

**CURE:**

All or most pre-therapy signs and symptoms were improved or resolved at the time of the Test of Cure Visit (Day+4 to +11) with the original therapy alone, without need for further antimicrobials. In addition, no new signs or symptoms of acute infection were present.

**SUSTAINED CURE:**

All or most pre-treatment signs and symptoms were resolved or improved at the Test of Cure Visit and no evidence of resurgence of these symptoms was documented at the Extended Follow-up visit (Day +25 to +50). No additional systemic antibiotic therapy was given for the original signs and symptoms after completion of study drug therapy.

**FAILURE:**

There was no apparent response to therapy with a continuation or worsening of most or all pre-treatment signs and symptoms; or new UTI signs and symptoms not associated with original complicating factor appeared.

**RELAPSE:**

Signs and symptoms were absent at the Test of Cure Visit (Day +4 to +11) but re-appeared, or new symptoms appeared, by the time of the Extended Follow-up (Day +25 to Day +50).

**UNABLE TO DETERMINE:**

Extenuating circumstances precluded classification of a response, such as:

1. no follow-up evaluation of signs and symptoms was performed during this period;
2. the patient received another presumably effective systemic antibiotic for an infection;
3. usually other than a UTI, prior to obtaining a urine specimen for culture during this period;
4. early discontinuation for an adverse event or voluntary withdrawal.

***Reviewer's note:*** *I have reviewed the case report forms (CRF), safety and efficacy data and believe that the Applicant adhered to these definitions of clinical outcome.*

**Indication: Uncomplicated Urinary Tract Infections**

#### 8.5.11.1.7 Sample Size and Statistical Plan

The bacteriologic eradication rate of patients with uncomplicated urinary tract infection treated with ciprofloxacin was estimated to be 90%. Assuming that ciprofloxacin and at least one dose of gatifloxacin possessed equivalent eradication rates, 224 evaluable patients per arm would yield 90% power to claim the eradication rate for at least one dose was no more than 10% less than the rate for ciprofloxacin (= 0.05, two-sided, using a  adjustment for two comparisons).

Assuming an evaluability rate of 90%, a target number of 250 patients per arm was intended for enrollment (i.e., 750 total patients). After 632 patients were enrolled, the evaluability rate was assessed on the pooled blinded data. The observed evaluability rate was 50% as opposed to the projected 90% in the original protocol. Therefore, the enrollment in the trial was extended to 1,300 patients in order to achieve appropriate statistical power.

The randomization system used was a dynamic balancing algorithm which adjusted assignment of patients to one of three treatment groups in a 1:1:1 ration within sites.

***Reviewer's note: Please refer to the FDA statistical review for further discussion regarding this dynamic balancing algorithm. Extension of study decision was made in a blinded manner.***

The primary efficacy analysis compared the bacteriologic eradication rates between each dosing regimen of gatifloxacin to ciprofloxacin in the Microbiologically Evaluable Population. The differences between gatifloxacin and ciprofloxacin and their associated 97.5% confidence intervals were computed using exact method (StatXact®). Equivalency of treatment was declared if the lower confidence limits were -0.10 or greater when the larger observed response rate was 90% or higher. All other data analyses of efficacy parameters were considered secondary.

#### 8.5.1.1.8 Study Results

Please see Appendix 1 for the table on Patient Disposition and Clinical Study Sites.

##### 8.5.1.1.8.1 Patient Disposition

**Indication: Uncomplicated Urinary Tract Infections**

Of the 1334 randomized patients, all but 11 received study medication, making a total of 1323 patients in the All Treated Population (Table 6). Thirty-one patients equally divided among treatment groups were ineligible. Twenty patients equally divided among treatment groups were ineligible since they had complicating factors for UTI. Other patients either lacked any of the required signs or symptoms of UTI, had no pyuria, or had vaginitis mimicing a UTI. Fifty-five percent of the eligible population was clinically unevaluable. Eighty-seven percent of the clinically unevaluable population equally divided among treatment groups had quantitative urine colony counts of  $<10^5$  cfu/mL. Other reasons for unevaluability included no Test of Cure Visit (or visit outside the study windows), less than one full day of therapy, and other systemic antibiotics administered before the Test of Cure Visit.

**Table 8:**

**Distribution of Patients in Study Populations and Reasons for Exclusion,  
All Treated Patients**

Study Population/Reason Excluded	Number (%) of Patients			
	Gatifloxacin 400 mg QD single dose	Gatifloxacin 200 mg QD x 3 days	Ciprofloxacin 100 mg BID x 3 days	Total
<b>All Treated</b>	<b>436</b>	<b>443</b>	<b>444</b>	<b>1323</b>
<b>Eligible</b>	<b>424</b>	<b>433</b>	<b>435</b>	<b>1292</b>
<b>Ineligible</b>	<b>12</b>	<b>10</b>	<b>9</b>	<b>31</b>
Complicating Factors for UTI	6	5	4	15
Did not have any of required signs/symptoms	3	1	1	5
>3 UTI past 12 months	1	2a	2a	5
No documentation of pyuria	2	1	1	4
Vaginitis mimicing UTI	0	1a	1	2
<b>Clinically Evaluable</b>	<b>207</b>	<b>208</b>	<b>203</b>	<b>618</b>
<b>Clinically Unevaluable</b>	<b>229</b>	<b>235</b>	<b>241</b>	<b>705</b>
Colony Count $<10^5$ cfu/mL	200	203	207	610
No Test of Cure Visit or Visit Outside Study Windows	12	18	19	49
Patient Ineligible	12	10	10a	32
Less than one full day of therapy	3	2	2	7

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061

Tequin™ (gatifloxacin)

Other Systemic Antimicrobial Administered before TOC visit	2	1	2	5
Pathogen Resistant Pre-treatment	0	1	1	2
Microbiologically Evaluable	202	201	201	604
Microbiologically Unevaluable	234	242	243	719
Clinically Unevaluable	229	235	241	705
No Test of Cure Visit Culture	5	6	2	13
Pathogen Resistant Pre-treatment	0	1a	0	1

<sup>1</sup> Applicant Analysis

***Reviewer's note: I concur with the Applicant's presentation of patient disposition.***

Several patients were classified incorrectly in the database. One multiple dose gatifloxacin patient (051-1253) was erroneously classified as microbiological evaluable. She had three or more UTI on the past 12 months and should have been ineligible. Another multiple dose gatifloxacin treated patient (003-526) had vaginitis mimicing a UTI, and should have been assessed as eligible. This patient was still clinically unevaluable due to insufficient colony counts in the pre-treatment urine culture. Another multiple dose gatifloxacin patient (027-198) had a resistant pathogen pre-treatment and was considered microbiologically unevaluable. This patient should also have been considered clinically unevaluable due to insufficient colony counts.

One ciprofloxacin treated patient (012-463) was inappropriately assessed as unevaluable. This patient was originally considered ineligible/unevaluable due to lack of documentation of pyuria. Subsequently, based on supplemental data, the eligibility was corrected but not the evaluability. The patient should have been both clinically and microbiologically evaluable. No further change in the database was made. This patient was assessed as eradication of the original uropathogen but new UTI at the extended follow-up. Another ciprofloxacin treated patient (029-643) was initially excluded from eligibility for more than 3 UTI's in the past.

**Table 9: Major Protocol Violations, Unevaluable Patients<sup>1</sup>**

Number of Patients

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061

Tequin™ (gatifloxacin)

Violation	Gatifloxacin 400 mg QD Single dose N = 442	Gatifloxacin 200 mg QD X 3 days N = 447	Ciprofloxacin 100 mg BID X 3 days N = 445	Total N = 1334
No Test of Cure Visit or Visit Outside Study Windows	12	18	19	49
Complicating Factors for UTI	6	5	4	15
Had Test of Cure Visit but no Test of Cure urine culture	5	6	2	13
Did not receive study medication	6	4	1	11
Received less than one full day of therapy	3	2	2	7
Did not have any of required signs/symptoms	3	1	1	5
Other systemic antibiotics administered before Test of Cure Visit	2	1	2	5
>3 UTI past 12 months	1	2	2	5
No documentation of pyuria	2	1	1	4
Vaginitis mimicing UTI	0	0	1	1
TOTAL	40	40	35	115

1. Applicant Analysis

***Reviewer's note: I concur with the Applicant's assignment of "unevaluable status" to the patients listed in Table 9. Overall, the number of protocol violation was small and well balanced across treatment groups. These would not be expected to bias the outcomes of the study.***

8.5.1.1.8.2 Patient Diagnoses

Medical history was generally comparable across all treatment groups. Approximately 40% of the patients in each group had allergies or drug sensitivities. Nearly 30% of the patients had gastrointestinal conditions, none of which were considered by the investigators to limit absorption of either gatifloxacin or ciprofloxacin or to prohibit the patient's participation in the study. A small percentage of patients (3%) had renal conditions that were generally descriptions of

Indication: Uncomplicated Urinary Tract Infections

e

NDA 21-061

Tequin™ (gatifloxacin)

their history of prior UTI's. Fifteen of 38 patients, equally divided among treatment groups, had urological conditions that disqualified their participation since they had complicating factors for UTI.

The history of urinary tract infections was generally comparable across all treatment groups (Table 10). Over 70% of patients had a history of prior UTI, but fewer than half of the patients had an episode of UTI in the previous year. The majority of the patients were sexually active and less than 1% of patients reported use of a diaphragm for birth control.

**Table 10: History of UTI, All Treated Patients<sup>1</sup>**

Prognostic Factor	Number of Patients (%)			
	Gatifloxacin 400 mg QD single dose N = 436	Gatifloxacin 200 mg QD x 3 days N = 443	Ciprofloxacin 100 mg BID x 3 days N = 444	Total N = 1323
<u>History of UTI</u>				
Yes	305 (70)	311 (70)	335 (75)	951 (72)
No	131 (30)	132 (30)	109 (24)	372 (28)
<u>Number of Episodes of UTI previous 12 months</u>				
0	251 (58)	257 (58)	255 (57)	763 (58)
1	118 (27)	121 (27)	112 (25)	351 (26)
2	64 (15)	59 (13)	72 (16)	195 (15)
3 or more	1 (<1)	3 (<1)	1 (<1)	5 (<1)
Not Reported	2 (<1)	3 (<1)	4 (<1)	9 (<1)
<u>Sexually Active</u>				
Yes	356 (82)	367 (83)	368 (83)	1091 (82)
No	79 (18)	75 (17)	76 (17)	230 (17)
Not Reported	1 (<1)	1 (<1)	0	2 (<1)

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061

Tequin™ (gatifloxacin)

Diaphragm Use

Yes	2 (<1)	3 (<1)	1 (<1)	6 (<1)
No	434 (99)	440 (99)	434 (99)	1317 (99)

---

Applicant Analysis

***Reviewer's note: There was no obvious imbalance or potential source of bias that was detected across treatment groups regarding prior history of UTI, sexual activity or diaphragm use.***

**1.1.1.2 Efficacy Analysis**

8.5.1.2.1 Efficacy

The Division's statistical reviewer, Dr. Nancy Silliman, performed several analyses to verify the Applicant's claims of efficacy. Case report forms were also reviewed to verify that the data in the forms was accurately reported in the data files. Much of the following information on the efficacy of gatifloxacin for the indication of uncomplicated UTI was taken from Dr. Silliman's review.

