year-old white male with signs and symptoms of pneumonia with a history of active alcohol dependence and COPD was enrolled on 13FEB98. The pre-treatment sputum specimen was positive for *M. catarrhalis* (susceptible to ceftriaxone and clarithromycin), *P. fluorescens* (resistant to ceftriaxone and clarithromycin and susceptible to gatifloxacin) and penicillin-susceptible *S. pneumoniae* (resistant to clarithromycin and susceptible to gatifloxacin). After 7 days of study drug (19FEB98) (4 days of ceftriaxone and erythromycin, followed by 3 days of clarithromycin) the patient was removed from the study because of pathogen resistance. Ticarcillin/clavulanate, [REDACTED] and ceftazidime were prescribed. The patient died on 12MAR98 from aspiration pneumonia secondary to alcoholism which the investigator considered unlikely related to study drug.

078-339: A 90 year-old white female with signs and symptoms of pneumonia and a history of CHF, tachycardia, atherosclerotic heart disease and permanent pacemaker was enrolled on 05FEB98. Concomitant medications were acetylsalicylic acid, oral and topical nitroglycerin. The patient was discharged from the hospital on 11FEB98. She completed 13 days of study medication (6 doses of ceftriaxone, 6 days of erythromycin and 7 days of clarithromycin). On 19FEB98 the patient was re-hospitalized for CHF. The patient died on 04MAR98 due to CHF. The investigator considered the death unlikely related to study drug.

STUDY 038: CAP

047-668: An 83 year-old white female with signs and symptoms of pneumonia and a history significant for buccal squamous cell carcinoma was enrolled on 16APR98. The patient initially presented with bleeding from the oral tumor, and was hospitalized for this reason before receiving gatifloxacin. On Day 2 of therapy, the tumor began to hemorrhage, and a morphine drip was started as a comfort measure. The patient expired on Day 4 of therapy from respiratory failure secondary to the morphine drip, anemia and squamous cell carcinoma. The investigator considered the death to be unrelated to study therapy.

Study 006: (CAP)NO DEATHS**STUDY 003: CAP**

041-002: This 87 year-old Hispanic/Latino female had a medical history of smoking, chronic bronchitis, asthma, palpitations, myalgia, and arthralgia. She presented for the study with a one day history of increased sputum production, increased cough, audible wheezing and malaise; pre-treatment sputum culture revealed *M. catarrhalis* and *S. pneumoniae* sensitive to gatifloxacin. Gatifloxacin was started on 09DEC97 and was discontinued after eight doses due to myocardial infarct and atrial fibrillation for which she was hospitalized. She was admitted on 16DEC97, developed a nosocomial pneumonia on 26DEC97 which was treated with ceftazidime, erythromycin, ceftriaxone and clindamycin. The patient subsequently suffered cardiac failure on 31DEC97 and expired. The investigator judged the myocardial infarct and atrial fibrillation not related to gatifloxacin.

STUDY 008 (Sinusitis), 007 (Sinusitis), 066 reported NO DEATHS**STUDY 001 (AECB) NO DEATHS****STUDY 020 (AECB)**

027-355: This 76 year-old white male smoker had a medical history of chronic bronchitis, COPD, emphysema, pneumothorax, hypertension, pyelonephritis, benign prostatic hypertrophy and inguinal hernia repair. The patient was hospitalized on 9DEC97 for severe emphysema. He presented for the study with a 15-day history of increased dyspnea and cough, increased sputum production and purulence, fever, headache and chills. His pre-treatment steroid medication included prednisone for COPD. His pretreatment physical revealed arrhythmia and decreased breath sounds, the CXR did not show pneumonia. *S. marcescens* and *M. catarrhalis* were isolated from a pre-treatment sputum. Study medication was started on 9DEC97 and were discontinued after 6 days due to the presence of resistant pathogens (*S. marcescens* showed resistance to cefuroxime). No adverse events were reported. On Day +1 the patient received ciprofloxacin 1500 mg po TDD to continue treatment for this acute episode. Post therapy medications included topical gentamicin, albuterol, hydrochlorothiazide, ipratropium, senna, potassium and prednisone (50 mg PO TDD). On 22DEC97 he was found unconscious and in respiratory failure. ON 26DEC97 the patients died. The investigator attributed the patient's death to his terminal COPD and in no way related to study medication. The clinical response was judged to be failure de to persistent primary signs/symptoms. The patient was randomized to gatifloxacin.

069-495: This 82 year-old white male had a medical history of chronic bronchitis, pneumonia, six episodes of acute bronchial infection within the past year, sinus infections, ulcer, hernia repair, cholecystectomy, arthritis, seasonal allergies, drug sensitivity to penicillin and 30 year history of smoking. He presented for the study with a three-day history of increased cough, increased sputum production and purulence, and ronchi. His pretreatment CXR showed no evidence of pneumonia. *H. parainfluenzae* was isolated from a pre-treatment sputum specimen. Study medication was started on 20MAR98 and received five days (10 doses) before discontinuation. Concomitant medications included multivitamins, lansoprazole and prednisone for asthmatic bronchitis. No adverse events were reported while the patient was on study medication. ON 25MAR98 (Day +1) the patient experienced shortness of breath and chest pain and was hospitalized for myocardial infarction and died that day. The investigator attributed the patient's death on

25MAR98 to an acute myocardial infarction with rupture. The patient's clinical response was judged unable to determine. The patient was randomized to gatifloxacin.

STUDY 004

015-013: This 72 year-old white male had a medical history of coronary artery disease, chronic obstructive pulmonary disease, chronic bronchitis, and anxiety. He present for the study with a two day history of increased sputum production, cough and dyspnea, chest tightness/pain and wheezing and rales; pretreatment sputum culture revealed normal flora. Gatifloxacin was started on 27MAR97 and the ten-day course was completed on 5APR97. In lieu of the post-treatment visit on 14APR97, the patient reported to the hospital, complaining of worsening of his dyspnea and chest pain. He as treated with doxycycline as alternative antibiotic. Repeat sputum culture while he was hospitalized continued to show normal flora. The patient's complaints were attributed to an exacerbation of his chronic bronchitis and not to gatifloxacin. The clinical response was judged to be Unsatisfactory as a result of the worsening signs and symptoms of AECB that led to the hospitalization. The patient was discharged from the hospital on 21APR97. On 29APR97, he was found unresponsive at home, and cardiopulmonary resuscitation was unsuccessful. Death was attributed to an acute myocardial infarction that was felt by the investigator not to be related to gatifloxacin but due to underlying coronary artery disease.

STUDY 005 (SKIN)

Patient (021-055), in the gatifloxacin arm, committed suicide 33 days after the end of study therapy. The investigator attributed this death to the patient's underlying history of anxiety and depression, and not to study therapy.

STUDY 010 (Uncomp. UTI) NO DEATHS

STUDY 011 (Comp. UTI)

Patient (04-00257) One gatifloxacin patient died on Day +3 from a cerebrovascular accident.

Patient (04-00263) The ciprofloxacin treated patient died from progressive cancer at Day +50 after completion of study medication

STUDY 031 (Comp. UTI)

patient (007-017) in the ciprofloxacin group. This patient died at Day +35 due to a cerebrovascular accident and progressive dementia. The death was assessed by the investigator to be unrelated to the study medication.

STUDY 012 (GC) NO DEATHS

9.2.1 Special Populations (Deaths by Age, Race and Gender)

Review of the patients who died according to gender reveals that in the gatifloxacin treated group 56.2% of deaths were females compared to the comparator group where 56.3% were females. Analysis of deaths by race is difficult to interpret because of the small number of non-white patients who died: 1 black patient in the comparator group, 2 Hispanic/Latino patients in the gatifloxacin group. From review of these data it appears that the number of deaths in the gatifloxacin group is similar to those in the comparator according to gender and race.

9.3 Laboratory Test Abnormalities:

The applicant reported laboratory test abnormalities according to treatment dose administered. The largest group of patients treated with any one dose was the 400 mg PO. The study populations included in this dose involve the following infections: urinary tract infection, pyelonephritis, community acquired pneumonia, acute exacerbation of chronic bronchitis, sinusitis, uncomplicated skin infections. FDA review of the

applicant's submission is in general agreement after review of SAS database. For the most part abnormalities appear to be mild to moderate in nature and are similar to the study drug comparator. It should be noted that various infections will cause laboratory abnormalities by themselves, and that it is important to consider the active control rates for various abnormalities. FDA review here will focus in detail on the large group of patients treated with 400 mg PO, and comment briefly on issues of interest in the IV-PO switch and the 600 mg dose as groups have fewer patients to analyze.

Gatifloxacin 400 mg PO:

Laboratory Abnormalities in Patients with Normal Baseline Values

The development of laboratory abnormalities in patients with normal baseline values was an infrequent occurrence. Among the more frequently developing abnormalities were: decreased bicarbonate (13% of all patients treated with the 400 mg strength gatifloxacin), anemia (8%), hyperglycemia (8%), neutropenia (6%), hyponatremia (5%), and elevated AST (5%) and ALT (also 5%). The aforementioned abnormalities in serum sodium and liver transaminases were somewhat more frequent in the non-comparative studies. In the comparative studies, there were no striking differences in the gatifloxacin and pooled comparator arms with respect to the occurrence of laboratory abnormalities. When laboratory abnormalities occurred, they were generally minimal (Grade 1). They should be interpreted in the context of contributing factors such as the patient's general medical history, underlying infection, and use of concomitant medications. Keeping in mind that the number of patients treated in countries outside North America is small, it is interesting to note that, with two exceptions, the development of laboratory abnormalities tended to be more common in other countries.

