Risk Factors Associated with Acute Pelvic Infection: modified from page 32 of the study report.

Among clinically evaluable subjects, the distribution of types of infection was similar between the two treatment groups. The majority of subjects in the alatrofloxacin/trovafloxacin group and the cefoxitin/amoxicillin/clavulanic acid group had endomyometritis (76% and 80%, respectively) present at baseline. In addition, the mean body mass index (30 kg/m^2) was the same for both treatment groups.

Of the clinically evaluable subjects, 50 in the alatrofloxacin/trovafloxacin group (47%) and 58 in the cefoxitin/amoxicillin/clavulanic acid group (49%) had at least one risk factor associated with treatment failure present at baseline. Subjects in the alatrofloxacin/trovafloxacin and cefoxitin/amoxicillin / clavulanic acid groups were comparable with respect to the incidence of risk factors, which included presence of diabetes, no health insurance, and delivery by cesarean section. Similar results were noted for clinically intent-to-treat subjects.

A summary of type of infection and risk factors associated with treatment failure for clinically evaluable subjects is presented by treatment group in the following applicant table, copied from page 33 of the study report.

Table C. Summary of Type of Infection and Risk Factors Associated With Treatment Failure
Clinically Evaluable Subjects according to Applicant

	Alatrofloxacin ⇒ Trovafloxacin		Cefoxitin ⇒ Amoxicillin/Clavulanic Acid	
	Number and Percentage (%) of Subjects			
Type of Infection	**(N=107)**	(100%)	**(N=119)**	(100%)
Endomyometritis	81	(76%)	95	(80%)
Parametritis	13	(12%)	10	(8%)
Phlegmon	1	(<1%)	0	
Pelvic Abscess	1	(<1%)	1	(<1%)
Post-Hysterectomy Pelvic Infection	5	(5%)	6	(5%)
Cuff Cellulitis	4	(4%)	5	(4%)
Septic Incomplete Abortion[a]	5	(5%)	8	(7%)
Other	7	(7%)	4	(3%)
Risk Factors For Treatment Failure[b]				
Number of Subjects with At Least One Risk Factor	50	(47%)	58	(49%)
Diabetes Present	6	(6%)	7	(6%)
Health Insurance None	8	(7%)	11	(9%)
Type of Delivery Cesarean	47	(44%)	48	(40%)

a Septic incomplete abortion combines spontaneous, elective, and self-induced abortions. **Ref.: Table 2.3.1**
b Counts may not add to number of subjects because subjects may fall into more than one category.

MO Comment: Sponsor Table C. was labeled as factors associated with treatment failure. Diabetes, (lack of) health insurance, and type of delivery are predisposing factors for developing an infection, as well as for treatment failure. The distribution of these risk factors was numerically equal between the two arms of the study.

Several major risk factors (such as prolonged ROM, prolonged labor, number of internal exams, anemia, time in surgery, and emergent Cesarean as opposed to elective scheduled Cesarean), that are also associated with both developing an infection and treatment failure were not included in the study report, because they were not part of the study protocol.

Concomitant Medications, including Antimicrobials: modified from page 34 of study report.

99% of patients in both groups received concomitant medications during study therapy. Most commonly used were analgesics, vitamins, electrolyte and water replacement, laxatives, iron-replacement, and drugs prescribed for gout and rheumatic diseases. During the study, 79 subjects in the trovafloxacin group and 60 subjects in the control arm received antibiotics other than the study antibiotics for the following reasons:

1. inadequate response (i.e., clinical failure): 10/160 (6.3%) Trovan® and 17/157 (10.8%) control arm
2. early discontinuation due to side effects: 20/160 (12.5%) Trovan® and 3/157 (1.9%) control arm
3. other infections or other reasons: 49/160 (30.6%) Trovan® and 40/157 (25.5%) control arm

MO Comment: All patients with inadequate response were carried forward as failures.

Study Discontinuations

Of the 160 Trovan® and 157 control arm subjects, 47 (29.4%) and 29 (18.5%), respectively, were prematurely discontinued from treatment as summarized in the following table copied from the study report:

Table B. Summary of Premature Discontinuations From Treatment (All-Treated Subjects per Sponsor)

	Alatrofloxacin ↓ Trovafloxacin (N=160)		Cefoxitin ↓ Amoxicillin/Clavulanic Acid (N=157)	
	Number and Percentage (%) of Subjects			
Total Discontinued	**47**	**(29%)**	**29**	**(18%)**
Discontinuations Related to Study Drug:	28	(18%)	16	(10%)
Adverse Event*	**21**	**(13%)**	**1**	**(<1%)**
Insufficient Response*	**7**	**(4%)**	**15**	**(10%)**
Discontinuations Unrelated to Study Drug:	19	(12%)	13	(8%)
Adverse Event	6	(4%)	4	(3%)
Did Not Meet Randomization Criteria	0		1	(<1%)
Lost to Follow-Up	4	(3%)	3	(2%)
Other	6	(4%)	0	
Protocol Violation	1	(<1%)	0	
Withdrawn Consent	2	(1%)	5	(3%)
Ref.: Table 4.1				

***Bolded by MO**

MO Comment: Most notable from Sponsor Table B. was the high percentage of Trovan® subjects (29%) who discontinued treatment as compared to those in the control arm (18%). There was a striking difference in the adverse event category (21 Trovan® versus 1 control arm). The next most notable difference was with the insufficient response in 15 control arm subjects versus 7 Trovan® subjects.

Further analysis of the 21 Trovan® patients who were discontinued prematurely related to an adverse event due to the study drug is found on page 42 of this report.

Evaluability Changes by MO: See Tables 144.2 and 144.3 below created by MO analysis and data.