Table 11 is the Applicant's summary of the bacteriologic response rates for the four analysis populations (verified by FDA). Eradication rates are slightly lower in the clinically eligible (83-89%) and all treated patients (83-89%) because missing values were imputed to be failures. In all populations, both gatifloxacin regimens were considered to be equivalent to ciprofloxacin.

The table below (Table 11) compares the difference in eradication rates of gatifloxacin single dose or gatifloxacin 3 day dose vs the comparator ciprofloxacin. The delta for equivalence was 10% in this study.

---

**Table 11: Eradication Rates by Analysis Population<sup>1</sup>**

Number Eradicated/Number of Patients (%)

**Indication: Uncomplicated Urinary Tract Infections**

NDA 21-061

Tequin™ (gatifloxacin)

Analysis Population	Gatifloxacin 400 mg x 1D N = 436		Gatifloxacin 200 mg x 3D N = 443		Ciprofloxacin N = 444	97.5% Confidence Interval* (gati 1D - cipro)	97.5% Confidence Interval* (gati 3D - cipro)
All Treated	186/223	(83%)	198/223	(89%)	188/227 (83%)	(-8.1%, 9.9%)	(-2.2%, 14.8%)
Clin Eligible	183/218	(84%)	194/219	(89%)	183/221 (83%)	(-7.3%, 9.6%)	(-2.1%, 13.7%)
Clin Evaluable	181/205	(88%)	190/207	(92%)	179/203 (88%)	(-7.5%, 7.8%)	(-3.5%, 10.7%)
Micro Evaluable	181/202	(90%)	190/201	(95%)	179/201 (89%)	(-7.8%, 8.9%)	(-2.1%, 13.2%)

1. Applicant analysis.

\*This is the confidence interval of the difference in eradication rates.

In addition, it should be noted that in the microbiologically evaluable population, the rates among patients for sustained eradication of all uropathogens in the three treatment groups were equivalent. Approximately, ten percent of patients overall had a "recurrence" of the original uropathogen. Similarly, 2% of patients overall had the growth of other uropathogens in significant numbers. At the extended follow-up visit, the three groups had comparable rates of sustained cure with an overall rate of 83%.

Table 12 summarizes bacteriologic response results stratified by site for the various analysis populations. Confidence intervals are calculated using a Mantel-Haenszel stratified approach (see reference given above). Results are generally consistent with those from the unstratified confidence intervals.

**Table 12: Stratified 97.5% Confidence Intervals by Analysis Population<sup>1</sup>**

Analysis Population	97.5% Confidence Interval for the Difference in Eradication Rates Stratified by Site	
	Gatifloxacin 1D - Ciprofloxacin	Gatifloxacin 3D - Ciprofloxacin
All Treated Patients	(-7.3%, 9.6%)	(-2.7%, 13.5%)
Clinically Eligible Patients	----	----
Clinically Evaluable Patients	----	----
Microbiologically Evaluable Patients	(-6.9%, 9.4%)	(-1.6%, 14.0%)

FDA Analysis

**Reviewer's Note:** I agree with the FDA statistical reviewer who believes that given the delta for equivalence was 10% in this study, these results are fairly robust for the 3 day regimen and a little less robust for the 1 day regimen. In this case, it is unlikely that performance of an analysis which would account for the dynamic randomization would produce results that are qualitatively different for the 3 day regimen. The 1 day regimen might also be acceptable given that we are already

Indication: Uncomplicated Urinary Tract Infections

using a conservative  correction, but these results are probably less robust. Efficacy rates of 90 % are acceptable against a comparator that is an approved product at the 3 day dose. The primary efficacy analysis utilizes the population of "microbiologically evaluable" patients.

Table 13 summarizes eradication rates using a very conservative imputation method for missing values. Missing ("unable to determine") gatifloxacin values are imputed to be failures and missing ciprofloxacin values are imputed to be cures. Given how conservative the imputation rule is, results in Table 14 are impressively robust for the 3 day regimen and reasonable for the 1 day regimen. Both lower bounds remain above -10% for the 3 day gatifloxacin regimen. This is due, in part, to the fairly good follow-up rates in this study. Only approximately 6-7% of patients with a baseline pathogen  $10^5$  cfu/mL had responses of "unable to determine".

Note that the sponsor's imputation rule was to impute all missing values as failures. In an equivalence trial, it is not clear that the sponsor's imputation rule is actually conservative as they state (e.g., a large amount of missing data could lead to a false conclusion of equivalence simply because missing values are treated the same in both arms).

**Table 13: Eradication Rates by Analysis Population: (FDA Analysis)  
Conservative Imputation of Missing Values\***

Analysis Population	Gatifloxacin 400 mg x 1D N = 436	Number Eradicated/Number of Patients (%)			
		Gatifloxacin 200 mg x 3D N = 443	Ciprofloxacin N = 444	97.5% Confidence Interval** <sup>1</sup>	97.5% Confidence Interval** <sup>1</sup>
All Treated	186/223 (83%)	198/223 (89%)	204/227 (90%)	(-14.1%, 1.1%) (gati 1D - cipro)	(-8.0%, 5.9%) (gati 3D - cipro)
Clinically Eligible	183/218 (84%)	194/219 (89%)	198/221 (90%)	(-13.3%, 2.0%)	(-8.1%, 6.1%)

\*Assuming that missing gatifloxacin values are failures and missing ciprofloxacin values are cures.

\*\*Calculated using the normal approximation to the binomial with the continuity correction.

<sup>1</sup>This is the confidence interval of the difference in eradication rates.

**Reviewer's note:** "Bacteriologic eradication" is defined as eradication of all uropathogens found at  $>10^5$  cfu/ml at study entry were reduced to  $<10^4$  cfu/jml. Although the following information on bacteriologic eradication and recurrence of

**Indication: Uncomplicated Urinary Tract Infections**

*urinary tract infection was not part of the primary efficacy analysis, it is provided to assist in the evaluation of whether one of the gatifloxacin doses might provide an advantage regarding prevention of relapse/recurrence.*

There were 711 pathogens isolated pre-treatment from All Treated Patients with colony counts of 10<sup>5</sup> cfu/mL. The most common isolate was *E. coli* (535 isolates). The next most frequent uropathogen was *K. pneumoniae* (35 isolates).

The table below (Table 14) summarizes the number of original uropathogens isolated from the microbiologically evaluable population which was the population used in the efficacy analysis and was much smaller than the "All Treated" population.

**Table 14: Bacteriologic Response of Original Uropathogen Test of Cure Visit, Microbiologically Evaluable Patient<sup>1</sup>**

	Number of Isolates (%)					
	Gatifloxacin 400 mg QD single dose N = 202		Gatifloxacin 200 mg QD x 3 days N = 201		Ciprofloxacin 100 mg BID x 3 days N = 201	
	Eradicated	Persisted	Eradicated	Persisted	Eradicated	Persisted
<b>Number of Uropathogens<sup>a,b</sup></b>	<b>196 (92)</b>	<b>16 (8)</b>	<b>208 (96)</b>	<b>8 (4)</b>	<b>202 (94)</b>	<b>12 (6)</b>
<i>E. coli</i>	140 (95)	8 (5)	161 (98)	3 (2)	159 (96)	6 (4)
<i>P. mirabilis</i>	11 (100)	0	5 (100)	0	11 (92)	1 (8)
<i>K. pneumoniae</i>	14 (100)	0	10 (83)	2 (17)	5 (83)	1 (17)
<i>S. saprophyticus</i>	6 (86)	1 (14)	5 (100)	0	1 (100)	0
<b>Other Gram-positive</b>	<b>17 (81)</b>	<b>4 (19)</b>	<b>11 (79)</b>	<b>3 (21)</b>	<b>13 (81)</b>	<b>3 (19)</b>
<i>S. agalactiae</i>	8 (73)	3 (27)	3 (60)	2 (40)	3 (75)	1 (25)
<i>S. aureus</i>	4 (80)	1 (20)	1 (100)	0	1 (100)	0
<i>Enterococcus sp.</i>	3 (100)	0	2 (100)	0	5 (100)	0

**Indication: Uncomplicated Urinary Tract Infections**

e

**NDA 21-061**

**Tequin™ (gatifloxacin)**

<i>E. faecalis</i>	2 (100)	0	4 (80)	1 (20)	3 (60)	2 (40)
<i>Aerococcus viridans</i>	-	-	1 (100)	0	-	-
<i>Gamella Morbillorum</i>	-	-	-	-	1 (100)	0
<b>Other Gram-negative</b>	<b>8 (73)</b>	<b>3 (27)</b>	<b>16 (100)</b>	<b>0</b>	<b>13 (93)</b>	<b>1 (7)</b>
<i>P. aeruginosa</i>	-	-	3 (100)	0	1 (100)	0
<i>Proteus sp.</i>	-	-	-	0	2 (100)	0
<i>Klebsiella sp.</i>	4 (80)	1 (20)	1 (100)	0	2 (100)	0
<i>Citrobacter sp.</i>	2 (67)	1 (33)	6 (100)	0	2 (67)	1 (33)
<i>Enterobacter sp.</i>	1 (50)	1 (50)	4 (100)	0	3 (100)	0
<b>Other Gram-negative rods</b>	<b>1 (100)</b>	<b>0</b>	<b>2 (100)</b>	<b>0</b>	<b>3 (100)</b>	<b>0</b>

A A patient may have more than one pathogen isolated pre-treatment.

B For those patients who had two types of the same organism, the worst response was used.