Laboratory Abnormalities in Patients with Normal Baseline Values, Gatifloxacin 400 mg PO

	No. Patients with Abnormal Value/Assessed (%)			
	Non-comparative trials	Comparative Trials		TOTAL
	Gatifloxacin	Gatifloxacin	Comparator	Gatifloxacin
Leukopenia	19/702 (3)	92/1899 (5)	63/1808 (3)	111/2601 (4)
Neutropenia	33/694 (5)	125/1890 (7)	79/1793 (4)	158/2584 (6)
Anemia	51/624 (8)	132/1696 (8)	134 /1591 (8)	183/2320 (8)
Thrombocytopenia	17/685 (2)	44/1884 (2)	35/1761 (2)	61/2569 (2)
BUN/Blood Urea	12/708 (2)	63/1960 (3)	53/1847 (3)	75/2668 (3)
Creatinine	25/708 (4)	42/1979 (2)	33/1857 (2)	67/2687 (2)
AST/SGOT	44/625 (7)	82/1889 (4)	87/1786 (5)	126/2541 (5)
ALT/SGPT	51/638 (8)	82/1887 (4)	86/1773 (5)	133/2525 (5)
Bilirubin	17/692 (2)	58/1932 (3)	44/1810 (2)	75/2624 (3)
Hypoglycemia*	2/87 (2)	0/79 (0)	1/67 (1)	2/166 (1)
Hyperglycemia*	6/87 (7)	8/79 (10)	5/67 (7)	14/166 (8)
Amylase	32/618 (5)	66/1901 (3)	39/1780 (2)	98/2519 (4)
Hyponatremia	44/635 (7)	80/1878 (4)	70/1749 (4)	124/2513 (5)

*This represents fasting values only, additional discussion regarding glucose homeostasis can be found in section 9.4.8.

An analysis of laboratory abnormalities by infection under study was discussed by the applicant. Hematologic abnormalities such as anemia and neutropenia developed more frequently in the pneumonia studies; as previously noted, these patients were among the sickest enrolled in the gatifloxacin program. The complicated UTI studies also had a higher incidence of anemia (15%). Not surprisingly, elevations in BUN and creatinine were more frequent in the complicated UTI studies; by definition, many of these patients had underlying structural abnormalities of their urinary tracts which may have contributed to increases in BUN and/or creatinine.

There was a slight trend toward more laboratory abnormalities the longer the course of gatifloxacin therapy. This trend was not seen for neutropenia, suggesting that myelosuppression was not related to gatifloxacin exposure.

The development of clinically relevant laboratory abnormalities (i.e., Grade 3 or 4 in severity) was infrequent (<1%) and comparable between treatment groups. Elevations in bilirubin were the most common such abnormality (10 gatifloxacin-treated patients and 8 for the comparator); they were noted more typically in the comparative studies and in these randomized studies, the incidence was comparable for gatifloxacin and the pooled comparator agents. All clinically relevant laboratory abnormalities occurred in ≤ 1 percent of patients in either geographic area. (See discussion of liver function abnormalities in section 9.4.4).

In an analysis by infection under study, the lowest incidence of clinically relevant laboratory tests was noted among patients in the uncomplicated skin and skin structure study (3 tests), the uncomplicated UTI study (1 test), and the gonorrhea study (3 tests); the latter two studies employed single dose gatifloxacin therapy. Even among sicker patients (e.g. those with pneumonia or complicated UTI), clinically relevant laboratory abnormalities were an unusual occurrence.

Clinically relevant laboratory abnormalities were most frequent among patients treated with between 7 and 10 days of gatifloxacin therapy; this category accounted for the greatest percentage of patients enrolled. There were no striking differences noted across geographic regions.

Laboratory Abnormalities in Patients with Abnormal Baseline Values

Among patients with abnormal baseline laboratory values, worsening results were not distinctly common. In the comparative studies, a worsening of baseline neutropenia was more frequently noted in the pooled comparator arm (27% vs. 13% gatifloxacin).

The worsening of abnormal baseline laboratory tests rarely resulted in clinically relevant values. Among all gatifloxacin-treated patients, a clinically relevant elevation in bilirubin was the most common such abnormality. In the comparative studies, gatifloxacin was comparable to the pooled comparator arm.

9.3.1 Special Populations (Laboratory Test Abnormalities by age, race and gender)

Normal Baseline Laboratory Values in patients treated with 400 mg Gatifloxacin PO.

The incidence of laboratory abnormalities tended to be higher among those patients ≥ 75 years of age. These included anemia (occurring in 24% of patients in this age group), elevated BUN (15%), and elevated creatinine (9%); the pattern was preserved across geographic regions. These results are not particularly surprising, as this age group is more likely to have concomitant medical conditions, as well as to be taking a greater number of concomitant medications that could contribute to laboratory aberrations.

An analysis of laboratory abnormalities by revealed no striking differences between the different categories. The occurrence of any kind of laboratory abnormality was unusual among the Asian patients enrolled in studies of the 400 mg PO dose of gatifloxacin.

An analysis of laboratory abnormalities by gender highlighted a few notable differences. The overall incidence of serum transaminase elevations was apparently higher among men than women (9% vs. 3% for both AST and ALT), while the incidence of decreased bicarbonate was higher among females (15% vs. 9%). As noted previously, there were a number of differences across geographic regions for the individual abnormalities, although the smaller number of patients treated outside North America must be taken into account.

An analysis of clinically relevant laboratory tests by race revealed no differences with respect to race, either overall or across geographic region. The highest incidence of clinically relevant laboratory tests was among patients less than 65 years of age. There were only four clinically relevant laboratory tests among patients ≥ 75 years of age.

9.4 CLASS EFFECTS

9.4.1 Phototoxicity : (The following was reported by the applicant and verified by the FDA review of the electronic database.)

Studies in Normal Volunteers

A double-blind placebo controlled randomized study was conducted to investigate the phototoxic potential of gatifloxacin compared to ciprofloxacin, lomefloxacin and placebo in 48 male patients (Study AI420-015, reported in detail in the Clinical Pharmacology section. Forty-eight volunteers were assigned to receive either gatifloxacin 400 mg QD, ciprofloxacin 500 mg BID, lomefloxacin 400 mg QD or placebo for 7 consecutive days. Using a [redacted] arc source, the phototoxic potential of these drugs was assessed at selected radiation wave lengths ranging from [redacted]. The minimal erythema dose (MED) was determined at baseline, and two hours after dosing on Day 5 and 6. Subsequent measurement of the MED were carried out on Day 8 and 9 in those patients who had a reduction in MED by more than 40% at the Day 5 or 6 measurement. Further follow-up measurements were performed on Day 11 and 12 and Day 21 and 22 if required, until the MED returned within 40% of the baseline value.

The phototoxicity potential of gatifloxacin was found to be comparable to that of placebo at all wave lengths tested; in contrast, ciprofloxacin and lomefloxacin produced statistically significant reductions in MED at [redacted]. Gatifloxacin did not appear to have any phototoxic potential as defined by the percent change in MED or the phototoxic factor whereas ciprofloxacin could be considered to have a mild photosensitizing effect and lomefloxacin to have a moderate photosensitizing effect. There was no demonstrable relationship between drug exposure and phototoxic potential.

Safety database

The entire safety database for the 15 efficacy trials was searched for potential adverse events linked with phototoxicity. This search included the following COSTART terms: erythema, photosensitivity, eye photosensitivity, rash, and vesiculobullous rash. A total of 114 such adverse clinical events were identified, with an incidence of 1.7% in the gatifloxacin-treated patients, 2.1% in patients treated with other quinolones and 2.0% in those treated with other antibiotics. Rash was the single most common adverse clinical event, with 91 events reported; the incidence was comparable between gatifloxacin and the other quinolones, and slightly higher in patients treated with other types of antibiotics. There was one incidence of a potential photosensitivity in a patient treated with levofloxacin and two eyes photosensitivity, one in the gatifloxacin group and one in the other quinolone group. All three consisted of watery eyes after minimum sun exposure. There were five instances of vesiculobullous rash. They consisted of ischemic buttock lesions (2 patients), herpes, accidental work lesion and forearm lesion (1 patient each). None were related to phototoxicity.

Sixty of these adverse clinical events were considered drug-related by the Investigators. In the gatifloxacin group, they consisted only of rash and one instance of vesiculobullous rash. The two potentially drug-related photosensitivity and eye photosensitivity were reported in the other quinolone group (levofloxacin).

Among the gatifloxacin-treated patients, the incidence of adverse clinical events possibly associated with phototoxicity was 1.9% in patients treated at a dose of 400 mg per day compared to those treated at daily doses of 200 and 600 mg (0.9% and 0.7%, respectively). The difference was related to a higher incidence of rash, not consistent with phototoxicity.

The incidence of rash appears to be slightly higher in patients 75 years or older. This difference was not apparent in the analysis of drug-related events. The incidence of these events was higher in patients treated for more than 10 days, both for events of all causes and for those which were considered drug-related.

In addition, three patients (1 gatifloxacin 200 mg and 2 clarithromycin) reported sunburn. The gatifloxacin patient was a 38 year old female treated for uncomplicated UTI. Mild sunburn was reported three days after the completion of therapy with prompt resolution.

Phototoxicity has severely limited the use of some quinolones, in particular lomefloxacin and sparfloxacin. The study of structure-activity relationships has clearly mapped this toxicity to the presence of a halogen atom at position eight. The chemical structure of gatifloxacin suggests that this molecule should not be associated with phototoxicity. Indeed, in extensive testing in animals, no such issues could be documented in various species.

A more rigorous model is the phototoxicity study performed in normal volunteers by Fergusson et al. This model is well-established and is considered predictive of the phototoxicity effect of quinolones. In this model, gatifloxacin was equivalent to placebo, and was significantly less toxic than the two positive controls, ciprofloxacin and lomefloxacin.