Table 144.2
EVALUABILITY Changes* by Patient, as per the MO

PID	Sponsor Status	MO Change	MO Reason	MO COMMENT
52380566	Evaluable	to Non	Cannot clearly tell UTI from PPE symptoms.	Postpartum; very mild Sx/Sn; mixed urine and endometrial cultures.
56010003	Evaluable	to Non	Insufficient Rx.	Received < 3 days Rx.
57500279	Evaluable	to Non	Insufficient Rx.	Received only 9 doses of control drug.
57500283	Evaluable	to Non	Insufficient Rx & concomitant Rx.	PPE, C-sec: study antibiotics on days 1-3 only.
Trovan Arm 52380250, 58990025*, 59000397, 59020239, 59020241, 59110296, 63470599	Evaluable	to Non per MO criteria	The protocol allowed Rx for 4-14 days, but IDSA and MO criteria allow only 10 days .	Change from cure to Non-evaluable, because of > 10 days Rx. ***One patient (58990025) would remain a failure because of > 14 days treatment.***
Control Arm 55290090, 55290091, 56010001, 58650161, 58990026, 59000079, 59020238*, 59020240, 59020242, 59110295, 61260725,63850605	Evaluable	to Non per MO criteria	The protocol allowed Rx for 4-14 days, but IDSA and MO criteria allow only 10 days .	Change from cure to Non-evaluable, because of > 10 days Rx. ***One patient (59020238) would remain a failure because of > 14 days treatment.***
59000401	Evaluable	to Non	Insufficient Rx.	Inadequate Rx (48 hr), and inappropriate Dx (?PID or UTI?).
59000402	Evaluable	to Non	Uncertain baseline Dx endometritis and parametritis	No fever; home day 1.
60770145	Evaluable	to Non	Uncertain Dx of phlegmon.	Day 5 laparoscopy saw no infection: home next day on no Rx
63470598	Evaluable	to Non	Prior antibiotic usage.	Prior Ampi/ Unasyn x 2+ days. Home on study day 2.

MO Change from EVALUABLE to NON-Evaluable status: 25 patients + 2 failures

Table 144.3
MO Change from NON-Evaluable to EVALUABLE (EVAL) Status

PID	Sponsor Status	MO Change	Sponsor Reason for Status	MO COMMENT
58980269	Non-Eval	to EVAL	Other	Evaluable + FAILURE
58980271	Non	to EVAL	Concomitant antibiotics	Evaluable + FAILURE
61090557	Non	to EVAL	Prior antibiotic usage	Had Doxy x 6 days with a clinical failure; then entered the study. Eval + CURE.
61090511	Non	to EVAL	> 24 hr prior antibiotic therapy	Clinical failure on Ampi, Clinda and Genta. Had study Rx x 4 days. Eval + CURE.
61540364	Non	to EVAL	Prior antibiotic usage	Clinical failure on Ancef & Genta x 2 days; study Rx x 8 days. Eval+ CURE.

MO Comment: The 30 patients (listed in the 2 tables above) with a change in evaluability status by the MO came from 15 different centers. 13 of these centers had only 1 or 2 patients' status changed by the MO. The 2 remaining centers, 5900 and 5902 (both in Philadelphia, PA), had 4 and 5 patients, respectively, with changes by the MO in their evaluability status. 7 of these 9 patients were determined to be non-evaluable due to prolonged duration of therapy (> 10 days), which was allowed by protocol, but not by the MO's criteria for evaluability.

Sponsor's Efficacy Analysis:

Sponsor-Defined Clinical Response:

Sponsor-defined clinical response rates at the end of treatment and at the end of study are shown for clinically evaluable subjects in Table D. Sponsor-defined clinical success rates (cure + improvement) were comparable between the Trovan® and control treatment groups at the end of treatment (89% and 84%, respectively) and at the end of study (90% and 86%, respectively). Comparisons (95% confidence intervals) of the difference between the two treatment groups in sponsor-defined clinical success rates at the end of study supported equivalence of the two treatment regimens (Trovan® , 90%; control, 86% [Sponsor CI: -4.5%, 12.5%]).

A summary of sponsor-defined clinical response rates for clinically evaluable subjects at the end of treatment and at the end of study was presented by treatment group in the following table copied and modified from page 38 of the study report.

Table F. Summary of Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study (Sponsor Clinically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=107)		Cefoxitin ↓ Amoxicillin/ Clavulanic Acid (N=119)		Sponsor 95% CI
	Number and Percentage (%) of Subjects				
End of Treatment:					
Number of Subjects Assessed	93	(100%)	104	(100%)	
Success (Cure + Improvement)	83	(89%)	87	(84%)	(-3.9%, 15.1%)
Distribution of Clinical Response:					
Cure	73	(78%)	77	(74%)	
Improvement	10	(11%)	10	(10%)	
Failure	10	(11%)	17	(16%)	
End of Study:[a]					
Number of Subjects Assessed	107	(100%)	119	(100%)	
Success (Cure + Improvement)	96	(90%)	102	(86%)	(-4.5%, 12.5%)
Distribution of Clinical Response:					
Cure	94	(88%)	100	(84%)	
Improvement	2	(2%)	2	(2%)	
Failure	11	(10%)	17	(14%)	

CI = Confidence Interval
[a] Sponsor-defined subject clinical response at end of study is the primary endpoint.
Ref.: Table 5.1.1

For a detailed description of clinically evaluable subjects with sponsor-defined clinical failure, see Section 8.3.5 of the study report.

MO Comment: The MO applied a 95% CI with CCF (Δ=10) to the EOS results (TOC). The results were (-5.4%, 13.4%). Therefore trovafloxacin was equivalent to the approved comparator for the primary efficacy variable of clinical response.

Table 144.4
Clinical Response Rates at EOT and EOS, Clinically Evaluable Subjects as per the MO

	Alatrofloxacin ↓ Trovafloxacin (N=96)		Cefoxitin ↓ Amoxicillin/ Clavulanic Acid (N=107)		95% CI
	Number and Percentage (%) of Subjects				
End of Treatment:					
Number of Subjects Assessed	84	(100%)	91	(100%)	(-5.9%, 17.3%)[c]
Success (Cure + Improvement)	74	(88.1%)	75	(82.4%)	
Distribution of Clinical Response:					
Cure	74	(88.1%)	75	(82.4%)	
Failure	10	(11.9%)	16	(17.6%)	
End of Study:[a]					
Number of Subjects Assessed	96	(100%)	107	(100%)	(-5.2%, 15.9%)[c]
Success (Cure)	85	(88.5%)	89	(83.2%)	
Distribution of Clinical Response:					
Cure	85	(88.5%)	89	(83.2%)	
Failure	11	(11.5%)	18	(16.8%)	

CI = Confidence Interval
a MO-defined subject clinical response at end of study is the primary endpoint; MO did not request data for EOT because this was not a primary endpoint.
c per MO calculation with continuity correction factor (CCF).

MO Comment: When comparing the success (cure) rates at the primary endpoint (EOS) and at the EOT, the 95% CI with CCF (Δ = 15) showed that Trovan was equivalent to the approved comparator for the FDA evaluable population at both timepoints.

Sponsor-Defined Types of Pelvic Infections: table created by MO from sponsor provided data.