1. Applicant analysis.

**APPEARS THIS WAY  
ON ORIGINAL**

**Indication: Uncomplicated Urinary Tract Infections**

NDA 21-061

Tequin™ (gatifloxacin)

**Table 15: Bacteriologic Response of Original Uropathogen, Extended Follow-up Visit  
Microbiologically Evaluable Patients<sup>1</sup>**

	Number of Isolates (%)						
	Gatifloxacin 400 mg QD single dose N = 202			Gatifloxacin 200 mg QD x 3 days N = 201			
	Sustained Eradication	Recur- rence	UTD	Sustained Eradication	Recur- rence	UTD	Susta Eradic
<b>Eradicated Pathogens<sup>a,b</sup></b>	<b>143 (73)</b>	<b>23 (12)</b>	<b>30 (15)</b>	<b>148 (71)</b>	<b>20 (10)</b>	<b>40 (19)</b>	<b>145 (72)</b>
<i>E. coli</i>	100 (71)	15 (11)	25 (18)	118 (73)	14 (9)	29 (18)	111 (72)
<i>P. mirabilis</i>	11 (100)	-	-	3 (60)	-	2 (40)	9 (90)
<i>K. pneumoniae</i>	13 (93)	1 (7)	-	6 (60)	1 (10)	3 (30)	4 (40)
<i>S. saprophyticus</i>	6 (100)	-	-	3 (60)	2 (40)	-	1 (20)
<b>Other Gram-positive</b>	<b>7 (41)</b>	<b>7 (41)</b>	<b>3 (18)</b>	<b>4 (36)</b>	<b>3 (27)</b>	<b>4 (36)</b>	<b>9 (45)</b>
<i>S. agalactiae</i>	4 (50)	2 (25)	2 (25)	2 (67)	1 (33)	-	2 (67)
<i>S. aureus</i>	2 (50)	1 (25)	1 (25)	-	-	1 (100)	1 (100)
<i>Enterococcus</i> sp.	1 (33)	2 (67)	-	1 (50)	1 (50)	-	2 (100)
<i>E. faecalis</i>	-	2 (100)	-	1 (25)	1 (25)	2 (50)	3 (75)
<i>G. morbillorum</i>	-	-	-	-	-	-	1 (100)
<i>A. viridans</i>	-	-	-	0	0	1 (100)	-
<b>Other Gram-negative</b>	<b>6 (75)</b>	<b>-</b>	<b>2 (25)</b>	<b>14 (88)</b>	<b>-</b>	<b>2 (13)</b>	<b>11 (69)</b>
<i>P. aeruginosa</i>	-	-	-	2 (67)	-	1 (33)	1 (33)
<i>Proteus</i> sp.	-	-	-	-	-	-	2 (100)
Other <i>Klebsiella</i> sp.	3 (75)	-	1 (25)	1 (100)	-	-	2 (100)
<i>Citrobacter</i> sp.	1 (50)	-	1 (50)	5 (83)	-	1 (17)	2 (33)

Indication: Uncomplicated Urinary Tract Infections

2  
4  
e

NDA 21-061

Tequin™ (gatifloxacin)

<i>Enterbacter</i> sp.	1 (100)	-	-	4 (100)	-	-	3 (
Other Gram-negative bacteria	1 (100)	-	-	2 (100)	-	-	1 (

a A patient may have more than one pathogen isolated pre-treatment.

b Pathogens eradicated at Test of Cure Visit.

<sup>1</sup> Applicant analysis.

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

Indication: Uncomplicated Urinary Tract Infections

***Reviewer's note:*** This study adequately represented the major pathogens i.e. *E.coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*, that cause uncomplicated urinary tract infection. Numbers of these major urinary tract pathogens were distributed similarly across treatment arms. Eradication rates for these specific pathogens, at the test of cure visit were similar across treatment groups (see Table 15). Consequently the indication was granted for these organisms.

***Inadequate numbers of Staphylococcus saprophyticus and other gram negative organisms were submitted and consequently the indication should not be granted for these pathogens.***

***Response rates at the extended follow-up visit were comparable across treatment groups for E.coli. Response rates at the extended follow-up visit for patients with Proteus mirabilis and Klebsiella pneumonia were highest in the single dose gatifloxacin group (Table 15).***

Recurrence was defined as successful eradication of the original pathogen at the Test of Cure visit. However, at the extended follow-up visit, the original pathogen was again present at  $\geq 10^4$  cfu/ml. Table 16 demonstrates that recurrence rates were equivalent across treatment arms.

**Table 16: Extended Follow-up Bacteriologic Response, Microbiologically Evaluable Patients<sup>1</sup>**

Bacteriologic Response	Number of Patients (%)			Total N = 604
	Gatifloxacin 400 mg QD single dose N = 202	Gatifloxacin 200 mg QD x 3 days N = 201	Ciprofloxacin 100 mg BID x 3 days N = 201	
<b>Patients with "Eradication" at Test of Cure Visit</b>	<b>181</b>	<b>190</b>	<b>179</b>	<b>550</b>
Sustained Eradication	127 (70)	134 (71)	125 (70)	386 (70)
Recurrence	20 (11)	18 (9)	16 (9)	54 (10)

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061	Tequin™ (gatifloxacin)			
New Infection	6 (3)	4 (2)	3 (2)	13 (2)
Unable to Determine	28 (15)	34 (18)	35 (20)	97 (18)

1. Applicant analysis.

***Reviewer's note:*** *The three day regimen of gatifloxacin does not appear to convey an advantage over single dose gatifloxacin in preventing recurrence of urinary tract infection.*

#### 8.5.1.2.2 FDA Efficacy Summary

Efficacy results for this study are fairly robust and suggest that both gatifloxacin regimens are similar to ciprofloxacin in terms of efficacy. The results for the 3 day gatifloxacin regimen are somewhat more promising and robust than those for the 1 day gatifloxacin regimen. In this study, the FDA statistical reviewer felt that it is unlikely that conclusions would change for the 3 day gatifloxacin regimen if one could perform an analysis to account for the dynamic randomization used. Given that she was already using the conservative [ ] adjustment, results also seem reasonable for the 1 day regimen.

***Reviewer's note:*** *Both the single dose and three day dose regimens of gatifloxacin proved efficacious when compared to ciprofloxacin 100 mg bid for 3 days. The rate of recurrence of urinary tract infection was equivalent across all treatments arms in this study at the extended follow-up visit.*

#### 8.5.2 Safety Assessment

The data obtained for evaluation of safety included clinical signs and symptoms, physical examinations, vital sign measurements, clinical laboratory tests, and reports of deaths, adverse clinical events, and pregnancies. These data were collected between the first day of study drug therapy and 30 days after the last day of study drug therapy, or the last efficacy assessment, whichever came last.

##### 8.5.2.1 Extent of Drug Exposure in Pivotal Study

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061

Tequin™ (gatifloxacin)

DURATION OF TREATMENT: Double-blind study treatment was administered for 3 days.

APPEARS THIS WAY  
ON ORIGINAL

EXTENT OF EXPOSURE:

Table 17: Study Medication Usage, All Treated Patients<sup>1</sup>

	Number (%) of Patients							
	Gatifloxacin 400 mg QD single dose N = 436		Gatifloxacin 200 mg QD x 3 days N = 443		Ciproflox 100 mg BID x 3 days N = 444		Total N = 1323	
<u>Number of Days</u>								
Mean	3.1		3.1		3.0		3.1	
Median	3		3		3		3	
Range								
<u>Number of Days</u>								
1	5	(1)	2	(<1)	3	(<1)	10	(<1)
2					1	(<1)	1	(<1)
3	401	(92)	411	(93)	416	(94)	1229	(93)
4	30	(7)	30	(7)	24	(5)	84	(6)

<sup>1</sup> Applicant analysis.

Indication: Uncomplicated Urinary Tract Infections

***Reviewer's note: The duration of therapy was comparable between the three treatment groups.. The majority of the patients were treated for 3 days. Patients who randomized to the single dose gatifloxacin arm received active drug on day 1 and matched placebos on the second and third day of the protocol. The half life of gatifloxacin is approximately 7 hours and consequently duration of exposure and potential for side effects to develop would include up to 35 days post-dose.***

### 8.5.2.2 Adverse Events

#### 8.5.2.2.1 All causalities

Approximately half of the patients in each treatment group experienced one or more adverse clinical events (Table 18). The most frequently occurring adverse clinical events were headache, nausea, and abdominal or back pain. Except for nausea, most of these adverse events were not related to study drug treatment.

The incidence of adverse events was in most cases comparable among the treatment groups. Only 40% of the overall adverse events were reported as drug related. Headache, nausea, and abdominal pain were the most common adverse events. The remaining adverse clinical events occurred with an overall frequency of less than 5% in All Treated Patients.

An adverse clinical event (ACE) was defined as any reaction, side effect or other undesirable event that occurred in conjunction with the use of a drug, biological product, or diagnostic agent, whether or not the event was considered drug related. Investigators were required to report all adverse clinical events to the Sponsor, along with their judgment of the causality (certainly, probably or possibly drug-related; not drug-related; or unknown relationship to study drug). For the purpose of analysis, events that were certainly, probably and possibly drug related were grouped and categorized as "drug related". Investigators also assessed the severity (mild, moderate or severe) of each adverse clinical event. Patients who experienced an adverse clinical event were to be followed until resolution, or stabilization if it became a chronic condition.

Patients who discontinued study drug because of an adverse clinical event were

**Indication: Uncomplicated Urinary Tract Infections**

e

**NDA 21-061**

**Tequin™ (gatifloxacin)**

examined as frequently as necessary to document that the reaction had subsided and that no complications persisted.

Adverse clinical events were recorded in the CRF using the Investigator's own descriptive terminology (Investigator terms). For uniformity, Investigators terms were assigned to unique primary terms defined in the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART), adverse clinical event classification system as modified by Bristol-Myers Squibb.