In our clinical database of almost 4,000 patients treated with gatifloxacin, there were no reports by Investigators of phototoxicity. In a more complex analysis of events associated with phototoxicity, we failed to identify any difference between gatifloxacin-treated patients and those who received either other quinolones or other antibiotics (cephalosporins or macrolides).

In conclusion, based on animal data, studies in volunteers, and an extensive search of the safety database, there was no evidence of a single episode of phototoxicity. Based on these observations, the applicant believes that the class labeling text regarding phototoxicity should not be included in the gatifloxacin label.

Medical Officer Comment: Review of these data by the FDA medical officer agrees with the data presented. It would appear that there is little risk of phototoxicity with gatifloxacin from the data presented. Additional discussion with the Division and Office Director must be undertaken for further recommendation regarding the class labeling issue. (see labeling recommendations section).

9.4.2 Cardiac Effects

Recently there has been concern regarding the potential cardiac effects produced by the quinolones as a class. During development of this drug it was not much of an issue. The applicant performed preclinical animal studies (see section 1.3 above), one study in particular is of interest to this review. This study was conducted in anesthetized dogs who were continuously monitored by ECG, and received bolus, intravenous injections of gatifloxacin at 3 mg/kg and 10 mg/kg. No QTc prolongation was detected in this model. Other, multiple dose animal studies were performed which failed to demonstrate cardiac effects; however, most ECGs were not performed at the anticipated C_{max} time for gatifloxacin in those models. The maximum intravenous dose of 10 mg/kg in dogs would be 4 times that being recommended in humans.

The applicant recently provided the FDA with a tissue model for the cardiac potassium ion channel (draft report only). It appears that Gatifloxacin is similar to ciprofloxacin with regard to its effect on the enzyme in this model. At this time there is no standard

model for this test and values may vary widely between tests. Additional clinical testing will be recommended in the phase IV requests.

Phase II clinical testing proceeded with gatifloxacin. Again, at the time of the protocol design, the applicant did not envision assessment of the PK/PD relationship between plasma gatifloxacin concentration and QTc as an issue for these studies. The three studies that were conducted are listed below:

- AI420-025, a sequential panel study of safety, tolerance and pharmacokinetics of ascending multiple intravenous doses of gatifloxacin in healthy male volunteers,
- AI420-036, a gatifloxacin - glyburide interaction study in non-insulin dependant diabetics,
- AI420-056, a gatifloxacin - midazolam interaction study in healthy male volunteers.

In AI420-025, ECGs were done at pre-dose, 2, and 6 hours post-dosing, where as the T_{max} was, with few exceptions, at the end of the 1 hour infusion. The applicant states that it would have been inconvenient to perform an ECG at the same time as disconnection from the intravenous infusion bolus and a blood draw. For AI420-036 in which T_{max} ranged from 0.5 to 4 hours (median = 1 hour) post dose, the same ECG schedule was used for the sake of consistency. For AI420-056 in which gatifloxacin T_{max} ranged from 0.5 to 4 hours (median = 1.125 hours) post-dose, the ECGs were scheduled at 0, 15, 30, 60 and 120 minutes after midazolam injection because of concerns about the effects of midazolam on QTc. The applicant stated the following in their analysis of this issue. "Therefore, the QTc intervals measured at 2 hours after dosing in all three studies were used in the analyses described below. In fact this may be preferable to measurements at T_{max}, since it allows time for peak perfusion into QTc- effect sites."

STUDY AI420-025:

It is felt that this study may provide the most clear documentation of the changes in QTc relative to concentration. While the ECGs were not performed at the anticipated C_{max}, the dose ranging study provided measurement of gatifloxacin plasma levels which span the anticipated C_{max} for the proposed dosing. In addition, levels in a few patients exceed the predicted C_{max} for gatifloxacin. Analysis of the QTc change from baseline was performed several ways. First a categorical evaluation for each patient to determine if the change was greater than +40 msec or the absolute value on treatment exceeded 450 msec. The second analysis was an evaluation of the mean change in QTc; however, it was felt by the applicant and agreed upon by the FDA that combining across doses would not provide useful data. Thus, the analysis was presented by dose, resulting in very small numbers of patients in each group, allowing for very wide variability in the mean values. Finally, a regression line analyzing the change from baseline QTc by plasma concentration was undertaken. The results of these three analysis are discussed below.

Categorical analysis:

**Cross tabulation of baseline QTc vs steady-state QTc Study AI420-025
Gatifloxacin treated patients**

QTc (msec) Before Treatment	At 2 Hours After Start of Infusion			Total
	<430	430-450	>450	
<430	26	0	0	26
430-450	0	0	0	0
>450	0	0	0	0

None of the patients had an absolute QTc value on gatifloxacin treatment that exceeded 430 msec. This was similar to that seen in the placebo group. A closer look at the changes within treatment group was undertaken.

**Changes in QTC from baseline (mean day 1 + day 4) on
day 1, day 10, and day 17 at 1 hour post-infusion (Study AI420-025)**

Changes in QTc (msec)	Gatifloxacin			Placebo		
	D1 T2	D10 T2	D17 T2	D1 T2	D10 T2	D17 T2
< 0	12 (40%)	11 (44%)	12 (57%)	4 (50%)	5 (50%)	8 (89%)
0-10	7 (23%)	6 (24%)	2 (10%)	1 (13%)	4 (40%)	1 (11%)
11-20	6 (20%)	6 (24%)	4 (19%)	1 (13%)	0	0
21-30	4 (13%)	1 (4%)	2 (10%)	2 (25%)	1 (10%)	0
31-40	1 (3%)	1 (4%)	1 (5%)	0	0	0
41-50	0	0	0	0	0	0
>50	0	0	0	0	0	0
TOTAL	30	25	21	8	10	9

FDA analysis

This study was a single and multiple dose infusion study. The single dose was administered on day 1 and then a 3 day washout followed. On day 4 baseline ECGs were taken at time 0 and again at 2 hours after the beginning of a 1-hour infusion, in other words at 1 hour after the infusion stopped. FDA analysis was undertaken utilizing a mean baseline ECG calculation that included time 0 on day 1 and day 4 ECG measurements. It can be seen from the table above that a large proportion of changes on gatifloxacin and placebo were negative. Roughly 60% of the ECG changes were in the range of 10 msec or less. None of the patients treated with gatifloxacin had a QTc change > 40 msec. These changes are displayed graphically below. The degree of intra- and inter-patient variability should be noted.

It is difficult to assign one mean QTc change for this group. The table below displays the mean QTc change for each dose group. Of note is the large change in the 600 mg group. This probably indicates a trend toward increases in QTc; however, it is apparent that the numbers are too small to draw definite conclusions given this degree of variability. The 800 mg group had a very small number of paired EKGs upon which to comment.

Individual changes in QTc from baseline corrected for mean baseline measurement on day 1, 10 and 17.