Table 144.5
Clinical Response at EOT and EOS by Type of Infection, as per the Sponsor

Sponsor Evaluable Population	Alatrofloxacin ⇒ Trovafloxacin (N=107)		Cefoxitin ⇒ Amoxicillin/Clavulanic Acid (N=119)		95% CI (Δ = 10)
	Number and Percentage (%) of Subjects				
Overall TOTALS at EOS	**114***	**(100%)**	**128***	**(100%)**	
Success (Cure + Improvement)	103	(90.3%)	110	(85.9%)	
ENDOMYOMETRITIS (EOT)					
Number of Subjects Assessed	68	(100%)	80	(100%)	(-3.9%, 17.1%) [a]
Success (Cure + Improvement)	64	(94%)	70	(87.5%)	
ENDOMYOMETRITIS (EOS)[a]					
Number of Subjects Assessed	81	(100%)	95	(100%)	(-4.9%, 13.6%)[a]
Success (Cure + Improvement)	**76**	**(93.8%)**	**85**	**(89.5%)**	
PARAMETRITIS (EOT)					
Number of Subjects Assessed	11	(100%)	8	(100%)	
Success (Cure + Improvement)	10	(90.9%)	6	(75%)	
PARAMETRITIS (EOS)					
Number of Subjects Assessed	13	(100%)	10	(100%)	
Success (Cure + Improvement)	**12**	**(92.3%)**	**8**	**(80%)**	
POST-HYST INFECTION (EOT)					
Number of Subjects Assessed	6	(100%)	10	(100%)	
Success (Cure + Improvement)	2	(33.3%)	7	(70%)	
POST-HYST INFECTION (EOS)					
Number of Subjects Assessed	6	(100%)	10	(100%)	
Success (Cure + Improvement)	**2**	**(33.3%)**	**7**	**(70%)**	
PHLEGMON/ABSCESS (EOT)					
Number of Subjects Assessed	2	(100%)	1	(100%)	
Success (Cure + Improvement)	2	(100%)	0	(0%)	
PHLEGMON/ABSCESS (EOS)					
Number of Subjects Assessed	2	(100%)	1	(100%)	
Success (Cure + Improvement)	**2**	**(100%)**	**0**	**(0%)**	
SEPTIC ABORTION (EOT)					
Number of Subjects Assessed	5	(100%)	8	(100%)	
Success (Cure + Improvement)	5	(100%)	8	(100%)	
SEPTIC ABORTION (EOS)					
Number of Subjects Assessed	5	(100%)	8	(100%)	
Success (Cure + Improvement)	**5**	**(100%)**	**8**	**(100%)**	
"OTHER" INFECTION (EOT)					
Number of Subjects Assessed	7	(100%)	4	(100%)	
Success (Cure + Improvement)	6	(85.7)	2	(50%)	
"OTHER" INFECTION (EOS)					
Number of Subjects Assessed	7	(100%)	4	(100%)	
Success (Cure + Improvement)	**6**	**(85.7)**	**2**	**(50%)**	

***the numbers total to > the number of assessable subjects because some subjects had > 1 infection listed.**
[a] per MO calculation with continuity correction factor (CCF).

MO Comment: The number trovafloxacin-treated subjects in each of the last five categories listed above was too small (from 2 to 13) to draw statistically meaningful conclusions. Therefore, only general comments were made about these categories. The 33.3% cure rate in the post-hysterectomy infections (2/6 subjects) was numerically inferior in the trovafloxacin group compared to the 62.5% (5/8) in the control arm. The Trovan® arm appeared numerically equal to the comparator for septic

abortion, and numerically superior for "parametritis" and "other " infections. No conclusions could be drawn for the category of phlegmon/abscess because of the small (3 subject) sample size.

In the control arm there are 14 more assessable subjects and each infection category had at least 8 subjects, except for abscess with 1 subject and "other" with 4 subjects. The "test of cure" visit was at the end of study (EOS), so this data was bolded by the MO.

The predominant infection in this study was postpartum endomyometritis, totaling 176/242 (72.7%) of the sponsor evaluable infections. Likewise, 15/23 patients diagnosed with parametritis and 3/11 patients with "other" infections had postpartum infections. Therefore 176+18= 194/242 (80.2%) of the evaluable patients had postpartum endomyometritis. Adding in the 8+5= 13 septic abortion subjects brings the total to **194+13= 207/242 (85.5%) of all the infections were directly related to pregnancy. Valid conclusions can be drawn only for pregnancy-related pelvic infections including endomyometritis, parametritis and septic abortion.**

Table 144.6
Clinical Response at EOT and EOS by Type of Infection, as per the MO

MO Evaluable Population	Alatrofloxacin ⇒ Trovafloxacin (N=96)		Cefoxitin ⇒ Amox/Clavulanic (N=107)		FDA 95% CI
	Number and Percentage (%) of Subjects				
Overall TOTALS at EOS	**101***	**(100%)**	**113***	**(100%)**	
Success (Cure + Improvement)	90	(89.1%)	95	(84.1%)	
ENDOMYOMETRITIS (EOT)					
Number of Subjects Assessed	62	(100%)	72	(100%)	(-4.1%, 19.0%)
Success (Cure + Improvement)	58	(93.5%)	62	(86.1%)	
ENDOMYOMETRITIS (EOS)					
Number of Subjects Assessed	73	(100%)	88	(100%)	(-3.7%, 17.3%)
Success (Cure + Improvement)	**68**	**(93.2%)**	**76**	**(86.4%)**	
PARAMETRITIS (EOT)					
Number of Subjects Assessed	10	(100%)	7	(100%)	
Success (Cure + Improvement)	9	(90%)	6	(85.7%)	
PARAMETRITIS (EOS)					
Number of Subjects Assessed	11	(100%)	8	(100%)	
Success (Cure + Improvement)	**10**	**(90.9%)**	**7**	**(87.5%)**	
POST-HYST INFECTION (EOS)					
Number of Subjects Assessed	6	(100%)	8	(100%)	
Success (Cure + Improvement)	**2**	**(33.3%)**	**5**	**(62.5%)**	
PHLEGMON/ABSCESS (EOS)					
Number of Subjects Assessed	0	(100%)	1	(100%)	
Success (Cure + Improvement)	**0**		**0**	**(0%)**	
SEPTIC ABORTION (EOS)					
Number of Subjects Assessed	5	(100%)	6	(100%)	
Success (Cure + Improvement)	**5**	**(100%)**	**6**	**(100%)**	
"OTHER" INFECTION (EOS)					
Number of Subjects Assessed	6	(100%)	2	(100%)	
Success (Cure + Improvement)	**5**	**(83.3%)**	**1**	**(50%)**	

***the numbers total to > the number of assessable subjects because some subjects had > 1 infection listed.**

MO Comment: The MO evaluable population had 28 fewer infections (242 - 214 = 28) than did the sponsor. Some subjects had > 1 infection listed, so the total number of infections was greater than the total number of assessable subjects. End of therapy (EOT) results were not provided by the sponsor for the last four categories of infection, because of the small number of infections and because the test of cure was at the EOS visit. The

interpretation of the data and the comments are the same for this Table 144.6 as for the previous Table 144.5; see MO Comments following Table 144.5 above.