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061

Tequin™ (gatifloxacin)

Table 18 Adverse Clinical Events of All Causes, All Treated Patients<sup>1</sup>

Adverse Clinical Event	Number of Patients (%)										
	Gatifloxacin 400 mg Single Dose N = 436				Gatifloxacin 200 mg QD X 3 days N = 443				Total	Related	N
	Related	Not Related	Not Assessed	Total	Related	Not Related	Not Assessed				
Any adverse event	78 (18)	116 (27)	7 (2)	202 (46) <sup>b</sup>	93 (21)	129 (29)	4 (<1)	226 (51)	80 (18)	1	
Headache	18 (4)	35 (8)	-	53 (12)	13 (3)	33 (7)	-	46 (10)	20 (5)		
Nausea	26 (6)	7 (2)	-	33 (8)	24 (5)	12 (3)	1 (<1)	37 (8)	20 (5)		
Pain abdomen	4 (<1)	12 (3)	1 (<1)	17 (4)	8 (2)	16 (4)	1 (<1)	25 (6)	8 (2)		
Dysuria	1 (<1)	16 (4)	-	17 (4)	1 (<1)	17 (4)	-	18 (4)	1 (<1)		
Urinary Frequency	1 (<1)	17 (4)	-	18 (4)	1 (<1)	16 (4)	-	17 (4)	-		
Pain	5 (1)	10 (2)	-	15 (3)	2 (<1)	14 (3)	-	16 (4)	2 (<1)		
Pain back	1 (<1)	13 (3)	1 (<1)	15 (3)	-	18 (4)	-	18 (4)	2 (<1)		
Diarrhea	6 (1)	7 (2)	-	13 (3)	8 (2)	3 (<1)	-	11 (3)	13 (3)		
Dizziness	7 (2)	5 (1)	-	12 (3)	6 (1)	5 (1)	-	11 (3)	6 (1)		
Vaginitis	5 (1)	6 (1)	-	11 (3)	24 (5)	7 (2)	-	31 (7)	10 (2)		
Urinary Urgency	1 (<1)	14 (3)	-	15 (3)	4 (<1)	13 (3)	-	17 (4)	1 (<1)		
Urinary Retention	-	10 (2)	1 (<1)	11 (3)	1 (<1)	6 (1)	-	7 (2)	-		
Infection	-	8 (2)	-	8 (2)	-	8 (2)	-	8 (2)	-		
Dysmenorrhea	-	8 (2)	-	8 (2)	-	9 (2)	-	9 (2)	-		
Pharyngitis	-	10 (2)	-	10 (2)	-	12 (3)	1 (<1)	13 (3)	-		
Dyspepsia	2 (<1)	5 (1)	1 (<1)	8 (2)	6 (1)	5 (1)	-	11 (2)	3 (<1)		
Vomiting	4 (<1)	3 (<1)	-	7 (2)	2 (<1)	3 (<1)	-	5 (1)	6 (1)		
Accidental Injury	-	7 (2)	-	7 (2)	-	2 (<1)	-	2 (<1)	-		

Indication: Uncomplicated Urinary Tract Infections

e

**NDA 21-061**

**Tequin™ (gatifloxacin)**

Sinusitis	-	7 (2)	-	7 (2)	-	5 (1)	-	5 (1)	-
Rhinitis	-	5 (1)	-	5 (1)	-	13 (3)	-	13 (3)	-
Hematuria	1 (<1)	5 (1)	-	6 (1)	-	7 (2)	-	7 (2)	1 (<1)
Nocturia	-	6 (1)	-	6 (1)	1 (<1)	3 (<1)	1 (<1)	5 (1)	-
Spasm	-	3 (<1)	-	3 (<1)	2 (<1)	4 (<1)	1 (<1)	7 (2)	-
Asthenia	-	-	1 (<1)	1 (<1)	1 (<1)	4 (<1)	2 (<1)	7 (2)	2 (<1)

a All adverse clinical events occurring in 2% or more of patients in any treatment group. For a complete listing see Appendix 16A.

b Adverse event relationship to treatment was not recorded on CRF for one patient.

<sup>1</sup> Applicant analysis.

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

**Indication: Uncomplicated Urinary Tract Infections**

Reviewer's note: Overall, both oral dose regimens of gatifloxacin were well-tolerated and symptoms such as nausea were similar across treatment arms of the study.

Because of the concern regarding the propensity of quinolone agents to cause cardiac dysrhythmias an additional evaluation was performed to assess the following adverse events: dizziness and cardiac rhythm disturbances.

Adverse events labeled as "dizzy, dizziness, palpitations, tachycardia, atrial fibrillation, syncope, hypotension, extrasystoles" were evaluated by reviewing case report forms (CRF's).

The majority of the cardiac symptoms 6/444 cases (1.35%) were in the ciprofloxacin treated group and not related to the medication. In the gatifloxacin treatment arms 2/436 (0.46%) patients in gatifloxacin single dose and 2/443 (0.45%) patients in the gatifloxacin 3 day dosing regimen experienced cardiac symptoms that were not medication related. Patients who experienced atrial fibrillation had a prior history of this disorder. There were no reported episodes of torsades de pointes.

The majority of the neurologically classified "dizzy" symptoms were not felt to be drug related and review of the CRF's did not raise any concerns about a cardiac basis for these symptoms. The ciprofloxacin treatment arm had 9/444 (2%) cases the gatifloxacin single dose arm had 12/436 (2.75%) cases and the gatifloxacin 3 day arm had 11/443 (2.5%) cases.

APPEARS THIS WAY  
ON ORIGINAL

Indication: Uncomplicated Urinary Tract Infections

NDA 21-061

Tequin™ (gatifloxacin)

## 8.5.2.2.2 Treatment Related Adverse Events

Table 19: Drug Related Adverse Clinical Events, All Treated Patients<sup>1</sup>

Adverse Clinical Event	Number (%) of Patients								
	Gatifloxacin 400 mg N = 436				Gatifloxacin 200 mg QD x 3 days N = 443				Cipro
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	Mild
<b>Any Related Adverse Clinical Events</b>	<b>40 (9)</b>	<b>31 (7)</b>	<b>7 (2)</b>	<b>78 (18)</b>	<b>46 (10)</b>	<b>40 (9)</b>	<b>6 (1)</b>	<b>93 (21)</b>	<b>45 (10)</b>
Headache	8 (2)	9 (2)	1 (<1)	18 (4)	6 (1)	6 (1)	1 (<1)	13 (3) <sup>b</sup>	12 (3)
Nausea	18 (4)	7 (2)	1 (<1)	26 (6)	13 (3)	9 (2)	2 (<1)	24 (5)	16 (4)
Vaginitis	3 (<1)	2 (<1)	-	5 (1)	9 (2)	15 (3)	-	24 (5)	5 (1)
Diarrhea	4 (<1)	2 (<1)	-	6 (1)	7 (2)	1 (<1)	-	8 (2)	9 (2)
Dizziness	3 (<1)	4 (<1)	-	7 (2)	3 (<1)	2 (<1)	1 (<1)	6 (1)	3 (<1)
Pain	3 (<1)	2 (<1)	-	5 (1)	2 (<1)	-	-	2 (<1)	1 (<1)
Pain abdomen	1 (<1)	1 (<1)	2 (<1)	4 (<1)	4 (<1)	4 (<1)	-	8 (2)	4 (<1)
Dyspepsia	-	1 (<1)	1 (<1)	2 (<1)	3 (<1)	3 (<1)	-	6 (1)	1 (<1)
Vomiting	2 (<1)	-	2 (<1)	4 (<1)	-	1 (<1)	1 (<1)	2 (<1)	2 (<1)

a Only those adverse events occurring in 1% or more of the patients in any treatment group are listed. For a complete listing see Appendix 16B.

b One 200 mg gatifloxacin patient had a very severe adverse event (004-402). See Text.

<sup>1</sup> Applicant analysis.

APPEARS THIS WAY  
ON ORIGINAL

Indications: Uncomplicated Urinary Tract Infections

***Reviewer's note: Incidences of adverse events both drug-related and otherwise were distributed equally across all treatment arms except for vaginitis which appeared more frequently in the 3 day gatifloxacin treatment regimen. The level of severity of side-effects across treatment arms was also similar.***

#### 8.5.2.2.3 Serious Adverse Events

The definition of a serious adverse clinical event included, but was not restricted to, an event that:

- Was life threatening or fatal;
- Resulted in a permanent disability;
- Required or prolonged hospitalization;
- Was a congenital anomaly or malignancy; or
- Was the result of an overdose.

There were eight serious adverse events (Table 20). None were reported to be related to study drug treatment. All resolved except in one single dose gatifloxacin patient (027-411), a 48-year-old female with muscular dystrophy who experienced muscle atrophy during the study. Another single dose gatifloxacin patient (027-200) had the development of a cystocele. Three multiple dose gatifloxacin patients (025-1493, 030-231, 045-885) had SAE that were asthma, cholecystitis, and pain, respectively. One ciprofloxacin treated patient (042-758) had multiple SAE's including dementia, dehydration, and depression. Two other ciprofloxacin patients (047-878, 055-077) had SAE that were depression and a bone fracture, respectively.

***Reviewer's note: I reviewed the case report forms on the patients who developed serious adverse events and I agree with the sponsor that these events did not appear to be related to study drug.***

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061

Tequin™ (gatifloxacin)

**Table 20: Serious Adverse Clinical Events of All Causes, All Treated Patients<sup>1</sup>**

Adverse Clinical Event	Number of Patients (%)									
	Gatifloxacin 400 mg Single dose N = 436					Gatifloxacin 200 mg QD X 3 days N = 443				
	Related	Not Related	Not Assessed	Total	Related	Not Related	Not Assessed	Total	Related	
Any serious event	-	2 (<1)	-	2 (<1)	-	3 (<1)	-	3 (<1)	-	
Cholecystitis	-	-	-	-	-	1 (<1)	-	1 (<1)	-	
Pain	-	-	-	-	-	1 (<1)	-	1 (<1)	-	
Asthma	-	-	-	-	-	1 (<1)	-	1 (<1)	-	
Atrophy muscle	-	1 (<1)	-	1 (<1)	-	-	-	-	-	
Cystocele	-	1 (<1)	-	1 (<1)	-	-	-	-	-	
Prolapse Mitral Valve	-	-	-	-	-	-	-	-	-	
Gastroesophageal Reflux	-	-	-	-	-	-	-	-	-	
Dehydration	-	-	-	-	-	-	-	-	-	
Bone Fracture	-	-	-	-	-	-	-	-	-	
Dementia	-	-	-	-	-	-	-	-	-	
Depression	-	-	-	-	-	-	-	-	-	

<sup>1</sup> Applicant analysis.

APPEARS THIS WAY  
ON ORIGINAL

Indication: Uncomplicated Urinary Tract Infections

## 8.5.2.2.4 Severe and Life-threatening Events

**Reviewer's Comments:** *There were no deaths in this study.*

## 8.5.2.2.5 Discontinuation from Studies

Early Discontinuation from Study

Most of the patients took the full course of study drug therapy. Eleven patients received less than three days of medication (Table 21). Eight patients (004-402, 004-709, 014-085, 014-090, 016-569, 023-146, 023-805, 024-375) that received less than three days of study medication were discontinued early due to adverse events.

One ciprofloxacin treated patient (030-1349) discontinued treatment after one full day due to voluntary withdrawal from the study. One multiple dose gatifloxacin treated patient (024-374) had early discontinuation after one dose when the patient requested alternative antibiotics. One ciprofloxacin treated patient (035-165) took only the first day of medication and then misplaced her medication. This patient was erroneously recorded in the database as having taken three days of study medication and classified as a "protocol violation."

Seven of these 11 patients received less than one full day of therapy and were excluded from clinical evaluability for this reason (Table 21)

**Table 21: Reason for Early Discontinuation from Study;  
Patients with Less than Three Days of Medication<sup>1</sup>**

	Number (%) of Patients			
	Gatifloxacin 400 mg QD N = 436	Gatifloxacin 200 mg QD x 3 days N = 443	Ciprofloxacin 100 mg BID x 3 days N = 444	Total N = 1323
Discontinued Therapy Less than Three Days	5 (1)	2 (<1)	4 (<1)	11 (1)

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061	Tequin™ (gatifloxacin)			
Adverse Event	5 (1)	1 (<1)	2 (<1)	8 (<1)
Other Antibiotic given	0	1 (<1)	0	1 (<1)
Patient request	0	0	1 (<1)	1 (<1)
Protocol violation	0	0	1 (<1)	1 (<1)

<sup>1</sup> Applicant analysis.