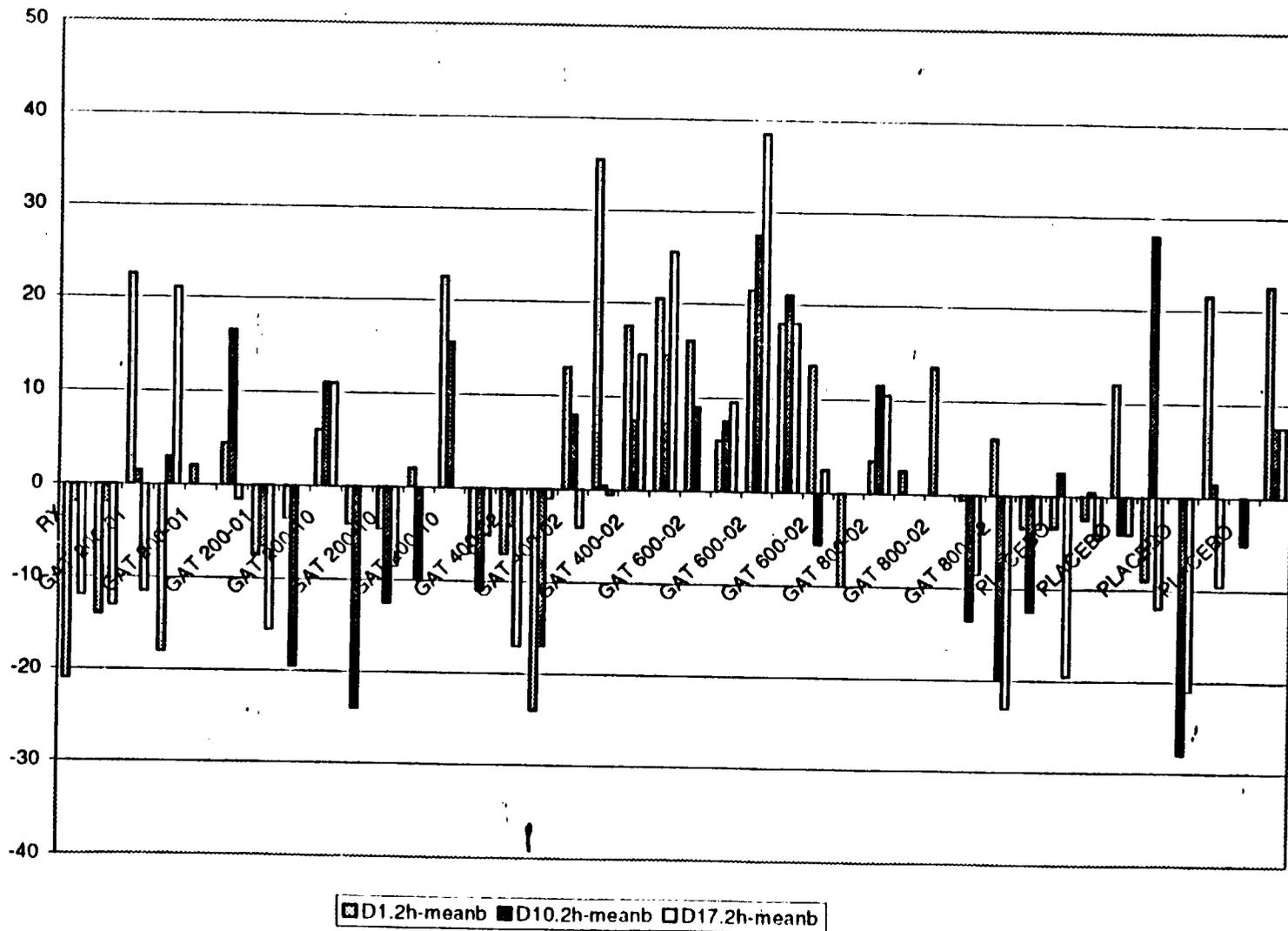
Subject	RX	D1.2h-meanb	D10.2h-meanb	D17.2h-meanb
501	GAT 200-01	-21	-2	-12
503	GAT 200-01	-14	-2	-13
504	GAT 200-01	23	2	-12
505	GAT 200-01	-18	3	21
506	GAT 200-01	2		
508	GAT 200-01	5	17	-2
1	GAT 200-10	-8	-7	-16
3	GAT 200-10	-4	-20	
4	GAT 200-10	6	11	11
5	GAT 200-10	-4	-24	
6	GAT 200-10	-5	-13	-9
8	GAT 200-10	2	-10	
MEANS	Std dev of values	-3 ± 12	-4 ± 12	-4 ± 13
9	GAT 400-02	23	16	
10	GAT 400-02	-7	-11	-5
11	GAT 400-02	-7	-4	-17
14	GAT 400-02	-24	-17	-1
15	GAT 400-02	13	8	-4
16	GAT 400-02	36	1	-1
MEANS	Std dev of values	6 ± 22	-1 ± 12	-6 ± 7
18	GAT 600-02	18	8	15
19	GAT 600-02	21	15	26
20	GAT 600-02	16	9	
21	GAT 600-02	6	8	10
22	GAT 600-02	22	28	39
23	GAT 600-02	18	21	18
MEANS	Std dev of values	17 ± 6	15 ± 8	21 ± 11
25	GAT 800-02	14	-6	3
26	GAT 800-02	-10		
28	GAT 800-02	4	12	11
29	GAT 800-02	3		
31	GAT 800-02	14		
32	GAT 800-02	-1	-14	-9
MEAN	Std dev of values	4 ± 9	-3 ± 13	2 ± 10
2	PLACEBO	6	-20	-23
7	PLACEBO	-4	-13	-4
12	PLACEBO	-4	3	-20
13	PLACEBO	-3	1	-5
17	PLACEBO	12	-4	-4
24	PLACEBO	-9	28	-12
27	PLACEBO	0	-28	-21
30	PLACEBO	22	2	-10
502	PLACEBO	0	-5	0
507	PLACEBO	23	8	8
MEAN	Std dev of values	4 ± 11	-3 ± 15	-9 ± 10

A graphical display of the above data follows.

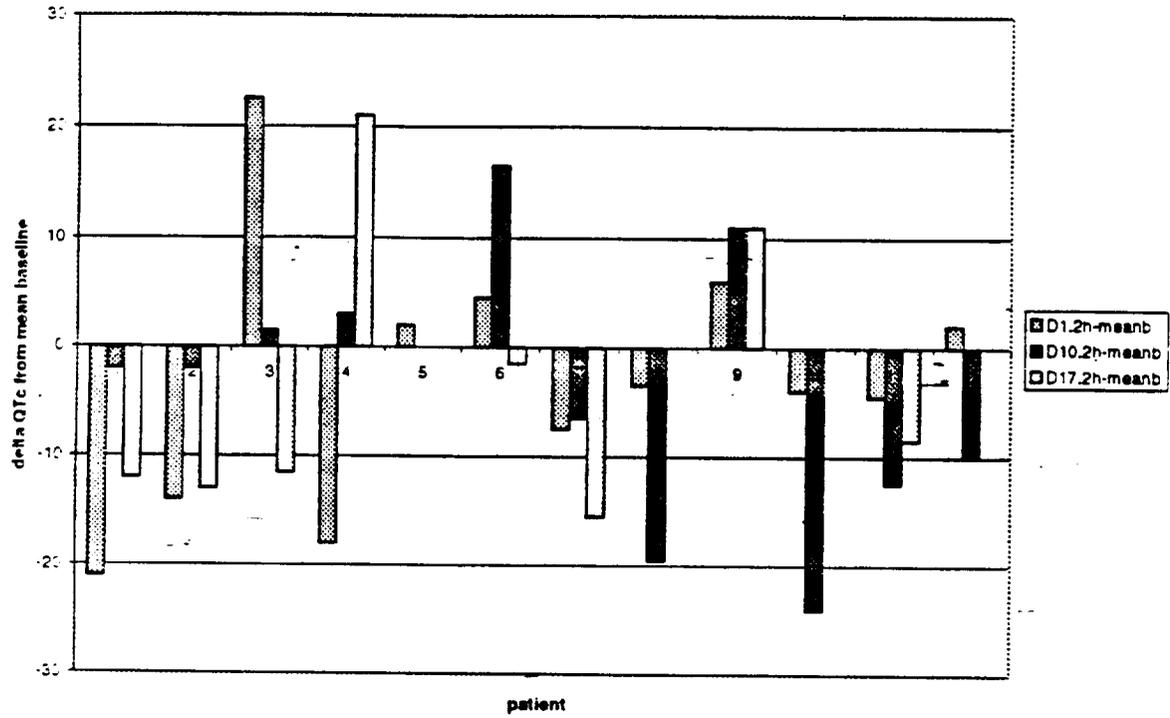
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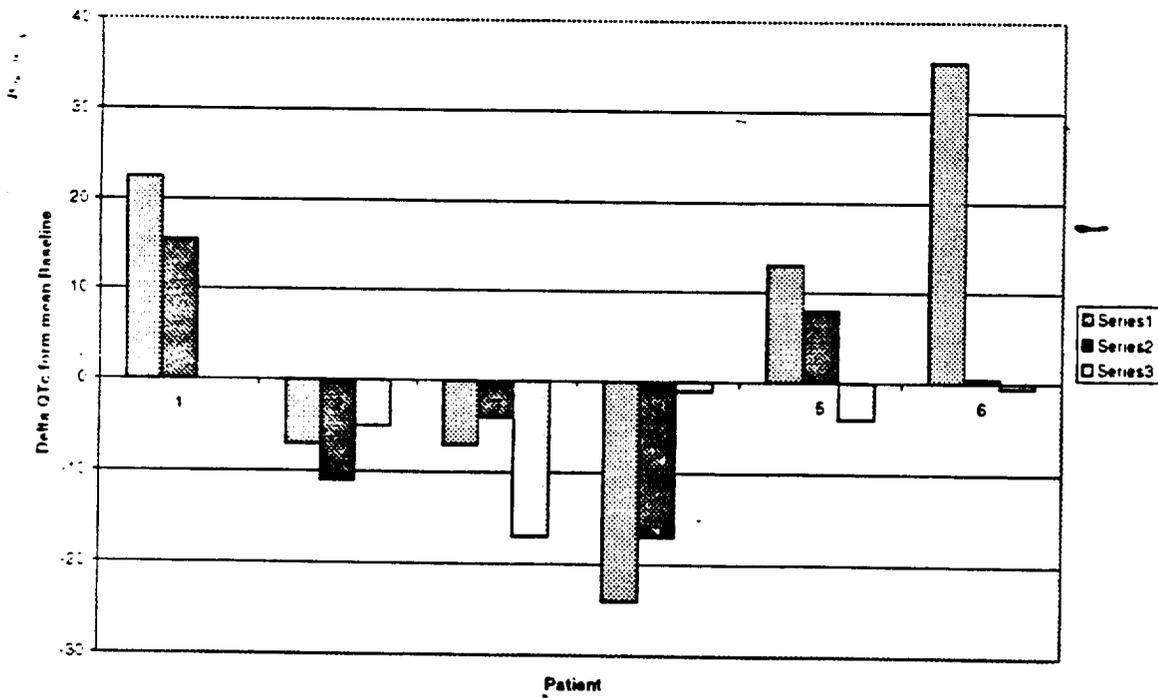
Change in QTc from mean baseline Study 025 (grouped by patient at 3 different time points)