Sponsor-Defined Clinical Response Versus Investigator-Defined Clinical Response: from study report.

At Day 3, clinical responses differed between the investigator and the sponsor for four subjects in the alatrofloxacin/trovafloxacin group and no subjects in the cefoxitin/amoxicillin/clavulanic acid group. At the end of treatment, clinical responses differed between the investigator and the sponsor for six subjects in the Trovan® group and for 14 subjects in the control group. At the end of study, clinical responses differed between the investigator and the sponsor for nine subjects in the Trovan® group and 12 subjects in the control group. A summary table of the differences between the investigator-defined and sponsor-defined clinical response was presented for clinically evaluable subjects in table G on page 39 of the study report.

MO Comment: The summary table included a total of 19 Trovan® patients and 26 control patients. In all 45 cases the investigator assessment was a non-failure category (improvement, cure, or not assessed) and the sponsor assessment was failure. The reason for the sponsor assessment of failure was 5 cases of treatment for > 14 days, 1 case of failure at Day 3, and 39 cases of concomitant antibiotics due to inadequate response. The MO agreed with this data and agreed to accept the sponsor-defined clinical response.

Clinically and Bacteriologically Evaluable Subjects

Sponsor-defined clinical response rates at Day 3, at the end of treatment, and at the end of study were analyzed for clinically and bacteriologically evaluable subjects. Sponsor-defined clinical success rates (cure + improvement) were comparable between the Trovan® and control treatment groups at Day 3 (92% and 87%, respectively), at the end of treatment (90% and 84%, respectively), and at the end of study (91% and 86%, respectively). See Table 5.1.3 below from the electronic submission list of tables.

Summary of Sponsor-Defined Clinical Response Rates
Day 3, at the End of Treatment, and at the End of Study
(Clinically and Bacteriologically Evaluable Subjects per Sponsor)

Sponsor Evaluable Population	Alatrofloxacin ↓ Trovafloxacin (N=88)		Cefoxitin ↓ Amoxicillin/Clavulanic (N=93)		95% CI # p-value*
	Number and Percentage (%) of Subjects				
Day 3:					
Number of Subjects Assessed	84	(100%)	89	(100%)	(-4.1%, 14.4%)
Success (Cure + Improvement)	77	(92%)	77	(87%)	0.187 *
Distribution of Clinical Response:					
Cure	26	(31%)	23	(26%)	0.298 *
Improvement	51	(61%)	54	(61%)	
Failure	7	(8%)	12	(13%)	
End of Treatment:					
Number of Subjects Assessed	77	(100%)	83	(100%)	(-5.1, 15.6)
Success (Cure + Improvement)	69	(90%)	70	(84%)	0.239 *
Distribution of Clinical Response:					
Cure	61	(79%)	62	(75%)	0.410 *
Improvement	8	(10%)	8	(10%)	
Failure	8	(10%)	13	(16%)	
End of Study:[a]					
Number of Subjects Assessed	88	(100%)	93	(100%)	(-4.4, 14.1)
Success (Cure + Improvement)	80	(91%)	80	(86%)	0.234 *
Distribution of Clinical Response:					
Cure	78	(89%)	78	(84%)	0.404 *
Improvement	2	(2%)	2	(2%)	
Failure	8	(9%)	13	(14%)	

95% CI # = Confidence interval based on normal approximation.
p-value* = Cochran-Mantel-Haenszel Test includes adjusting for center effect.
[a]Sponsor-defined subject clinical response at end of study is the primary endpoint.
Ref.: Table 5.1.3

MO Comment: The MO agreed with this analysis. For the sponsor's clinically and bacteriologically evaluable subjects, trovafloxacin was shown to be statistically-similar to the approved comparator regimen.

Table 144.7
Clinical Response at EOS
Clinically and Bacteriologically Evaluable Subjects, as per the MO

	Alatrofloxacin ↓ Trovafloxacin (N=78)		Cefoxitin ↓ Amoxicillin/Clavulanic (N=87)		95% CI #
	Number and Percentage (%) of Subjects				
End of Study:[a]					
Number of Subjects Assessed	78	(100%)	87	(100%)	
Success (Cure + Improvement)	70	(89.7%)	72	(82.8%)	(-4.6%, 18.6%)
Distribution of Clinical Response:					
Cure	70	(89.7%)	72	(82.8%)	
Failure	8	(10.3%)	15	(17.2%)	

95% CI # = per MO calculation with continuity correction factor (CCF).
[a]MO-defined subject clinical response at end of study was the primary endpoint.
Ref.: Table RA:xx- version 05DEC97 from sponsor.

MO Comment: When comparing the success (cure) rates at the primary endpoint (end of study), the 95% CI with CCF ($\delta = 15$) indicated that Trovan was statistically-similar to the approved comparator for the FDA clinically and bacteriologically evaluable population..

Clinical Response by Baseline Pathogen

Modified from page 41 of the study report: sponsor-defined clinical response rates by all baseline pathogens are presented for clinically evaluable subjects in the following table 144.8. Among clinically evaluable subjects, sponsor-defined clinical success rates were higher in subjects in the Trovan® group with baseline isolates of 26/26 *Enterococcus* sp. (100% cure) and 18/19 *Streptococcus agalactiae* (95% cure) compared to the respective cure rates of 81% and 67% in subjects with these two isolates in the control group at EOS.

Sponsor defined clinical success rates were comparable between the two treatment groups for all other baseline isolates.