Twenty-eight patients were considered by Investigators to have prematurely discontinued from the study (Table 22). These patients actually took three days of study medication but were erroneously classified by the Investigators to have not completed the study. One multiple dose gatifloxacin treated patient (019-944) was recorded in the database as a "protocol violator", but the patient really only missed the last dose of study medication.

***Reviewer's note: Rates of discontinuation of study medication were comparable across treatment groups.***

**Table 22: Reason for Early Discontinuation from Study; Patients with Three or Four Days of Medication<sup>1</sup>**

	Number (%) of Patients			
	Gatifloxacin 400 mg QD N = 436	Gatifloxacin 200 mg QD x 3 days N = 443	Ciprofloxacin 100 mg BID x 3 days N = 444	Total N = 1323
<b>Reason Early Discontinuation From Study</b>	<b>9 (2)</b>	<b>6 (1)</b>	<b>13 (2)</b>	<b>28 (2)</b>
Adverse Event	3 (<1)	1 (<1)	5 (1)	9 (<1)
Lost to Follow-up	4 (<1)	2 (<1)	5 (1)	11 (1)
Other Antibiotic Given	0	1 (<1)	1 (<1)	2 (<1)
Patient request	0	1 (<1)	0	1 (<1)
Protocol violation	0	1 (<1)	0	1 (<1)

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061	Tequin™ (gatifloxacin)			
Worsened signs/symptoms	1 (<1)	0	1 (<1)	2 (<1)
Lack of improvement signs/symptoms	0	0	1 (<1)	1 (<1)
Therapy ineffective	1 (<1)	0	0	1 (<1)

<sup>1</sup> Applicant analysis

#### 8.5.2.2.5.1 Discontinuations due to Adverse Event

Overall there were very few patients discontinued from the study for adverse clinical events (Table 23). There were even fewer patients when only those adverse events thought to be drug related were considered.

Eight single dose gatifloxacin treated patients (2%) had drug related adverse clinical events and were discontinued from the study. Gastrointestinal symptoms and headache were the most frequent reasons. Two patients (009-326, 014-085) developed rashes of moderate intensity that resolved with symptomatic care.

Two multiple dose gatifloxacin treated patients (<1%) had drug related adverse clinical events and were discontinued from the study. One patient (004-402) had a history of migraine headaches and developed a very severe migraine headache. The other patient (004-1380) had increased suprapubic pain.

Seven ciprofloxacin treated patients (2%) had drug related adverse clinical events and were discontinued from the study, predominantly for gastrointestinal symptoms.

**Table 23: Discontinuation of Study Medication Due to Adverse Clinical Events, All Treated Patients<sup>b1</sup>**

Adverse Clinical Event	Number of Patients (# drug related)		
	Gatifloxacin 400 mg Single Dose N = 436	Gatifloxacin 200 mg QD X 3 days N = 443	Ciprofloxacin 100 mg BID X 3 days N = 444
<b>Number Discontinued</b>	<b>8</b>	<b>2</b>	<b>7</b>

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061	Tequin™ (gatifloxacin)		
Pain Abdomen	4 (2)	1 (1)	2 (1)
Dysuria	3 (0)	0	0
Headache	3 (3)	0	0
Urinary Frequency	3 (0)	0	0
Nausea	2 (2)	0	4 (4)
Nocturia	2 (0)	0	0
Urinary Retention	1 (0)	0	2 (0)
Urinary Urgency	2 (0)	0	0
Rash	2 (2)	0	0
Hematuria	1 (0)	0	1 (1)
Pain Back	1 (0)	0	2 (0)
Vomiting	1 (1)	0	3 (3)
Diarrhea		0	2 (2)
Fever		0	2 (0)
Migraine		1 (1)	0

a Except for migraine, only events that occurred in 2 or more patients are included in this table.

b Patients may be counted in one or more adverse events.

<sup>1</sup> Applicant Analysis

***Reviewer's note:*** The number of patients who discontinued study medication due to adverse clinical events was least in the three day gatifloxacin regimen. The number of patients who discontinued study drug in the single dose gatifloxacin group was greater than in the three day gatifloxacin group but similar to the ciprofloxacin comparator. Three patients discontinued the study due to headaches in the single dose gatifloxacin arm. This may be an important finding that would argue in favor of the better tolerance of the three day dosing regimen.

#### 8.5.2.2.5.2 Discontinuations due to Laboratory Abnormalities

Indication: Uncomplicated Urinary Tract Infections

***Reviewer's comment:*** *There were no discontinuations due to laboratory abnormalities because the duration of therapy was brief i.e. three days. However, various laboratory abnormalities were detected in followup-visits as outlined below.*

#### 8.5.2.2.6 Assessment of Drug Relationship for Selected Adverse Events

##### 8.5.2.2.6.1 Abnormalities in the Hepatobiliary System

The following table (Table 24) outlines the percentages of patients in the 3 treatment arms who had normal baseline liver function tests (LFT's) and developed elevations in alanine transferase(ALT) and total bilirubin (TBILI) in the post-treatment period.

Table 24 LFT elevations in patients with normal pre-treatment values

LFT elevations Normal baseline	Cipro 3 days N=379-388*	Gati 3 days N=386-390*	Gati 1 day N=372-374*
Normal pre-study ALT, elevated ALT on therapy	7 (N=379) (2%)	5 (N=386) (1%)	5 (1%)
Normal pre-study TBIL, elevated TBILI on therapy	5 (N=388) (1%)	5 (N= 390 ) ( 1%)	2 (N= 374) (0.5 %)
Normal pre-study ALT and TBILI, elevated ALT and TBILI on therapy	0	0	0

\*Numbers of patients who had each type of liver function test done varied.

***Reviewer's note:***

*One patient on ciprofloxacin had an ALT elevation from pre-treatment of 9 to post-treatment of 171 on day 7(00050-01627). Otherwise, the highest elevation in ALT in all of the treatment groups was 76.*

*In the group of patients who had normal pre-treatment bilirubin and developed post-treatment elevations, the highest total bilirubin was 1.8. This occurred at*

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061

Tequin™ (gatifloxacin)

*day 7 post treatment in a patient with a pre-treatment value of 0.3 who had been on single dose gatifloxacin.*

*No patient in this study who began the trial with normal values ALT and or TBILI manifested a rise in both TBILI and ALT.*

*Elevations in liver function tests do not appear to be problematic in any of the patients treated with either the one or three day course of gatifloxacin for uncomplicated UTI.*

Table 25 LFT elevations in patients with abnormal pre-treatment values

LFT elevations	Cipro 3 days	Gati 3 days	Gati 1 day
Abnormal baseline	N=*9-16	N=*13-14	N=11-12*
abnormal pre-study ALT elevated ALT on therapy	(N=16) 7(44%)	(N=14) 6(43%)	(N=11) 3(27%)
abnormal pre-study TBILI, elevated TBILI on therapy	(N=9) 2( 22%)	(N=13) 0( 0 %)	(N= 12) 1(8%)

\*The number of patients who had each type of liver function test done varied.

***Reviewer's note:*** *In these patients who had pre-treatment elevations in ALT and/or TBILI, the majority of patients in all treatment arms did not significantly increase their elevated baseline liver function parameters.*

Amylase

Amylase was considered elevated if the serum laboratory value was greater than 102 U/L.

In this study, 18 patients (6 ciprofloxacin, 1 gatifloxacin three day regimen, 11 gatifloxacin single dose) had normal baseline amylase values that increased on therapy. These elevations were asymptomatic and the majority were mild elevations. One patient on ciprofloxacin with a normal baseline amylase

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061

Tequin™ (gatifloxacin)

developed an asymptomatic elevation to 827. Otherwise, the highest value for elevated amylase was 150 in a patient who received single dose gatifloxacin

Nine patients had abnormal baseline amylase values (4 ciprofloxacin, 2 gatifloxacin three day regimen, 3 gatifloxacin single dose) and seven patients experienced mild asymptomatic elevations of amylase on therapy. Two patients actually experienced a decrease in amylase post treatment (both patients on ciprofloxacin).

In the single dose gatifloxacin group, eleven patients had normal baseline amylase values and increased their amylase on therapy. These elevations were asymptomatic and mild with the highest recorded value being 150. Three single dose gatifloxacin patients had abnormal baseline amylase values and asymptotically increased their amylase on therapy with the highest elevation recorded at 183.

***Reviewer's note: Elevated amylase values were asymptomatic in this study and although the incidence was increased in the single dose gatifloxacin arm, the majority of the elevations were mild (grade 1-2).***

#### 8.5.2.2.6.2 Abnormalities of Glucose Metabolism

No patient on either dose of gatifloxacin had a glucose value of less than or equal to 60 in this study.

#### 8.5.2.2.7 Mortality Experience

There were no deaths in this study.

#### 8.5.2.3 Special Populations

##### 8.5.2.3.1 Gender

All patients in this study were female.

**Indication: Uncomplicated Urinary Tract Infections**

e

**NDA 21-061**

**Tequin™ (gatifloxacin)**

#### 1.1.1.1.2 Age

Patients in this study ranged in age from 18 years to 88 years old. There was no age-related increased incidence of adverse events.

#### 1.1.1.1.3 Ethnicity

The majority of patients in this study were Caucasian (75%), Hispanic/Latino patients comprised 11-13% of the study population, African-American patients (11-13%) Asian patients (2%) and other (<1%). The numbers of non-Caucasian patients were too small to detect any meaningful differences in efficacy or safety parameters.

#### 1.1.1.1.4 Other Conditions Related to Safety

##### Pregnancy

If pregnancy was suspected in a patient while she was receiving study drug, study treatment was to be immediately withheld until pregnancy testing was completed. If pregnancy was confirmed, study drug was to be permanently discontinued and the patient withdrawn from the trial (exceptions in life-threatening situations required approval of the BMS Medical Monitor). Investigators were to notify the Sponsor immediately of any pregnancy associated with study drug exposure (i.e., at least six half-lives after drug administration). Follow-up information regarding the course of the pregnancy, including the perinatal and neonatal outcome, was to be provided to BMS. Infants were to be followed for a minimum of eight weeks.