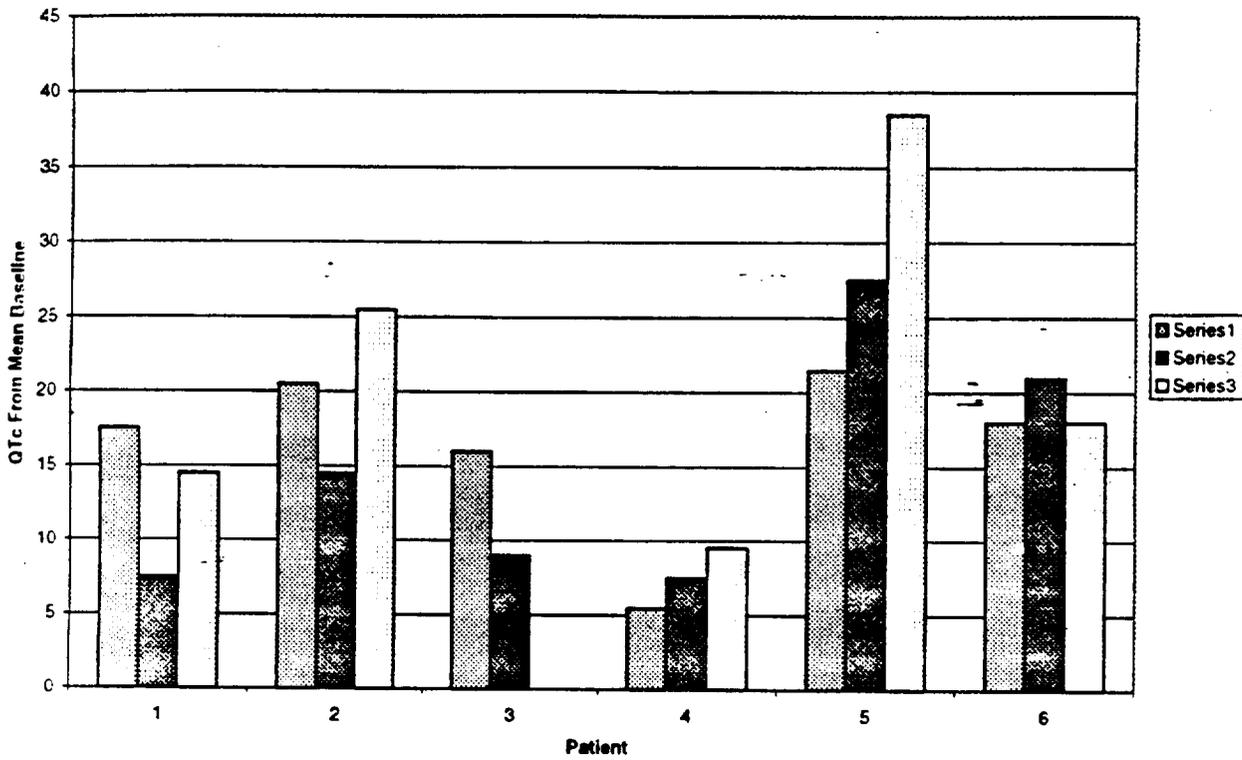
Delta QTc Gatifloxacin 200 mg IV



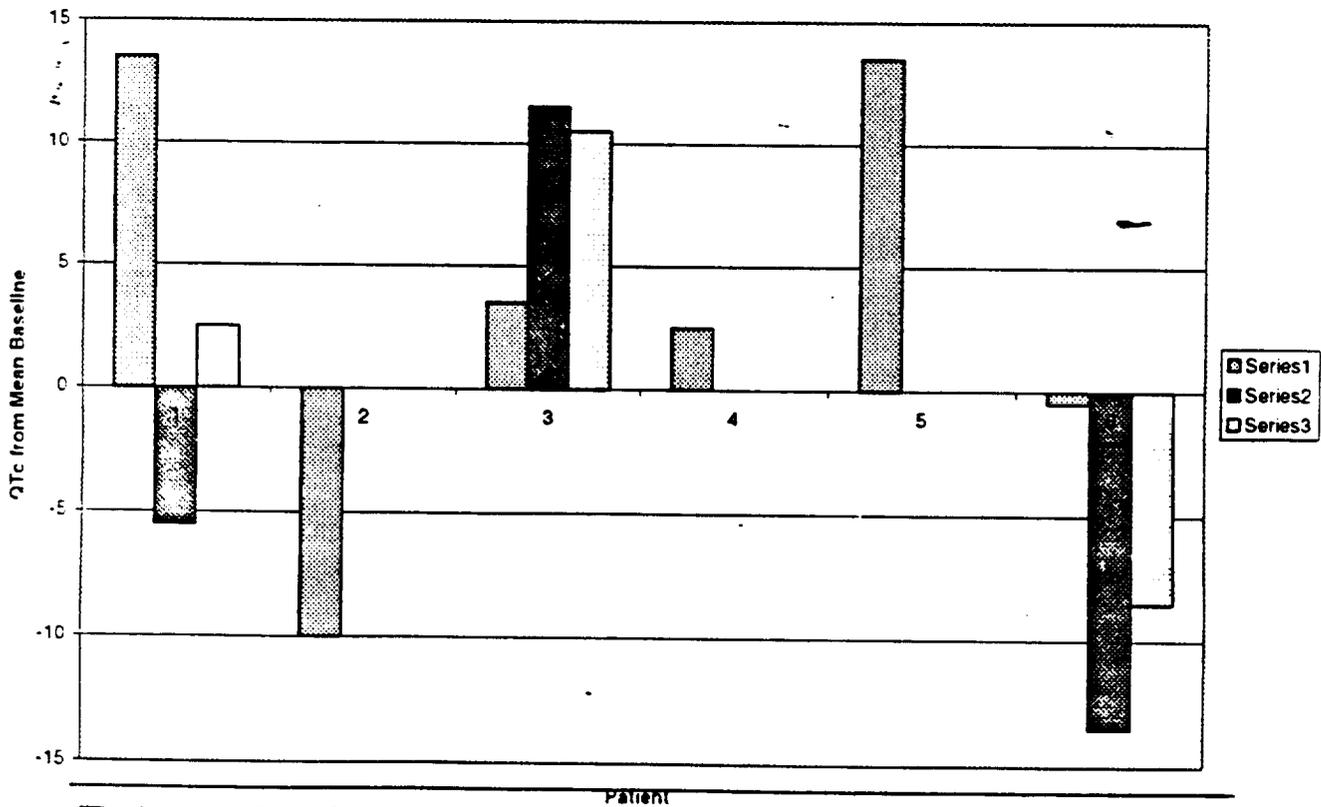
QTc Change from Baseline: 400 mg IV Gatifloxacin