Table 144.8
Clinical Response by Baseline Pathogen at EOS
(Clinically Evaluable Population as per the Sponsor)

All Baseline Bacterial Isolates	Alatro → Trova			Cefoxitin → Augmentin		
	N	Success Rate		N	Success Rate	
	#	n	n/N = %	#	n	Percent
Acinetobacter calcoaceticus	1	1	100	1	1	100
Acinetobacter calcoaceticus v. Anitratus	2	2	100	1	1	100
Acinetobacter calcoaceticus v. Lwoffi	1	1	100	0	0	--
Actinomyces meyeri	3	3	100	1	1	100
Aerococcus viridans	1	1	100	1	0	0
Alpha hemolytic streptococcus	2	2	100	6	4	67
Anaerobic gram positive coccus	1	1	100	0	0	--
Anaerobic gram positive rods	2	2	100	1	1	100
Bacteroides distasonis	1	1	100	1	1	100
Bacteroides fragilis	3	3	100	1	1	100
Bacteroides gracilis	0	0	--	1	1	100
Bacteroides melaninogenicus	2	2	100	0	0	--
Bacteroides ovatus	2	2	100	0	0	--
Bacteroides spp.	2	3	67	1	2	50
Bacteroides thetaiotaomicron	4	4	100	0	0	--
Bacteroides uniformis	2	1	50	0	0	--
Bacteroides ureolyticus	1	0	0	2	2	100
Bacteroides vulgatus	1	1	100	1	1	100
Beta hemolytic streptococcus	1	1	100	1	0	0
Beta hemolytic streptococcus group B	0	0	--	1	1	100
Beta streptococcus group A	0	0	--	1	1	100
Beta streptococcus group F	0	0	--	1	1	100
Citrobacter diversus	2	1	50	3	3	100
Citrobacter freundii	0	0	--	3	3	100
Citrobacter koseri	0	0	--	1	1	100
Citrobacter spp.	0	1	0	1	1	100
Clostridium spp.	1	1	100	0	0	---
Coagulase negative *Staphylococcus*	10	10	100	7	6	86
Corynebacterium jeikeium	1	1	100	2	1	50
Corynebacterium spp.	23	20	87	16	12	75
Coryneform organism	3	4	75	1	1	100
Eikenella corrodens	1	1	100	0	0	--
Enterobacter aerogenes	1	1	100	0	0	--
Enterobacter cloacae	2	2	100	2	0	0-
Enterococcus faecalis	29	28	97	32	29	91
Enterococcus faecium	1	0	0	0	0	--
Enterococcus spp.	26	26	100	27	22	81
Escherichia coli	12	10	83	16	16	100
Eubacterium lentum	0	0	--	1	1	100
Ewingella spp.	1	1	100	0	0	--
Fusobacterium necrophorum	3	3	100	0	0	--
Fusobacterium nucleatum	1	1	100	0	0	--
Fusobacterium spp.	4	3	75	0	0	--
Gamma hemolytic streptococcus	1	1	100	1	0	0
Gardnerella vaginalis	11	10	91	13	13	100
Gemella spp.	2	2	100	1	1	100
Gram negative anaerobic rods	3	3	100	2	2	100

All Baseline Bacterial Isolates	Alatro → Trova			Cefoxitin → Augmentin		
	N	Success Rate		N	Success Rate	
	#	n	n/N = %	#	n	Percent
Gram negative bacilli	1	1	100	1	1	100
Gram negative coccobacilli	1	1	100	0	0	--
Gram negative rods	3	3	100	2	0	0
Gram positive bacilli	0	0	--	1	1	100
Gram positive cocci	1	1	100	2	1	50
Gram positive rods	1	1	100	1	0	0
Group G beta streptococcus	0	0	--	1	0	0
Haemophilus parainfluenzae	0	0	--	1	0	0
Klebsiella pneumoniae	4	3	75	5	5	100
Lactobacillus acidophilus	1	1	100	0	0	--
Lactobacillus spp.	11	8	73	15	14	93
Micrococcus spp.	1	0	00	0	0	--
Mobiluneus spp.	2	2	100	0	0	--
Moraxella lacunata	0	0	--	1	1	100
Morganella morganii	1	1	100	0	0	---
Peptostreptococcus magnus	4	3	75	4	4	100
Peptostreptococcus prevotii	3	3	100	2	2	100
**Peptostreptococcus* spp.*	16	14	88	19	18	95
Prevotella intermedia	3	3	100	0	0	--
**Prevotella* spp.*	18	17	94	15	14	93
Propionibacterium acnes	2	1	50	0	0	---
Proteus mirabilis	3	2	67	7	6	86
Pseudomonas aeruginosa	0	0	--	3	3	100
Pseudomonas spp.	1	1	100	0	0	--
Staphylococcus aureus	5	4	80	13	10	77
Staphylococcus epidermidis	16	14	88	12	10	83
Staphylococcus haemolyticus	4	2	50	2	1	50
Staphylococcus hominis	2	2	100	4	4	100
**Staphylococcus* spp.*	3	2	67	9	7	78
Streptococcus acidominus	1	1	100	0	0	--
Streptococcus agalactiae	19	18	95	12	8	67
Streptococcus anginosus	12	12	100	6	6	100
Streptococcus bovis	1	1	100	0	0	--
Streptococcus group D (non-enterococcus)	3	3	100	2	2	100
Streptococcus intermedius	1	1	100	2	2	100
Streptococcus milleri	1	1	100	0	0	--
Streptococcus mitis	1	1	100	3	2	67
Streptococcus pyogenes	1	0	0	1	1	100
Streptococcus salivarius	0	0	--	1	1	100
Streptococcus sanguis i	1	1	100	0	0	---
Streptococcus sanguis ii	4	4	100	3	3	100
**Streptococcus* spp.*	13	13	100	13	12	92
Streptococcus viridans	5	5	100	2	2	100
Veillonella spp.	0	0	--	4	4	100

MO Comment: the long list above includes all the baseline bacteria from the study.