There were five documented pregnancies in this study. Three of the patients received ciprofloxacin (024-470, 030-229, 042-1012), while two patients received gatifloxacin 400 mg (030-342, 061-1594). Reported methods of birth control used were contraceptive gel (024-470), abstinence (042-1012), and condoms (030-229, 061-1594). One patient (030-229) randomized to the ciprofloxacin treatment

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061

Tequin™ (gatifloxacin)

arm was on Desogen when conception occurred. Pregnancy outcomes reported were elective abortion (024-470), healthy infant (030-229), and one infant with medical problems (030-342). This infant swallowed amniotic fluid and required pure oxygen therapy for four hours; however, the infant was discharged in good health with no further medical problems. One patient's pregnancy (042-1012) was lost to follow-up and one (061-1594) was due for postpartum follow-up January, 1999—safety data on this pregnancy outcome has not yet been submitted for my review.

#### 8.5.2.3.5 Pediatric Database

There were no pediatric patients enrolled in the clinical studies designed to support this indication. However, with the submission of the 4-month safety update (Amendment No.12, Submission date 5 May 1999), the applicant indicated that they have begun clinical studies in the pediatric population. The first study is a pharmacokinetic assessment of an oral suspension in children under the age of 16 years.

#### 8.5.2.3.6 Summary of Safety for this Indication

The results of this study indicate that gatifloxacin at either 400 mg as a single dose or 200 mg QD for three days is safe and equally effective for the treatment of uncomplicated urinary tract infections when compared against 100 mg BID ciprofloxacin for three days. Gatifloxacin efficacy was demonstrated for the uropathogens *E. coli*, *K. pneumoniae* and *P. mirabilis*.

Nearly half of the All Treated Patients in all three treatment groups had adverse clinical events. In the overall study, the most common adverse events involved gastrointestinal symptoms including nausea (7%), diarrhea (3%), and abdominal pain (5%). Central nervous system symptoms including headache (12%) and dizziness (2%) were also frequent adverse events.

The overall incidence of adverse drug-related clinical events was low. Vaginitis was more frequent in the three day gatifloxacin treatment group and least frequent in the single dose gatifloxacin treatment group. Most of the drug-related adverse events were mild to moderate in severity. Symptoms were classified as severe in

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061

Tequin™ (gatifloxacin)

only 1-2% of all treated patients. There were eight serious adverse events in the study, but none were drug related. The 17 patients that were discontinued due to adverse clinical events were nearly equally distributed among the treatment groups. Nausea, vomiting and/or headache were the most common drug related reasons for discontinuation. There were no deaths in the study.

Very few patients with normal baseline values in laboratory tests in either treatment group developed abnormal test results during or post-treatment period. If abnormalities occurred, they were usually mild.

This study was not designed to ascertain whether there was a significant difference in side-effects when comparing the 3 day vs single dose regimen of gatifloxacin. Overall, the types, incidence and severity of side-effects between the two dose regimens of gatifloxacin appeared to be similar. However, when compared to ciprofloxacin, the single 400 mg dose regimen of gatifloxacin is as effective as the three day gatifloxacin regimen and may improve patient compliance. Recurrence rates for urinary tract infection were similar across treatment arms. Patients who had recurrent infection did so with organisms that were sensitive to the quinolones except for one patient who received the three day gatifloxacin regimen (patient 012-449) and whose initially quinolone sensitive *E.coli* developed quinolone resistance. The original *E.coli* MIC was 0.015 ug/ml to gatifloxacin and 0.008 ug/ml to ciprofloxacin. The recurrent *E.coli* MIC was 16 ug/ml to both gatifloxacin and ciprofloxacin.

This product would be the first quinolone approved for single dose usage for uncomplicated urinary tract infection.

#### 8.5.3 Regulatory Recommendations

The reviewing medical officer recommends:

1. Approval of both the single dose and three day dose regimens of gatifloxacin for the indication of treatment of uncomplicated urinary tract infection (UTI).
2. The label should indicate the pathogens for which the applicant was able to provide sufficient data to support their claims of efficacy.
3. There was an insufficient number of uncomplicated urinary tract infections due to

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061

Tequin™ (gatifloxacin)

*Staphylococcus saprophyticus* to support the indication for treatment of this organism, therefore this indication should not be granted for this pathogen.

#### 8.5.4 Label Review

The portion of the label for this indication should be amended to read as follows:

Gatifloxacin is indicated for the treatment of "...uncomplicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*."

#### 8.5.5 Phase IV Commitments

There are no Phase IV commitments for this indication.

---

Rosemary Tiernan, M.D.  
Reviewing Medical Officer

**APPEARS THIS WAY  
ON ORIGINAL**

**Indication: Uncomplicated Urinary Tract Infections**

e

**NDA 21-061**

**Tequin™ (gatifloxacin)**

**Concurrences:**

---

Joyce Korvick, M.D., M.P.H.  
Lead Medical Officer  
Division of Special Pathogen and  
Immunologic Drug Products

---

Marc Cavaille-Coll, M.D., Ph. D.  
Medical Team Leader  
Division of Special Pathogen and  
Immunologic Drug Products

---

Mark Goldberger, M.D., M.P.H.  
Division Director  
Division of Special Pathogen and  
Immunologic Drug Products

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061

Tequin™ (gatifloxacin)

## Appendix 1 Patient Disposition-Clinical Study Sites

Site	Investigator	Number (%) of Patients			
		Number Randomized	Number Treated	Number Clinically Eligible	Number Microbiologically Evaluable
027	J. Durden, M.D.	99 (100)	99 (100)	96 (97)	32 (32)
030	J. Kirstein, M.D.	93 (100)	93 (100)	91 (98)	40 (43)
013	A. Lewin, M.D.	84 (100)	84 (100)	78 (93)	25 (30)
004	D. Orchard, M.D.	69 (100)	69 (100)	69 (100)	31 (45)
029	L. Gilderman, D.O	64 (100)	63 (98)	61 (95)	28 (44)
050	G. Richard, M.D.	60 (100)	60 (100)	60 (100)	32 (53)
025	M. Brown, M.D.	58 (100)	58 (95)	55 (95)	26 (45)
016	W.Gooch, III, M.D.	57 (100)	57 (100)	56 (98)	20 (35)
039	C.P. Matthew, M.D.	51 (100)	51 (100)	51 (100)	43 (84)
012	K. Wingert, M.D.	50 (100)	50 (100)	48 (96)	26 (52)
006	G. Ruoff, M.D.	45 (100)	45 (100)	45 (100)	27 (60)
051	R. Wade, D.O.	41 (100)	41 (100)	41 (100)	17 (41)
007	S. Bowman, M.D.	41 (100)	39 (95)	39 (95)	27 (66)
036	M. McAdoo, M.D.	39 (100)	39 (100)	39 (100)	17 (44)

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061		Tequin™ (gatifloxacin)			
003	R.Z. Paster, M.D.	37 (100)	35 (95)	34 (92)	10 (27)
038	M. Rosemore, D.O.	32 (100)	32 (100)	31 (97)	16 (50)
022	B. Bock, D.O.	31 (100)	31 (100)	31 (100)	16 (52)
005	F. Maggiacomo, D.O.	31 (100)	30 (97)	30 (97)	9 (29)
035	C.A. DeAbaate, M.D.	31 (100)	30 (97)	30 (97)	25 (81)
040	S. Horn, M.D.	26 (100)	26 (100)	25 (96)	11 (42)
023	P. McElvaine, M.D.	26 (100)	23 (88)	22 (85)	6 (23)
042	W.M. Yarbrough, M.D.	24 (100)	24 (100)	24 (100)	7 (29)
010	B. Corser, M.D.	23 (100)	23 (100)	23 (100)	10 (43)
019	D.C. McCluskey, M.D.	18 (100)	18 (100)	17 (94)	7 (39)
024	W. Coxwell, M.D.	18 (100)	17 (94)	17 (94)	11 (61)
011	G. Gottschlich, M.D.	15 (100)	15 (100)	15 (100)	9 (60)
028	A. Chavez, M.D.	14 (100)	14 (100)	14 (100)	3 (21)
009	C. Steidle, M.D.	13 (100)	13 (100)	9 (69)	3 (23)
060	H. M. Faris, Jr., M.D.	13 (100)	13 (100)	13 (100)	6 (46)
061	E. Trupin-Campbell, M.D.	13 (100)	13 (100)	13 (100)	4 (31)
026	D. Morrison, D.O.	11 (100)	11 (100)	11 (100)	6 (55)
055	M. Suchyta, D.O.	11 (100)	11 (100)	11 (100)	9 (82)
014	R. Kroll, M.D.	10 (100)	10 (100)	10 (100)	6 (60)
037	T. Littlejohn, III., M.D.	10 (100)	10 (100)	10 (100)	6 (60)
059	J. Dixon, M.D.	10 (100)	10 (100)	10 (100)	5 (50)
020	D. Laury, M.D.	9 (100)	9 (100)	8 (89)	4 (44)
031	S. Touger, M.D.	9 (100)	9 (100)	9 (100)	5 (56)
054	B. Bowling, M.D.	7 (100)	7 (100)	7 (100)	3 (43)
046	J. Young, M.D.	6 (100)	6 (100)	4 (67)	2 (33)

**Indication: Uncomplicated Urinary Tract Infections**

e

NDA 21-061		Tequin™ (gatifloxacin)			
043	M. Reynolds, M.D.	6 (100)	6 (100)	6 (100)	1 (17)
045	S. Childs, M.D.	5 (100)	5 (100)	5 (100)	4 (80)
047	C. de la Garza, M.D.	4 (100)	4 (100)	<u>4</u> (100)	2 (50)
049	M. D. Stadiem, M.D.	4 (100)	4 (100)	4 (100)	1 (25)
056	G. Bland, M.D.	4 (100)	4 (100)	4 (100)	2 (50)
057	R. Fulton, M.D.	3 (100)	3 (100)	3 (100)	0 -
058	J. Rosen, M.D.	3 (100)	3 (100)	3 (100)	2 (67)
008	K. Jacoby, M.D.	2 (100)	2 (100)	2 (100)	0 90
053	R. Gove, M.D.	2 (100)	2 (100)	2 (100)	2 (100)
048	F. Oliver, M.D.	1 (100)	1 (100)	1 (100)	0 -
052	C. Herring, M.D.	1 (100)	1 (100)	1 (100)	0 -
Totals		1334 (100)	1323 (99)	1292 (97)	604 (45)

APPEARS THIS WAY  
ON ORIGINAL

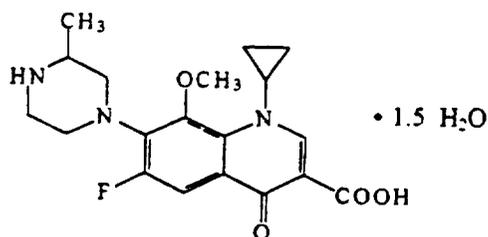
Indication: Uncomplicated Urinary Tract Infections

## 8.6. Medical Officer Review of NDA 21-061: Gatifloxacin (Tequin <sup>TM</sup>) for the treatment of complicated urinary tract infections and pyelonephritis

Date Submitted: 28 December 1998  
Date Received: 29 December 1998  
Date Assigned: 29 December 1998  
Date Completed: 17 November 1999

Applicant: Bristol-Myers Squibb Company  
5 Research Parkway  
Wallingford, Connecticut 06492  
Telephone number: 203-677-6883  
Contact person: Douglas Kriesel, Ph.D.