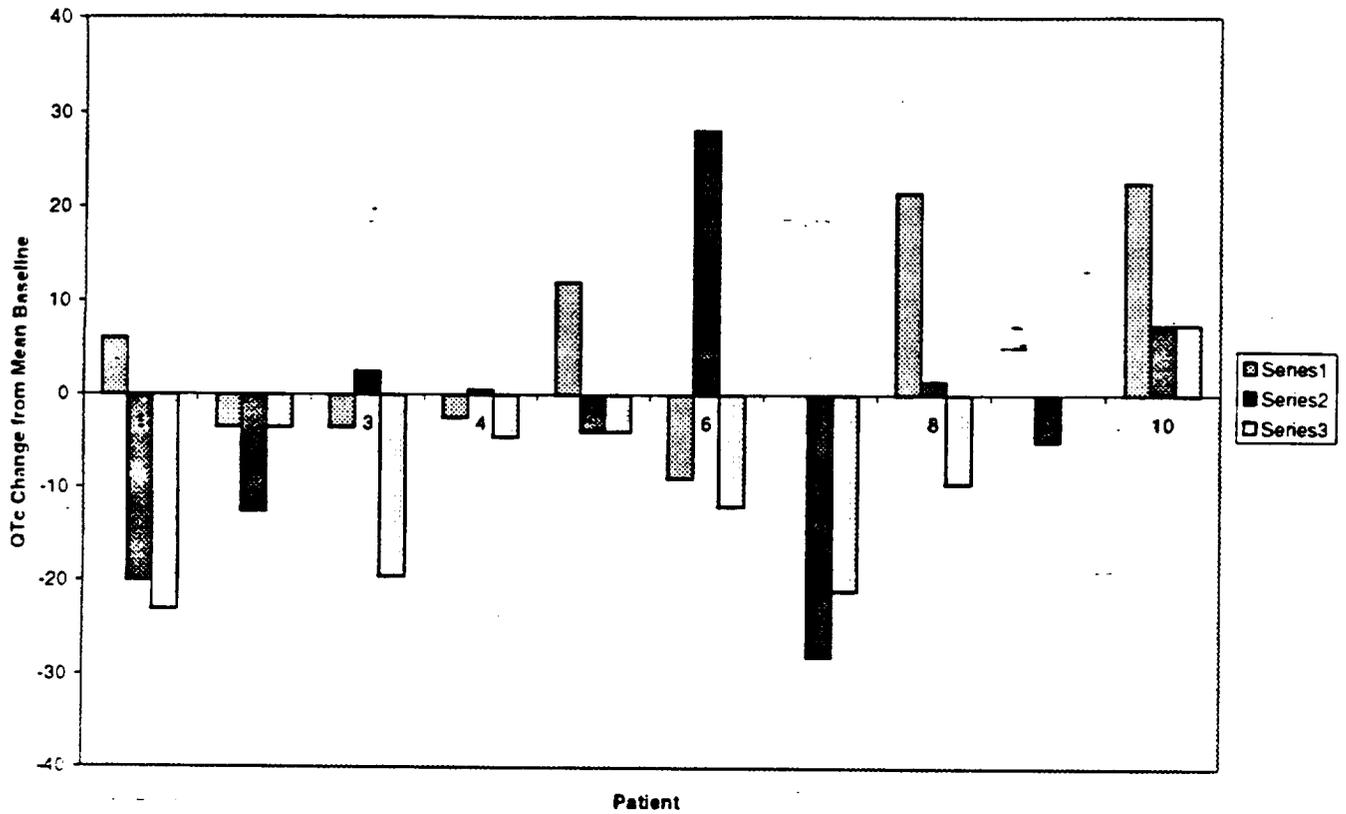
QTc Change: 600 mg IV Gatifloxacin



QTc Change: 800 mg IV Gatifloxacin



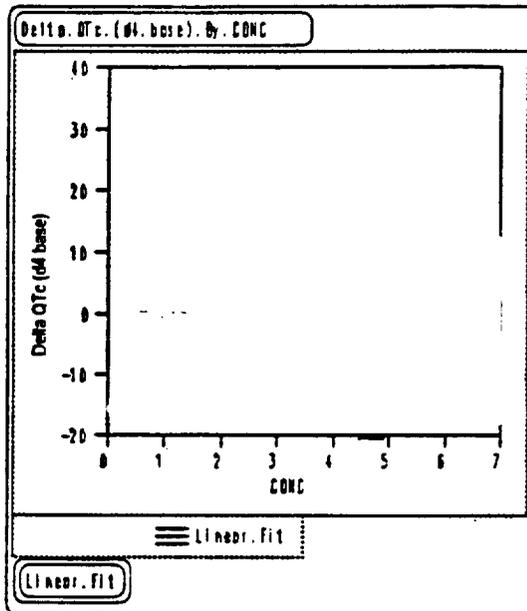
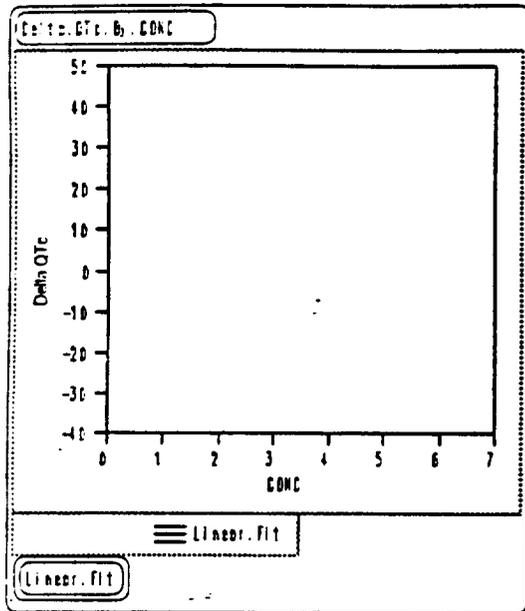
QTc Change: Placebo



In an attempt to understand the change in QTc as the plasma concentration varies, the graphs below were produced. The slopes vary, depending upon which baseline ECG values are used. They range from 2.7 (-1.26, 6.66; 95% C.I.) to 3.4 (-1.56, 8.26; 95% C.I.). The applicant also calculated the slope and obtained the value of 4.17 (-0.03, 8.38; 95% CI). The applicant stated that the regression line should be adjusted for baseline QTc since it was not well distributed across all levels of concentration, with a large cluster of patients with high baseline QTc intervals at lower gatifloxacin concentrations (< 3 mcg/ml). The adjusted slope was 2.94 (-0.81, 6.69; 95% CI).

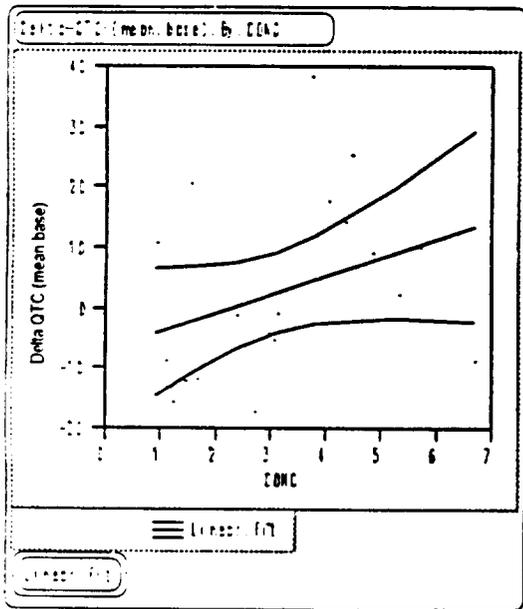
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Delta QTC
(Day 17 time 2 hr - Day 1 Time 0)

Delta QTC
(Day 17 time 2 hr - Day 4 Time 0)



Delta QTC
(Day 17 time 2 hr - Mean Time 0)

In conclusion, review of this data indicates that there is a small increase in the delta QTc as the dose increases. The delta QTc at the 400 mg dose for six patients ranged from 6 to - 6 msec. It should be noted that this study was conducted in healthy males only. It would be important to study this effect in a larger number of patients and in women as well. The clinical significance of this measure is unknown, but may be associated with an increase in cardiac events.

Study AI4201-036 was a double-blind, randomized, placebo controlled, parallel group study of the effects of multiple dose gatifloxacin on oral glucose tolerance, glucose and insulin homeostasis and steady state glyburide pharmacokinetics, in subjects with Type II Non-insulin Dependent Diabetes Mellitus (NIDDM) controlled on stable, once-daily doses of glyburide. Thirty two patients were randomized to either placebo or 400 mg gatifloxacin orally. Of the fifteen patients treated with gatifloxacin only two patients had greater than 30 msec increase in QTc from baseline. One was a 52 year old male who had a baseline QTc of 405 msec and a reading of 440 msec on day 8, two hours after dosing. The other patient was a 67 year old male with a baseline QTc of 437 and a reading of 482 msec on day 8, two hours after dosing. Neither patient had any clinical cardiac symptoms. Five females were studied in this trial. The slope of the regression line of QTc intervals at Day 8 on plasma gatifloxacin concentration supplied by the applicant was (22.42, 6.25; 95%, CI). This is a different analysis than the preceding one; however, there appears to be little change in the QTc interval when the outlier analysis is studied. Most of the changes from baseline were negative.

Study AI4201-056 was an open-label, non-randomized study to assess the effect of multiple-dose gatifloxacin on the pharmacokinetics of concomitantly administered midazolam. All subjects had QTc measurement which were under 430 msec at all times. This study enrolled 14 male patients.

Phase III studies did not contain paired ECG measurements nor did they exclude patients on concomitant cardiac medication which may increase the QTc. In this regard, the applicant had the ability to review only adverse clinical events relative to the cardiovascular system. Although gatifloxacin is not metabolized extensively in the liver and does not interfere with the cytochrome P450 system, the potential interaction was studied by the applicant as a result of consultation with the FDA after the October 1999 FDA Advisory Committee on

An analysis by the applicant was conducted to assess the potential for adverse cardiac consequences arising in patients who received concomitant drugs associated with QTc prolongation. A total of 118 patients treated with gatifloxacin 400 mg and 89 patients treated with various comparators were identified. The most common potentially cardiotoxic agents were amitriptyline, cisapride and nortriptyline. These drugs were relatively evenly distributed between the two treatment groups. Overall, no difference was detected between the four subsets (gatifloxacin 400 mg with/without concomitant drugs prolonging QTc and comparators with/without concomitant drugs).

**Cardiovascular Adverse Events- All Causes-
Patients With/Without Concomitant Cardiac Drugs**

	Gatifloxacin 400 mg and Concomitant drugs N = 115	Gatifloxacin 400 mg and NO Concomitant drugs N=3088	Comparator and Concomitant drugs N=89	Comparator and NO Concomitant drugs N=2189
Hypertension	1	8	1	14
Palpitation	--	12 (0.39%)	1	9 (0.41%)
Tachycardia	1	6	--	9
CHF	2	6	--	6
Hypotension	1	5	1	6
Migraine	--	11	--	2
Myocardial Infarction	2	7	--	1
Syncope	--	6 (0.2%)	--	2 (0.1%)
Arrhythmia	--	3	1	4
Extrasystoles	--	1	--	6
Atrial fibrillation	--	4	--	4
Cardiac Arrest	--	3	--	1
Bradycardia	--	2	--	1

Of the patients in the gatifloxacin treatment group, only 6 tachycardia patients in each group were considered to be related to study medication, and for tachycardia it was noted by the investigator to be related to study drug in only 3 comparator patients.

In summary, review of the pre-clinical animal data, no striking effect on QT could be detected. However, the applicant could have extended the dose of gatifloxacin to higher levels in the beagle model. The Phase II/III data, on a small number of patients, provided a small positive association between concentration and delta QTc; eg. a shallow rise in the slope of the delta QTc measurement associated with increase in plasma concentration of gatifloxacin. The evaluation of the Phase III clinical adverse event database related to the cardiovascular system in over 8,500 patients treated with gatifloxacin did not reveal any striking differences between gatifloxacin and comparator, although paired ECGs were not performed in a prospective manner within this study population. Given the data at hand, it would appear that gatifloxacin may have a weak effect on the QTc and thus potential to cause cardiac arrhythmia; however, at this time the clinical relevance of the small change in QTc is unknown. A more precise evaluation of the effect of gatifloxacin on the cardiovascular conduction system could be described by studying additional patients at higher doses (800 mg, 600mg) where the ECG would be taken during the expected peak serum concentration. (see phase IV commitments)

9.4.3 CNS

CNS side effects were uncommon. In particular, dizziness occurred in about 3% of all patients exposed to gatifloxacin. There was no evidence that dizziness was dose-related, and there was no evidence that dizziness occurred more frequently in females and in younger patients, as has been described with other quinolones. In general, dizziness was minimal and led to treatment discontinuation in very few patients. Other CNS side effects were rare, and were reported in one or two patients.

There were five patients reported to have had convulsions in the data base. One patient was treated with ciprofloxacin and 4 patients were treated with gatifloxacin (400mg PO). None of these cases were felt to be related to study drug by the site investigators. The cases are reviewed in detail in the review of clinical trials section (section 8.0).

9.4.4 Hepatotoxicity

In addition to the original NDA submission, the applicant supplied analyses of liver function tests requested by the FDA. They separated study patients into two groups: patients with normal and abnormal pre-treatment values. Information regarding duration and route of administration, as well as review of patients with combinations of abnormal liver function tests (AST, ALT and Total Bilirubin) was requested.

The results suggest that liver test abnormalities seen in the gatifloxacin treatment group were mild in nature and that abnormalities seen in the gatifloxacin group are similar to the approved comparators. The abnormalities described may be due to the underlying infectious disease (eg pneumonia) or underlying pathology specific to that subject (concomitant medications, etc). Further description of the patients who had normal baseline values and abnormal tests, especially focusing on the combinations of AST/ALT and Total Bilirubin, are provided below.