Table 144.9
Clinical Response by Baseline Pathogen at EOS
(Clinically Evaluable Population as per the MO)

Baseline Bacteria isolates	Alatro → Trova			Cefoxitin → Augmentin		
	N	Success Rate		N	Success Rate	
	#	n	n/N = %	#	n	n/N = %
Acinetobacter calcoaceticus	1	1	100	1	1	100
Acinetobacter calcoaceticus v. Anitratus	2	2	100	2	1	50
Acinetobacter calcoaceticus v. Lwoffi	1	1	100	0	0	--
Actinomyces meyeri	2	2	100	1	1	100
Aerococcus viridans	0	0	--	1	0	00
Bacteroides distasonis	0	0	--	1	1	100
Bacteroides fragilis	3	3	100	1	1	100
Bacteroides gracilis	0	0	--	1	1	100
Bacteroides melaninogenicus	2	2	100	0	0	--
Bacteroides ovatus	2	2	100	0	0	--
Bacteroides thetaiotaomicron	3	3	100	0	0	--
Bacteroides uniformis	2	1	50	0	0	--
Bacteroides ureolyticus	1	0	0	2	2	100
Bacteroides vulgatus	0	0	--	1	1	100
Citrobacter diversus	2	1	50	4	4	100
Citrobacter freundii	0	0	--	2	2	100
Citrobacter koseri	0	0	--	2	2	100
Coagulase negative *Staphylococcus*	9	9	100	6	5	83
Corynebacterium jeikeium	1	1	100	2	1	50
Corynebacterium spp,	20	17	85	15	9	60
Eikenella corrodens	1	1	100	0	0	--
Enterobacter aerogenes	1	1	100	0	0	--
Enterobacter cloacae	1	1	100	3	0	0
Enterococcus faecalis	26	25	96	30	26	87
Enterococcus faecium	1	0	0	0	0	--
Escherichia coli	12	10	83	15	14	93
Eubacterium lentum	0	0	--	1	1	100
Fusobacterium necrophorum	3	3	100	0	0	--
Fusobacterium nucleatum	1	1	100	0	0	--
Gardnerella vaginalis	9	8	89	10	10	100
Haemophilus parainfluenzae	0	0	--	1	0	0
Klebsiella pneumoniae	3	2	67	4	4	100
Moraxella lacunata	0	0		1	1	100
Morganella morganii	1	1	100	0	0	--
Peptostreptococcus magnus	4	3	75	3	3	100
Peptostreptococcus prevotii	3	3	100	2	2	100
Peptostreptococcus spp.	14	12	86	17	16	94
Porphyromonas gingivalis	0	0	--	1	1	100
Prevotella intermedia	3	3	100	0	0	--
Prevotella spp.	17	16	94	16	15	94
Propionibacterium acnes	2	1	50	0	0	--
Proteus marabilis	3	2	67	8	7	88
Pseudomonas aeruginosa	0	0	--	3	3	100
Staphylococcus aureus	4	3	75	12	9	75
Staphylococcus epidermidis	14	12	86	8	6	75

Baseline Bacteria isolates	Alatro → Trova			Cefoxitin → Augmentin		
	N	Success Rate		N	Success Rate	
	#	n	n/N = %	#	n	n/N = %
Staphylococcus haemolyticus	4	2	50	2	1	50
Staphylococcus hominis	2	2	100	3	3	100
Staphylococcus* spp.	3	2	67	8	4	50
Streptococcus agalactiae	14	13	93	13	9	69
Streptococcus anginosus	11	11	100	5	5	100
Streptococcus bovis	1	1	100	0	0	--
Streptococcus group D (non-enterococcus)	3	3	100	1	1	100
Streptococcus intermedius	1	1	100	2	2	100
Streptococcus milleri	1	1	100	0	0	--
Streptococcus mitis	1	1	100	3	2	67
Streptococcus pyogenes	1	0	0	1	1	100
Streptococcus sanguis i	1	1	100	0	0	--
Streptococcus sanguis ii	4	4	100	2	2	100
Streptococcus* spp.	11	11	100	13	12	92
Streptococcus viridans	4	4	100	0	0	--

MO Comment: Table 144.9 includes all speciated bacteria and selected genera (e.g., *Staphylococcus* spp.) grown from the MO's clinically and bacteriologically evaluable subjects and analyzed at the primary endpoint (EOS). Similar results were noted at Day 3 and EOT, and among clinically intent-to-treat subjects, so those results were not listed in this table or elsewhere in this MO review.

MO Comment: Based on the number of isolates, the clinical response at the end of study (EOS) as per the MO, and comparisons between the two arms of the study, the MO concluded that the following pathogens could be included in the Indications and Usage label:

1. *Enterococcus faecalis*- 25/26 (96%) success (cure) rate compared to 26/30 (87%) in the control arm.
2. *Escherichia coli*- 11/12 (92%) success rate compared to 14/15 (93%) in the control arm.
3. *Streptococcus agalactiae*- 13/14 (93%) success rate compared to 9/13 (69%) in the control arm.
4. *Streptococcus anginosus*- 11/11(100%) success rate compared to 5/5 (100%) in the control arm.

There were 3 other isolates that required further consideration:

1. *Garderella vaginalis*- This organism is commonly found in acute pelvic infections and considered by most experts to be a potential pathogen, although it is often found in the "normal" flora of the vagina. In the MO evaluable population, the cure rate in the trovafloxacin group was 8/9 (89%), compared to 10/10 in the control arm. Because there were only 9 isolates in the study group, this does not strictly meet the 1992 PTC document which stated that to include an organism in an indication, only those organisms which are generally considered pathogenic and represent at least 10% of the evaluable cases OR 10 total (whichever is higher) AND the organism's eradication rate must be clinically acceptable. The MO elected to include *Garderella vaginalis* because it is generally considered pathogenic or associated with pelvic infections, had a 89% eradication rate, and needed only one more isolate to meet both the 10% and 10 total isolate PTC guidance for being listed in the label.

2. *Prevotella* species- These anaerobes (former *Bacteroides* spp.) are also commonly found in the "normal" vaginal flora; they are definitely considered pathogenic and are commonly isolated from polymicrobial acute pelvic infections. In the MO evaluable population, there were 3 *Prevotella intermedia* and 17 *Prevotella* spp. isolates with a 19/20 (95%) cure rate. From the complicated intra-abdominal study 154-124, there were 16 *Prevotella* spp. isolates with a 12/16 (75%) cure rate. This combined data, plus the widely-accepted pathogenicity of *Prevotella* spp., warranted the inclusion of *Prevotella* spp. in the approved label.

3. *Peptostreptococcus* species- These organisms are considered pathogenic and are commonly isolated from mixed (polymicrobial) acute pelvic infections with anaerobic and aerobic bacteria. In the MO evaluable patients, there were 3 *Peptostreptococcus prevotii,* 4 *Peptostreptococcus magnus,* and 14 *Peptostreptococcus* spp. isolates with a 18/21 (86%) cure rate. From the complicated intra-abdominal study 154-124, there were 14 *Peptostreptococcus* spp. isolates with a 11/14 (79%) cure rate. This combined data, plus the widely-accepted pathogenicity of *Peptostreptococcus* spp., warranted the inclusion of *Peptostreptococcus* spp. in the approved label.