Drug: Proprietary name - Tequin <sup>TM</sup>  
Generic name - Gatifloxacin  
Chemical name - (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-  
7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolone  
carboxylic acid sesquihydrate  
Molecular formula - C<sub>19</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub> • 1.5 H<sub>2</sub>O  
Molecular weight - 402.42 (sesquihydrate)  
Molecular structure -

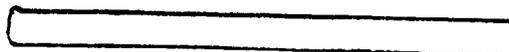


Drug Class: 8-methoxyfluoroquinolone antibacterial

Formulation: (capsule, suspension, lyophilized powder, etc.)

Route of administration: Oral; 200 mg and 400 mg tablets

Related NDA: 21-062



## Table of Contents

Executive Summary.....	i
Review Team.....	i
<b>8.6.1 Protocol A1420-031: A Randomized, Double-Blind, Multicenter, Phase II/III Comparison of Gatifloxacin to Ciprofloxacin in the Treatment of Complicated Urinary Tract Infection and Pyelonephritis.....</b>	<b>1</b>
8.6.1.1 Efficacy Evaluation.....	1
8.6.1.1.1 Study Design and Objectives.....	1
8.6.1.1.2 Eligibility Criteria.....	1
8.6.1.1.3 Study Drugs and Randomization Methods.....	3
8.6.1.1.4 Study Endpoints.....	4
8.6.1.1.5 Termination and Clinical Follow-up.....	5
8.6.1.1.6 Sample Size and Statistical Plan.....	5
8.6.1.1.7 Study Results.....	6
8.6.1.1.7.1 Enrollment and Description of Patients Enrolled in the Study.....	6
8.6.1.1.7.2 Patient Diagnoses and Complicating Factors at Entry.....	9
8.6.1.1.7.3 Patient Disposition.....	11
8.6.1.1.8 Applicant Analyses.....	12
8.6.1.1.8.1 Primary Analyses.....	12
8.6.1.1.8.2 Additional Analyses.....	14
8.6.1.1.9 FDA Analyses.....	16
8.6.1.2 Safety Assessment.....	17
8.6.1.2.1 Extent of Drug Exposure.....	17
8.6.1.2.2 Adverse Events.....	18
8.6.1.2.2.1 All Causalities.....	18
8.6.1.2.2.2 Treatment Related.....	20
8.6.1.2.2.3 Serious Adverse Events.....	22
8.6.1.2.2.4 Severe and Life-threatening Events.....	25
8.6.1.2.2.5 Discontinuation from Studies.....	25
8.6.1.2.2.5.1 Discontinuations Due to Adverse Events.....	25
8.6.1.2.2.5.2 Discontinuations Due to Laboratory Abnormalities.....	26
8.6.1.2.2.6 Assessment of Drug Relationship for Selected Adverse Events.....	27
8.6.1.2.2.6.1 Hepatobiliary System Abnormalities.....	27
8.6.1.2.2.6.2 Pancreatic Enzyme Abnormalities.....	28
<b>8.6.2 Protocol A1420-011: A Randomized, Double-Blind, Multicenter, Phase II/III Comparison of Gatifloxacin to Ciprofloxacin in the Treatment of Complicated Urinary tract Infection and Pyelonephritis.....</b>	<b>30</b>
8.6.2.1 Efficacy Evaluation.....	30
8.6.2.1.1 Study Design and Objectives.....	30
8.6.2.1.2 Eligibility Criteria.....	31
8.6.2.1.3 Study Drugs and Randomization Methods.....	31
8.6.2.1.4 Study Endpoints.....	31
8.6.2.1.5 Termination and Clinical Follow-up.....	31
8.6.2.1.6 Sample Size and Statistical Plan.....	31
8.6.2.1.7 Study Results.....	32
8.6.2.1.7.1 Enrollment and Description of Patients Enrolled in the Study.....	32
8.6.2.1.7.2 Patient Diagnoses and Complicating Factors at Entry.....	34
8.6.2.1.7.3 Patient Disposition.....	36
8.6.2.1.8 Applicant Analyses.....	38
8.6.2.1.8.1 Primary Analyses.....	38
8.6.2.1.8.2 Additional Analyses.....	40

8.6.2.1.9. FDA Analyses.....	41
8.6.2.2 Safety Assessment.....	42
8.6.2.2.1 Extent of Drug Exposure.....	42
8.6.2.2.2 Adverse Events.....	43
8.6.2.2.2.1 All Causalities.....	43
8.6.2.2.2.2 Treatment Related.....	44
8.6.2.2.2.3 Serious Adverse Events.....	46
8.6.2.2.2.4 Severe and Life-threatening Events.....	48
8.6.2.2.2.5 Discontinuation from Studies.....	48
8.6.2.2.2.5.2 Discontinuations Due to Laboratory Abnormalities.....	49
8.6.2.2.2.6 Assessment of Drug Relationship for Selected Adverse Events.....	50
8.6.2.2.2.6.1 Hepatobiliary System Abnormalities.....	50
8.6.2.2.2.6.2 Pancreatic Enzyme Abnormalities.....	50
8.6.2.2.2.7 Mortality Experience.....	51
8.6.3 FDA Summary.....	52
8.6.3.1 Efficacy Summary for this Indication.....	52
8.6.3.2 Safety Summary for this Indication.....	52
8.6.3.2.1 Extent of Drug Exposure in this Indication.....	52
8.6.3.2.2 Summary of Adverse Events.....	53
8.6.3.2.2.1 All Causalities.....	53
8.6.3.2.2.2 Causally-Related.....	55
8.6.3.2.2.3 Serious Adverse Events.....	57
8.6.3.2.2.4 Severe or Life-Threatening Adverse Events.....	57
8.6.3.2.3 Discontinuation from Clinical Studies.....	57
8.6.3.2.3.1 Discontinuation from Clinical Studies due to Adverse Events.....	57
8.6.3.2.3.2 Discontinuation from Clinical Studies due to Abnormal Laboratory Values.....	57
8.6.3.2.4 Hepatobiliary Abnormalities.....	57
8.6.3.2.5 Pancreatic Enzyme Abnormalities.....	57
8.6.4 Special Populations.....	58
8.6.4.1 Gender, Age, and Ethnic Group.....	58
8.6.4.2 Pediatric Database.....	58
8.6.5 Regulatory Recommendations.....	58
8.6.6 Label Review.....	58
8.6.7 Phase IV Commitments.....	59
Appendix A.....	62
Appendix B – List of Investigators (Study AI420-031).....	64
Appendix C – Adverse Clinical Events of All Causes, All Treated Patients (Study AI420-031).....	66
Appendix D - List of Investigators (Study AI420-011).....	68
Appendix E - Adverse Clinical Events of All Causes, All Treated Patients (Study AI420-011).....	69

## Executive Summary

### Background

Bristol-Myers Squibb has submitted a New Drug Application (NDA) 21-061 for seven indications. One of the indications, and the subject of this review, is for the treatment of complicated urinary tract infections and pyelonephritis. The proposed dose is 400 mg per day, for 7 to 10 days; following is the indication as it appears in the proposed label:

“Complicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, or *Enterobacter* spp.

Pyelonephritis caused by *Escherichia coli*.”

Appendix A contains a list of the quinolone products currently approved for this indication in the United States. It is noted that the ciprofloxacin label does not make a distinction between complicated or uncomplicated urinary tract infections. However, the section on Dosage and Administration indicates that complicated infections should be treated with 500 mg every 12 hours. This was the ciprofloxacin regimen that was utilized in the clinical trials.

### Clinical Studies

The clinical data in the applicant's NDA submission for this indication were derived from two clinical trials. They were multicenter, randomized, double-blind active control trials. There were a total of 70 centers recruited, of which 59 were able to enroll patients. Study AI420-031 was conducted entirely in the United States; Study AI420-011 was predominantly conducted in the United States, however it did contain 5 Canadian sites. Appendixes B and D list the centers involved. The table below outlines the clinical trials:

Study Number	Study Design	Start - Completion Dates	Number of Subjects	Age Range	Dose	Duration of Treatment
AI420-031	Randomized, double-blind, multi-center, Phase III study	20 August 1997 – 9 July 1998	376 enrolled; 372 received at least one dose of therapy	18-90 years	Daily doses of either 400 mg of gatifloxacin, or 500 mg of ciprofloxacin twice a day	7 to 10 days
AI420-011	Randomized, double-blind, multi-center, Phase III study	27 July 1997 – 3 June 1998	354 enrolled; 350 received at least one dose of therapy	18-90 years	Daily doses of either 400 mg of gatifloxacin, or 500 mg of ciprofloxacin twice a day	7 to 10 days

*Efficacy*

In the microbiologically evaluable population, the applicant reported a response rate that was equivalent to the comparator.

	Response/Number of patients (%)		
	Gatifloxacin	Ciprofloxacin	95% Confidence Interval of the Difference
<b>Clinically eligible patients</b>	172/260 (68)	173/264 (66)	-6.1, +10.1
Complicated UTI	147/221 (67)	149/222 (66)	
Pyelonephritis	29/39 (74)	27/42 (64)	
<b>Microbiologically evaluable</b>	155/177 (88)	157/189 (83)	-4.5, +14.2
Complicated UTI	128/147 (87)	132/161 (82)	
Pyelonephritis	27/30 (90)	25/28 (89)	
<b>Sustained Eradication</b>	102/132 (77)	93/129 (72)	-5.5, +15.5
Complicated UTI	82/106 (77)	75/106 (71)	
Pyelonephritis	20/26 (77)	18/23 (78)	

Adapted from Table 7.10 (ISSE, p. 340)

Additional analyses by Dr. Silliman to assess the strength of the data included evaluation of the response rates based on the patient populations, site, and diagnoses. The analyses helped to confirm that the data submitted appeared to be robust, and support the applicant's claim of comparable efficacy to ciprofloxacin in this indication.

The microbiological data submitted by the applicant however, was not sufficient to support their claim of efficacy for all of the pathogens that were listed in the proposed label.

*Safety*

More than half of the patients that took study drug experienced an adverse event in both treatment groups. Overall, there were more adverse events reported in the gatifloxacin treatment group than in the ciprofloxacin treatment group. The most common were gastrointestinal related – nausea and vomiting, followed by headaches and dizziness. Most of the drug related adverse events were mild to moderate in severity (Grade I to Grade II).