Of the patients with normal baseline laboratory values reviewed in the study database, 3,043 were treated with gatifloxacin and 1731 comparator drug. Of these patients, 25 (1%) gatifloxacin treated patients and 29 (2%) comparator treated patients were exposed to more than 15 days of therapy. Patients with an abnormal ALT of any level were 118 (3.9%) in the gatifloxacin group and 89 (5.1%) in the comparator group. However, patients with abnormal ALT and/or AST plus Total Bilirubin were seen in 9 (0.2985%) patients treated with gatifloxacin and 2 (0.1155%) treated with comparator (ofloxacin and ceftriaxone). None of the patients had liver failure, liver transplant or death due to possible hepatic etiology. The sponsor also states that none of the patients were discontinued from study drug due to concerns about liver toxicity.

The applicant provided line listings and CRT for each of the patients with abnormal combinations (11 patients). FDA statistician reviewed the electronic database for the major comparative trials and was able to duplicate this number, but found one additional patient. A table of these patients and additional clinical description derived from the CRFs and CRTs is below.

Of those 9 patients treated with gatifloxacin, none of the patients had the pattern of elevated ALT and T. Bilirubin only. Of the 9 cases reported only 4 patients had elevated ALTs (0.1325%). Only the patient receiving the ceftriaxone had an isolated elevated ALT. Of these 4 gatifloxacin patients all of the AST elevations were mild, grade 1 elevations (1.4-1.6x ULN). Two patients were from the gonorrhea study, and one admitted to drinking heavily prior to the follow-up visit, the other admitted to smoking marijuana daily. Neither had symptoms of hepatitis. The third patient was treated for acute exacerbation of chronic bronchitis, was 76 years old and had a history of hypertension and heart disease. He complained of moderated nausea and was discontinued due to nausea. The final patient was a 26 year old male treated for community acquired pneumonia, diagnosed with severe pneumonia and was hospitalized. He did well and was discharged.

From the above analysis it appears that there is no serious or significant hepatotoxicity in the gatifloxacin treated patient group reported (3,043 patients). In addition, liver test abnormalities were seen at a rate and level comparable to the "comparator" drugs. These abnormal values may be in part a result of the infection under treatment, or the underlying disease. When compared to drugs with no known potential for sever hepatotoxicity, based on substantial post-marketing experience, gatifloxacin did not demonstrate any significant increase in liver abnormalities.

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Patients on Gatifloxacin	Increase on	MAX Liver Values	Post-XULN (Grade)	Indication	# Doses	Comment
001, 00015 00058	AST and TBili	34 to 40 U/L (ALT) 22 to 44 U/L (AST)* 0.8 to 1.1 mg/dL (Bili)*	----- 1.2x (grade 1) 1.1x (grade 2)	AECB	7 po	37 yo, AA, male with history of Chronic bronchitis. Physician noted this to be insignificant and not related to drug. (Smoker). No AEs reported.
038, 00031 00197	AST and T.Bili	40 to 45 U/L (ALT) 27 to 38 U/L (AST)* 0.3 to 1.3 mg/dL (Bili)*	----- 1.02x (grade 1) 1.3x (grade 2)	CAP	18 po	83 yo W female. Hx of CHF, severe pneumonia. AST reverted to baseline at 7 days post RX. Patient survived and discharged from hospital. No AEs reported.
003, 00040 00001	AST and T.Bili	16 to 25 U/L (ALT) 27 to 51 U/L (AST)* 0.6 to 1.4 mg/dl (Bili)*	----- 1.4x (grade 1) 1.4x (grade 2)	CAP	14 po	66 yo Hispanic Female, HX of DM, CHF on furosamide. AST reverted to nl at 10 days post RX.
007, 00030 00006	AST and T.Bili	12 to 13 U/L (ALT) 27 to 33 U/L (AST)* 1 to 1.8 mg/dl (Bili)*	----- 1.1x (grade 1) 1.4x (grade 2)	Sinusitis	10 po	44 yo Hispanic Female, No AEs reported
007, 00042 00005	AST and T.Bili	39 to 74 U/L (ALT) 26 to 78 U/L (AST)* 0.9 to 1.5 mg/dl (Bili)*	----- 2.3x (grade 1) 1.2x (grade 2)	Sinusitis	10 po	44 yo Male, history of allergies, No AEs reported.
001, 00020 00098	AST, ALT and T.Bili (**T.Bili high pre-trt)	41 to 91 U/L (ALT)* 31 to 103 U/L (AST)* 1 to 1.3 mg/dl (Bili)*	1.4x (grade 1) 2.8x (grade 2) 1.3x (grade 2)	AECB	3 po	76 yo W male, High blood pressure, heart disease, Digoxin, Lasix, lisinopril. Co Nausea (moderate) DC'd drug due to AE. Resolution Sxs. No further fu of labs.
012, 00002 00020	AST, ALT and T.Bili	11 to 61 U/L (ALT)* 19 to 340 U/L (AST)* 1.2 to 1.3 mg/dl (Bili)*	1.5 x(grade 1) 9.4x (grade 3) 1.1x (grade 2)	Gonorrhca	1 po	19 yo AA male, no AEs. All LFTs were normal at day 55 post study RX. Dinking heavily prior to second visit.
012, 00004 00021	AST, ALT and T.Bili	34 to 67 U/L (ALT)* 28 to 40 U/L (AST)* 0.5 to 1.3 mg/dl (Bili)*	1.6x (grade 1) 1.1x (grade 1) 1.1x (grade 2)	Gonorrhca	1 po	20 yo AA male, No AEs noted. No further follow after day 6 post rx. Smokes marajuana every day.
037, 00052 00200	AST, ALT and T.Bili	50 to 101 U/L (ALT)* 26 to 45 U/L (AST)* 0.9 to 1.5 mg/dl (Bili)*	1.6x (grade 1) 1.2x (grade 1) 1.5x (grade 3)	CAP	14 iv to po	26 yo W male, COPD, severe pneumonia, albuterol, ipratropin, alprazolam, prednisone. No AEs. Did NOT die.

Patients on Comparator	Increase on	Liver Values	Max Grade	Indication		
012, 00001 00154	AST and T.Bili	17 to 22 U/L (ALT) 21 to 39 U/L (AST)* 1.1 to 1.5 mg/dl (Bili)*	----- 1.3x (grade 1) 1.3x (grade 2)	Gonorrhea (ofloxacin)	1 po	20 yo AA male. No AEs reported.
037, 00010 00231	AST, ALT and T.Bili	34 to 71 U/L (ALT)* 27 to 57 U/L (AST)* 0.7 to 2.3 mg/dl (Bili)*	1.1x (grade 1) 1.5x (grade 1) 2.3x (grade 3)	CAP (ceftriaxone)	4 po	57 yo W Male. Copd, severe pneumonia, hospitalized on ventilator. Discharged.
Additional Patients						
Patients on Gatifloxacin	Increase on			Indication		
037, 00029 00314	AST and T.Bili	30 to 50 18 to 43 1 to 1	----- 1.2x (grade 1) -----	CAP	12 iv - po	35 yo AA male, Occasional beer on weekends, marijuana and crack.

AST/ALT TOXICITY GRADES: Grade 1 = 1.1 - 2.5 x ULN, Grade 2 = 2.6 - 5.0x ULN, Grade 3 = 5.1 - 20 x ULN, Grade 4 = > 20 x ULN.
T. BILIRUBIN TOXICITY GRADES: Grade 1 -----, Grade 2 = 1.1-1.4 X ULN, Grade = 3 1.5 - 3.0 x ULN, Grade 4 = > 3.0 ULN.

(ULNs for Study 001, 003, 037, 038 : ALT ULN = 65 U/L, AST ULN = 37 U/L, T.Bili ULN = 1.0 mg/dl)
(UNLs for Study 007: ALT = 35 U/L, AST = 29 U/L, T.Bili = 1.3 mg/dl)
(UNLS for Study 012: ALT = 43 U/L, AST 36 U/L, T. Bili = 1.2 mg/dl)

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9.4.5 [redacted] syndrome (Hemolytic Uremic Syndrome, HUS)

The applicant reports that there were no reports of a [redacted] like syndrome in the entire database. They searched the safety database for the association of fever and other signs of hemolytic anemia, thrombocytopenia or renal failure. No such cases were identified.

FDA requested an additional analysis of the laboratory abnormality database to search for this syndrome. These were post hoc analysis and prospective program for identifying this event was not in place beyond the usual review of the safety database. Review of this analysis did not identify any cases of HUS. The applicant reported that they searched the safety database for any patients with all three of the following laboratory findings: a total bilirubin of > Grade III toxicity, an increase in serum creatinine of one toxicity grade, and a drop in serum hemoglobin of one toxicity grade. They state that no such patients were found.

The FDA is satisfied with these analyses. These analyses were similar to those asked of other quinolones currently being reviewed for approval.

9.4.5 Tendon rupture

The applicant reported that there was no report in the entire database of any rupture of any tendon, in particular the Achilles tendon. To further investigate the potential for gatifloxacin-induced tendonitis, we looked at four specific adverse events: contraction tendon, disorder joint, disorder tendon, and tenosynovitis. Overall, the incidence of these events was lower among gatifloxacin-treated patients (<0.1%) compared to those treated with quinolones or non-quinolones antibiotics (0.3% in each). The most common of these abnormalities was an unspecified disorder tendon, which occurred in 8 patients total. Only 3 of these events were considered drug-related; these were one disorder joint and two disorder tendon, all three occurring in patients treated with quinolones other than gatifloxacin.