4. **In addition to the above, the sponsor requested approval for the following:** *Bacteroides fragilis, Streptococcus viridans, Bacteroides thetaiotaomicron, Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus, Enterobacter* species, *Enterococcus* species, *Corynebacterium* species, *Fusobacterium* species, *Streptococcus* species, *Bacteroides* species. These organisms or species were not considered approvable because of the low number of isolates or because they were not speciated.

Safety Results: copied from page 11 of the study report.

Number of Subjects with Adverse Events. The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation from treatment due to adverse events and clinically significant laboratory values are presented in the following table.

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values				
	Alatrofloxacin ↓ Trovafloxacin		Cefoxitin ↓ Amoxicillin/Clavulanic Acid	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	83/160	(52%)	56/157	(36%)
Treatment-Related Adverse Events	38/160	(24%)	10/157	(6%)
Discontinuations From Treatment Due to Adverse Events[a]	30/160	(19%)	9/157	(6%)
Clinically Significant Laboratory Values	103/146	(71%)	99/152	(65%)

a Twenty-one (21) and one discontinuation(s) in the alatrofloxacin/trovafloxacin and cefoxitin/amoxicillin/clavulanic acid treatment groups, respectively, were treatment-related.

Ref.: Tables 1.2, 4.1, 4.2, 6.1, 6.3, 7.1, and Appendix I, Table 3.1

MO Comment: an additional reference is Appendix V, Table 10, "Listing of All Adverse Events" from the study report. There were 21 Trovan® subjects who were "prematurely" discontinued from the study due to an AE felt to be related to the drug (see Table C. Summary of Premature Discontinuations From Treatment on page 20 of this review). In contrast, only one control arm subject was listed in this category. Approximately half of the 21 Trovan® subjects had >1 AE, e.g., rash, pruritus, and dizziness; 7/21 (33%) had 3 or more AEs listed. Four of the reactions were considered by the investigator to be severe (2 allergic reactions, 1 IV site reaction, and 1 pseudo-membranous colitis), while all the remaining ones were either mild or moderate. A large majority of subjects (17/21= 81%) received only one day of IV alatrofloxacin; 2 received two days, and 2 received three days. None of the 21 discontinued subjects received po trovafloxacin.

Adverse Events in 21 Trovan® Subjects Prematurely Discontinued from Study*			
Adverse Event (AE)	17 Subjects with 1 Day IV Rx	2 Subjects with 2 Days IV Rx	2 Subjects with 3 Days IV Rx
Allergic reaction: severe	2		
Allergic reaction: mild/moderate	2		
Pruritus	5		
Rash	5		
Dizziness	6		
Nausea and/or vomiting	3		
CV: palpitations, flushing	5		
Neuro: headache, numbness	3		
IV site reaction	3	1	1
Leg symptoms	2		
Diarrhea	1		
Pseudo-membranous colitis		1	
Peri-orbital edema			1

*MO table created from data found in 83 page Table 10 in Appendix V.

MO Comment: The above MO table lists the general types of reactions experienced by these 21 subjects. The total number of AEs is > 21 because of the fact that half the subjects had > 1 AE. As mentioned, all 21 subjects received only IV alatrofloxacin. The large majority of the AEs were judged to be mild by the site investigator, and the large majority were cleared in 24 to 48 hours. Thus, although there was a 21 Trovan® subjects "prematurely" (before 4 days of therapy) discontinued from the study, the MO did not ascertain any area or AE of particular concern.

A summary of the most commonly reported treatment-related adverse events is presented by body system in the following table copied from page 58 of study report.

Table D. Summary of the Most Commonly Reported Treatment-Related Adverse Events[a,b] by Body System (All Treated Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=160)		Cefoxitin ↓ Amoxicillin/Clavulanic Acid (N=157)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	38	(24%)	10	(6%)
BODY SYSTEM WHO Term				
APPL./INJ./INCISION/INSERTION SITE	6	(4%)	0	
Appl./Inj./Incision/Insertion Site Reaction	5	(3%)	0	
AUTONOMIC NERVOUS SYSTEM	5	(3%)	0	
Flushing	5	(3%)	0	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	14	(9%)	1	(<1%)
Dizziness	9	(6%)	1	(<1%)
Headache	4	(3%)	0	
GASTROINTESTINAL	11	(7%)	6	(4%)
Diarrhea	1	(<1%)	5	(3%)
Nausea	9	(6%)	2	(1%)
Vomiting	6	(4%)	1	(<1%)
SKIN/APPENDAGES	14	(9%)	3	(2%)
Pruritus	8	(5%)	2	(1%)
Rash	5	(3%)	2	(1%)

APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion Site
a ≥3 % of subjects in any treatment group.
b Includes data up to 7 days after last dose of active study medication.
Ref.: Tables 6.3 and 6.5

MO Comment: The most commonly (>5%) reported treatment-related AEs in the trovafloxacin group were nausea and dizziness, and in the control group was diarrhea. The data from the sponsor's overall summary of safety report showed that females aged 16-44 had the highest incidence of nausea (189/1845=10%) and dizziness (304/1845=16%) compared to other age groups and to all male groups. The acute pelvic infection study showed a much lower incidence here (6% and 6%, respectively) for both these AEs, and there was no obvious explanation from the sponsor or the MO for this finding.

Serious Adverse Events/Deaths. No subjects in either treatment group died during this study. Fifteen (15) subjects in the alatrofloxacin/trovafloxacin group and 10 subjects in the cefoxitin/amoxicillin/clavulanic acid group had serious adverse events. Two subjects in the

alatrofloxacin/trovafloxacin group had serious adverse events (acute anaphylactoid reaction and allergic reaction) that were considered by the investigator to be related to study drug. All other serious adverse events were attributed to other illnesses, the disease under study, "other" reasons, or concomitant treatment.

No subjects in either treatment group were discontinued from treatment due to laboratory abnormalities. For liver function parameters, the percentage of subjects with clinically significant abnormalities in aspartate aminotransferase (SGOT) was 2 subjects (1%) in the trovan group and 7 subjects (5%) in the control arm group. The number of subjects with clinically significant alanine aminotransferase (SGPT) values was 4 subjects (3%) in the trovan group and 6 subjects (4%) in the control group. One subject (<1%) in the control group had clinically significant total bilirubin values.

No subjects in either treatment group had clinically significant creatinine values; and 15 subjects (10%) in the trovan group and 14 subjects (9%) in the control group had clinically significant decreases in hemoglobin values.