There were three deaths between the two studies; all were assessed as being unrelated to study drug treatment by the clinical investigators. Review of the case report forms did not yield any additional information to warrant changing the investigator's assessment.

*Special Populations**Efficacy*

There were no differences observed in the efficacy rates between the treatment groups with respect to gender, age, or ethnic group.

**Safety**

In Study AI 420-031, there were no differences observed in the incidence of adverse events or laboratory abnormalities with respect to race or gender. More adverse events were observed in the older age groups for both treatment arms. This is not unexpected since older patients are more likely to have complicated medical histories and are more likely to be on multiple medications. Nevertheless, more events were observed in the gatifloxacin treatment arm than in the ciprofloxacin treatment arm. The significance of this finding is presently unknown.

In Study AI420-011, there were no differences observed in the incidence of adverse events or laboratory abnormalities with respect to race or age. There was a greater number of females with events in the gatifloxacin treatment group, but this was mirrored in the ciprofloxacin treatment group.

**Recommendation**

The medical officer recommendations for gatifloxacin regarding complicated the indications of urinary tract infection and pyelonephritis are:

1. Approval of gatifloxacin for the indication of treatment of complicated urinary tract infections (UTI) and pyelonephritis.
2. The label should indicate the pathogens for which the applicant was able to provide sufficient data to support their claims of efficacy.

The portion of the label for this indication should be amended as follows:

Gatifloxacin is indicated for the treatment of "...complicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*.

Pyelonephritis caused by *Escherichia coli*."

APPEARS THIS WAY  
ON ORIGINAL

### Review Team

Regulatory Project Management Officer:	Brenda Atkins, B.S. Dolores Bernato,
Chemistry Reviewer:	John Smith, Ph.D.
Microbiology Reviewer:	Sousan Altaie, Ph.D. Peter Dionne, Ph.D.
Pharmacokinetics/Biopharmaceutics Reviewer:	Kathleen Uhl, Ph.D. Philip Colangelo, Ph.D.
Pharmacotoxicologist Reviewer:	Amy Ellis, Ph.D.
Biometrics Reviewer:	Nancy Silliman, Ph.D.
Medical	
Medical Reviewer:	R. Roca, M.D.
Lead Medical Reviewer:	J. Korvick, M.D., M.P.H.
Medical Team Leader:	M. Cavaille-Coll, M.D., Ph. D.

**APPEARS THIS WAY  
ON ORIGINAL**

## 8.6.1 Protocol AI420-031: A Randomized, Double-Blind, Multicenter, Phase II/III Comparison of Gatifloxacin to Ciprofloxacin in the Treatment of Complicated Urinary Tract Infection and Pyelonephritis.

### 8.6.1.1 Efficacy Evaluation

#### 8.6.1.1.1 Study Design and Objectives

The study was a randomized, double-blind outpatient study. Forty-three centers were recruited in the United States; thirty-four centers enrolled patients. Appendix B is a listing of the clinical investigators involved in the study, reproduced from the applicant's Study Report (Table 4, p. 26).

Patients were randomized to gatifloxacin, 400 mg daily, or ciprofloxacin, 500 mg, every 12 hours. The duration of treatment was 7 to 10 days. In order to maintain the double blind, a double dummy technique was employed.

There were three objectives in this study:

1. Assess the microbiological efficacy of gatifloxacin at a dose of 400 mg, orally, once a day, for 7 to 10 days, in the treatment of complicated urinary tract infection and pyelonephritis.
2. Evaluate the safety profile of gatifloxacin in the above-mentioned regimen, in this patient population.
3. Compare the safety and efficacy of the above-mentioned regimen to a standard regimen of ciprofloxacin, 500 mg twice daily, for 7 to 10 days, in this patient population.

#### Reviewer's Comment

*Ciprofloxacin's labeled indications include treatment of urinary tract infections due to the following organisms: Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rergeri, Morganella morgagni, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis, or Enterococcus faecalis.*

*The Indications and Usage section of the label does not make a distinction between complicated or uncomplicated urinary tract infections, however, the section on Dosage and Administration indicates that complicated infections should be treated with 500 mg every 12 hours. Therefore, the regimen of ciprofloxacin chosen by the sponsor is an appropriate comparator.*

#### 8.6.1.1.2 Eligibility Criteria

##### *Inclusion Criteria*

Male and female patients were eligible if they were older than 18 years of age, able to give consent, and had presumptive evidence of a complicated urinary tract infection (UTI) or pyelonephritis. Female subjects were to have a negative pregnancy within 48 hours of

initiating therapy, and commitment to use effective birth control until the Day +5 to Day +9 post-treatment visit.

Complicated UTI was defined as:

1. One or more of the following symptoms

- *Dysuria*
- *Frequency*
- *Flank pain*
- *Urgency*
- *Suprapubic pain*
- *Costovertebral angle tenderness*
- *Clinical evidence of fever ( $>38^{\circ}\text{C}$  or  $100.4^{\circ}\text{F}$ ), with or without chills*

2. Presence of one or more of the following factors:

- Indwelling catheter or intermittent catheterization
- Impaired bladder emptying
- Obstructive uropathy due to bladder outlet obstruction, a calculus, or other causes
- Vesicourethral reflux or other urologic abnormalities, including surgically created ileal loops
- Renal transplantation

3. Documented pyuria, by one of the following methods:

- $\geq 10$  WBC/mm<sup>3</sup> in an unspun urine specimen
- a dipstick test positive for leukocyte esterase
- $\geq 10$  WBC/high power field (hpf) of resuspended, unstained urine sediment

Pyelonephritis was defined as:

1. Clinical evidence of fever ( $>38^{\circ}\text{C}$  or  $100.4^{\circ}\text{F}$ ) within 24 hours of enrollment, without or with chills, and flank pain (or equivalent back pain)
2. Documented pyuria by one of the following methods:
  - $\geq 10$  WBC/mm<sup>3</sup> in an unspun urine specimen
  - a dipstick test positive for leukocyte esterase
  - $\geq 10$  WBC/hpf of resuspended, unstained urine sediment
3. No history or current evidence of urologic abnormalities

#### *Exclusion Criteria*

Patients would be ineligible if there was any evidence of the following

1. Received any antibiotic therapy with documented activity against the pathogen within the 3-day period prior to randomization or likelihood of receiving other presumably effective systemic antibiotics during participation in the study.
2. Current clinically significant hepatic disease (ALT and/or AST and/or total bilirubin  $\geq 3$  times the upper limit of normal).
3. Known renal insufficiency (serum creatinine  $\geq 1.5$  mg/dL or requiring renal dialysis).
4. Evidence of active epididymitis or prostatitis.
5. Pregnancy or lactation.
6. History of serious hypersensitivity reaction to any fluoroquinolone compound.
7. Previous treatment with gatifloxacin in any clinical trial.

8. Malabsorption syndromes or other gastrointestinal disturbances that could affect drug absorption.
9. Diseases which, in the opinion of the investigator, might have a bearing on the outcome of the study.

Reviewer's Comments

*Sixteen patients had deviations from the enrollment criteria. They are summarized below, in a table adapted from Table 7.3 in the applicant's Study Report (p. 62).*

Protocol Violations of Enrollment Criteria (Study AJ420-031)

Violation	Number of Patients		
	Gatifloxacin N = 190	Ciprofloxacin N = 186	Total N = 376
No complicating factors	6	4	10
Did not have all of required signs/symptoms	2	3	5
Did not have pyuria	0	1	1
TOTAL	8	8	16

*Of the 10 patients that were ineligible because they did not have any complicating factors, 4 were from one center (Patients #041-00468, #041-00521, #041-0522, and #041-0523). Two had been assigned to gatifloxacin and the other two to ciprofloxacin. The remaining six patients (4 gatifloxacin patients, 2 ciprofloxacin patients) were from different centers.*

*The two gatifloxacin patients that were ineligible because they did not have all the required signs and symptoms (Patients #041-0466, and #041-0467) also came from the same clinical site as the patients that were ineligible because they lacked complicating factors. The ciprofloxacin patients were from different centers.*

*Although it is disturbing that many of the patients with enrollment criteria violations were from one clinical center, it is important to note that none of these patients were considered microbiologically evaluable. Therefore, none of these patients was included in the primary efficacy analyses.*

### 8.6.1.1.3 Study Drugs and Randomization Methods

The applicant used a dynamic balancing algorithm in their randomization system, which was intended to minimize any imbalance in the treatment arms within each site, within each clinical diagnosis, and for the entire clinical study.

Since the study utilized a double-dummy design, each patient received a blister card containing 10 tablets (gatifloxacin or placebo) and 40 capsules (ciprofloxacin or placebo).

The actual content of the study drug blister card depended on the treatment group that the patient was assigned to.

**Reviewer's Comments**

*Please refer to Dr. Nancy Silliman's review for details about the implications of this randomization method. In brief, Dr. Silliman notes this randomization method could be useful when there are large number of covariates that are to be balanced at the randomization stage. However, Dr. Silliman notes that there is currently no known way to extend this type of analysis to an active-controlled trial with binary outcome data.*

*Dr. Silliman felt that the efficacy results observed were such that it was unlikely that the conclusions would change if an analysis was performed that would account for the dynamic randomization used.*

**8.6.1.1.4 Study Endpoints**

The primary efficacy analysis was performed on the patients' bacteriologic response data. The proportion of patients with complete eradication of pathogens was determined in each treatment arm. The difference between gatifloxacin and ciprofloxacin and their associated 95% confidence intervals were computed using exact method (StatXact®) when feasible, otherwise a binomial distribution was used.

There were four study populations of interest:

1. **All Treated Patients:** All patients who were known to have received at least one dose of study drug.

2. **Eligible Patients:** All treated patients that had:

- Documented pyuria:

leukocyte esterase (trace or more), *or*  
microscopic WBC ( $\geq 5$ /high power field) *or*  
quantitative WBC from unspun specimen ( $\geq 10$  WBC/mm<sup>3</sup>)

- If patient was enrolled with diagnosis of complicated UTI, then at least one of the following signs/symptoms need to present at the pre-treatment visit:

- Dysuria
- Urinary urgency
- Urinary frequency
- Suprapubic pain
- Fever
- Costovertebral angle pain tenderness

- If patient was enrolled with diagnosis of pyelonephritis, then both of the following had to be present:

- Fever ( $>38^{\circ}\text{C}$  or  $100.4^{\circ}\text{F}$ ) with or without chills within 24 hours of entry
- Flank pain or clinically equivalent back pain

- At least one of the following complicating factors:

- Indwelling catheter or intermittent catheterization
- Impaired bladder emptying