FDA medical review agrees with the conclusions drawn by the applicant, and differs in the conclusion that there were no ruptured tendons. FDA review of the electronic database revealed there to be one damaged tendon reported in the database under the Adverse Event Text Fields as TORN TENDON. This occurred in a patient in the comparator group (ciprofloxacin) and it was a shoulder tendon. The applicant reported no further data on this patient.

9.4.6 Anaphylaxis

There were 13 cases of "allergic reaction" which were further classified as urticaria, hives or drug reaction. Nine of these were in the gatifloxacin group and 4 were in the comparator group (1 patient given clarithromycin; 3 patients given ciprofloxacin). Only one of the patients were reported to have a severe allergic reaction (#06-04-00001). This 30 year old, white male was given a dose of gatifloxacin orally and after 15-20 minutes, left the emergency room where he was enrolled. As he was waiting for a bus his throat tightened up and he became short of breath. He returned to the emergency room where he was treated with benedryl and epinephrine. He was admitted to the ICU for

observation and was discharged the next day without further problems. He was discontinued from study drug. The rate of allergic reactions was very low (<1%).

9. 4.5 Glucose Homeostasis

As a result of the animal toxicology study findings, the applicant performed several studies in patients in order to understand the potential clinical effect of gatifloxacin regarding glucose homeostasis. The following section reviews that experience, as well as the results from the Phase III clinical trials.

Studies in Normal Volunteers

To assess the effect of gatifloxacin on glycemic control in diabetic patients, two studies (AI420-032 and 036) were conducted in volunteers. The first one was performed in patients with Type II diabetes controlled with diet and exercise, and the second one was done in patients with Type II diabetes treated with glyburide. In addition, glucose homeostasis was assessed in another multiple dose trial (AI420-025). All three studies are summarized below.

Type II Diabetes Controlled with Diet and Exercise:

This randomized, double-blind, placebo-controlled study (AI420-032) compared the effects of gatifloxacin 400 mg QD for 10 days and ciprofloxacin 500 mg BID for 10 days relative to placebo on glycemic control. It included a total of 48 patients and the main endpoints were the oral glucose tolerance test, with measurements of changes in CMAX and AUC for serum glucose, serum insulin and C-peptide, both pre- and post-dosing with either quinolone and the placebo.

There was a lack of effect of gatifloxacin on glucose tolerance and pancreatic β -cell function. Of note, there was a slight increase in fasting insulin levels on Day 1 with a decrease in fasting glucose which was not found on subsequent days. This effect was not clinically significant. An acute effect of gatifloxacin on insulin release could not be ruled out.

Study in Type II Diabetes Controlled by Glyburide

This double-blind, randomized, placebo-controlled trial accrued 32 patients treated with either gatifloxacin 400 mg QD for 10 consecutive days or placebo (Study AI420-036). The endpoints of the study were the pharmacokinetic parameters of glyburide, glucose tolerance test, and serum insulin and C-peptide levels both before and after the course of gatifloxacin.

Overall, gatifloxacin had no effect on the steady-state pharmacokinetics of glyburide. There was also no effect on glucose tolerance or insulin homeostasis, although a modest decrease in insulin production with multiple dose administration could not be ruled out.

Study of Oral Glucose Tolerance and Glucose and Insulin Homeostasis

This randomized, double-blind, placebo-controlled study in healthy volunteers assessed the effect of intravenous gatifloxacin, at doses of 200 to 800 mg, and placebo on oral glucose tolerance, glucose and insulin homeostasis, and fasting predose serum glucose, insulin and C-peptide in healthy volunteers. Each subject received a single-dose of study drug on Day 1, followed by repeated, once daily dosing on Days 4 through 17. There was no change apparent in serum insulin or C-peptide and the effect on serum glucose was less on Day 10. Changes in pre-dose, fasting serum glucose insulin and C-peptide levels over a 20-day period were similar in all treatment groups, including placebo. There was no effect of gatifloxacin on oral glucose tolerance. Fasting serum glucose, insulin and C-peptide concentrations were also measured over a 6 hour period following the start of the one hour infusion of gatifloxacin on Days 1 and 10. There was a transient decrease in serum glucose at all dose levels at the one hour time point on Day 1 with a prompt recovery by the end of the second hour.

Safety Database in Phase III Trials

There were seven episodes of hypoglycemia reported as an adverse event by Investigators, six in patients treated with gatifloxacin 400 mg and one in a clarithromycin-treated patient. One gatifloxacin patient did not have a history of diabetes. On Day 2, the glucose level was 33 mg/dL. The reason for this symptomatic hypoglycemic episode is unknown. The five other gatifloxacin patients had a history of diabetes; three were treated with glyburide, one with insulin and one with both glyburide and insulin. In all five of these patients, the glucose value at the time of hypoglycemia was not available, and hyperglycemia was consistently reported in non-fasting glucose tests pre- and/or post- the "hypoglycemia" episode.

To further assess the potential hypoglycemic effect of gatifloxacin, the applicant searched their database which included a total 4,733 patients for whom glucose levels were available both pre- and either during- or post-treatment. Potential hypoglycemia was defined as a serum glucose (fasting or non-fasting) below 60 mg/dL. Seventy-nine patients were identified, translating to an incidence of 1.7% in the gatifloxacin-treated group, 1.4% in patients treated with other quinolones, and 1.8% in patients treated with other antibiotics. In most cases, the glucose levels ranged from 50 to 60 mg/dL. Among gatifloxacin-treated patients, there were 4/3000 patients with a value <40 mg/dL, the lowest being 31 mg/dL, 0/1183 in the other quinolone group and 1/550 in the non-quinolone group, this value being 27 mg/dL in a patient treated with ceftriaxone.

Patient 04-08-00003: A 35 year old, black, female treated with gatifloxacin was reported to have a glucose value of 34 mg/dL which was considered a laboratory error; inorganic phosphorus was high as well. Repeat labs were normal. The patient did not suffer symptoms of hypoglycemia. The patient's medical history was only positive for COPD.

Patient 04-08-00005: A 39 year old, black, female treated with gatifloxacin was noted to have a glucose of 34 mg/dL. This value was considered a laboratory error by the investigator. A repeat value was within normal limits. The patient did not suffer symptoms of hypoglycemia. The patient's medical history included chronic bronchitis, lumbar strain, insomnia.

Patient 031-05-00046: A 75 year old white, male treated with gatifloxacin was noted to have a glucose of 31 mg/dL. This patient had a medical history of NIDDM, gout, generalized osteoarthritis, Alzheimer's disease, and coronary artery disease. The patient was on concomitant medication including glipizide, amitriptyline, prozac, and allopurinol. The patient completed 10 days of therapy without further hypoglycemia. Additional blood tests were slightly elevated, as would be expected in a diabetic patient.

Patient 02-62-00430: An 83 year old white, male treated with gatifloxacin was noted to have a glucose of 33 mg/dL. The medical history was negative except for a cholecystectomy in 1995. The patient was given a dose of diabetia on the same day as the hypoglycemia was reported. This patient was reported to have been confused and agitated. He was hospitalized with pneumonia. The patient's gatifloxacin was discontinued on the second treatment day. It is unclear what role the gatifloxacin played in this patient's hypoglycemia.

Among the gatifloxacin patients, the low serum glucose was seen at equal frequency in patients treated with the 200 or 400 mg doses; hypoglycemia (glucose <60 mg/dL) was not seen in patients treated with 600 mg single dose. Seventy-five percent (39/53 patients) of these episodes of hypoglycemia occurred in patients who were less than 65 years of age, 15.4% (8/52 patients) in patients 65 - 74 years of age and 9.6% (5/52 patients) in patients greater than 75 years of age. There was no clear evidence that hypoglycemia was related to duration of therapy; the highest incidence occurred in patients who received between 6 and 10 days of treatment. The episodes occurred mainly among Caucasian patients. There was a greater number of female patients than male patients in this group; however, many of the female patients came from the urinary tract infection study which enrolled only female patients.

Summary

The three studies conducted in volunteers demonstrated a lack of gatifloxacin effect on glucose homeostasis. There was no evidence of hypoglycemia, significant changes in insulin production, or interaction with glyburide in patients with Type II diabetes. In the safety database, the incidence of hypoglycemia (serum glucose below 60 mg/dL) was similar in gatifloxacin-treated patients and in those treated with other antibiotics. There were six episodes of "hypoglycemia" in gatifloxacin-treated patients but low serum glucose was documented in only one of them. In the remaining four patients who had a history of diabetes and treatment with glyburide and/or insulin, hypoglycemia was possibly related to other factors (e.g., poor nutrition) rather than to a direct toxicity/interaction of gatifloxacin.

In conclusion, based on data in volunteers and from the clinical safety database, hypoglycemia appears to be a rare event not clearly associated with the administration of gatifloxacin. No special precautions need to be taken by the general population treated with gatifloxacin, or by diabetic patients on oral hypoglycemic agents.

9.5 Pregnancy

There were 12 pregnancies documented during the conduct of the trials. Five women were being treated for uncomplicated UTI, two for complicated UTI, two for sinusitis, and one each for pneumonia, acute exacerbation of chronic bronchitis and gonococcal cervicitis. Ten were White and two were Black. Ages ranged from 18 to 29 years. Seven women were treated with gatifloxacin and five with ciprofloxacin. Among the gatifloxacin-treated women, two had healthy babies, two had elective abortions, one had a normal pregnancy with delivery expected in January 1999, one had medical problems during delivery and one was lost to follow-up.

Concurrences:

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Original NDA 21-061
HFD-550/Div. Dir/Goldberger
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HFD-590/TI/Cavaille-Coll
HFD-590/MO/Korvick
HFD-590/MO/Roca
HFD-590/Chem/Smith
HFD-520/Micro/Altaie
HFD-880/BioPharm/Uhl
HFD-520/Pharmtox/Ellis
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