MO Comment: The MO agreed with the above statements and did not find any areas of concern in terms of the safety or adverse events with trovafloxacin. The issues of dizziness, lightheadedness, and abnormal hepatic function are discussed in a separate MOR.

Concentration of Trovafloxacin in Breast Milk. Trovafloxacin was found in measurable concentrations up to 2.1 µg/mL in a subset population of lactating subjects. 113 breast milk samples were obtained from 14 subjects randomized to the trovan group; of these, a total of 18 samples were analyzed from 3 subjects, and the average (range) measurable concentration was 0.8 µg/mL (

MO Comment: This data clearly shows that trovafloxacin is present in the breast milk of lactating women. Because the potential for serious adverse reactions has not been studied in nursing newborns and infants from mothers taking trovafloxacin, the sponsor and MO recommended that nursing women should either discontinue nursing or discontinue taking the antibiotic.

Resistance: modified from the study report and Table 5.6.

Two (2) superinfecting pathogens (one isolate each of *S. viridans* and *Corynebacterium* sp. from abscess fluid) were isolated from one subject (<1%) in the alatrofloxacin/trovafloxacin group and seven superinfecting pathogens (one isolate of *E. cloacae* from the endometrial cavity; one isolate each of *Enterococcus* sp. *and Lactobacillus* sp. from the supravaginal space; one isolate of *E. faecalis* from supra-vaginal swabs; one isolate each of *Corynebacterium* sp., coagulase-negative *Staphylococcus*, and Gram-negative *bacilli* from surgical wound discharge; and one isolate of *Enterococcus* sp. from vaginal washout) were isolated from four subjects (3%) in the cefoxitin/amoxicillin/clavulanic acid group.

Colonizing organisms were isolated from three subjects (2%) in each treatment group.

There was no evidence for resistance.

MO Comment: The MO reviewed the study report and Table 5.6 and agreed with the sponsor.

SUMMARY and CONCLUSIONS of SPONSOR: modified from page 63-4 of the study report.

One hundred sixty-one (161) subjects were randomized to treatment with alatrofloxacin/trovafloxacin (Trovan®) and 159 subjects were randomized to treatment with cefoxitin/amoxicillin/clavulanic acid (the "control group"). Of the randomized subjects, 160 subjects in the Trovan® group and 157 subjects

in the control group received treatment; one and two enrolled subjects in the Trovan® and control groups, respectively, were randomized but did not receive active treatment. One hundred seven (107) subjects in the Trovan® group and 119 subjects in the control group were clinically evaluable; 88 subjects in the Trovan® group and 93 subjects in the control group were bacteriologically evaluable. All treated subjects were included in analysis of adverse events.

The two treatment groups were generally comparable with respect to characteristics at baseline, including diseases/syndromes at study entry and use of prior and concomitant medications.

Trovan® was statistically equivalent to the control antibiotcs for sponsor-defined clinical success (cure + improvement) rates in clinically evaluable and intent-to-treat subjects with acute pelvic infections at the end of study. Sponsor-defined clinical success rates were comparable between the two treatment groups at Day 3 and at the end of treatment for both clinically evaluable and intent-to-treat subjects.

Success rates among clinically evaluable subjects in the Trovan® and control groups were 91% and 86%, respectively, at Day 3, 89% and 84%, respectively, at the end of treatment, and 90% and 86%, respectively, at the end of study. These findings were supported by marked decreases from baseline to Day 3, to the end of treatment, and to the end of study in the presence of clinical signs and symptoms of acute pelvic infections in both treatment groups.

Among bacteriologically evaluable subjects, sponsor-defined pathogen eradication rates for *Enterococcus* spp. were higher in the Trovan® group compared to the control group at Day 3 (100% and 81%, respectively), at the end of treatment (100% and 80%, respectively), and at the end of study (100% and 81%, respectively). Sponsor-defined eradication rates for baseline pathogens of *Enterococcus faecalis*, *Peptostreptococcus* spp., *Prevotella* spp., and *Corynebacterium* spp. were comparable between the two treatment groups at all three evaluation timepoints. Similar results were observed among bacteriological intent-to-treat subjects.

Thirty subjects, (30/160, 19%) in the Trovan® group and nine subjects (9/157, 6%) in the control group were discontinued from treatment due to adverse events. Twenty-one (21) subjects in the Trovan® group and one subject in the control group were discontinued due to adverse events that were considered by the investigator to be study drug-related.

Ten (10) Trovan® subjects were discontinued due to rash and/or pruritus and eight subjects were discontinued due to headache, dizziness and/or hypoesthesia that were considered by the investigator to be treatment related. One subject in the control group was discontinued due to dizziness, nausea and vomiting that were considered by the investigator to be treatment related.

Thirty-eight (38) subjects (24%) in the Trovan® group and ten subjects (6%) in the control group reported treatment-related adverse events. The most commonly reported treatment-related adverse events were dizziness and nausea for subjects in the Trovan® group and diarrhea for subjects in the control group. Treatment-related injection site reactions were reported by 4% of subjects in the Trovan® group.

No subjects in either treatment group died during this study.

Fifteen (15) subjects in the Trovan® group and 10 in the control group had serious adverse events. With the exception of two subjects in the Trovan® group who had serious adverse events (acute anaphylactoid reaction and allergic reaction) that were considered by the investigator to be treatment related, all serious adverse events that occurred during this study were considered to be unrelated to study drug.

No subjects in either treatment group were discontinued from treatment due to laboratory abnormalities.

Clinically significant post-baseline laboratory abnormalities were observed for 71% (103/146) of subjects in the Trovan® group and 65% (99/152) of subjects in the control group. These abnormalities were observed at comparable incidence rates in both treatment groups.

MO Comment: The MO agreed with the sponsor's overall summary and conclusions. The biggest difference in the overall analysis was the fact that the MO had fewer clinically and bacteriologically evaluable patients in each arm; see Table 144.12 below.

Table 144.12

Population Data, as per the Sponsor and the MO

	SPONSOR DATA		MO DATA	
POPULATION	Trovan® Arm	Control Arm	Trovan® Arm	Control Arm
Randomized Subjects	161	159	161	159
Treated Subjects	160	157	160	157
Clinically Evaluable	107	119	96	107
Bacteriologically Evaluable	88	93	78	87
Clinical Success at EOS	96/107 (90%)	102/119 (86%)	85/96 (88.5%)	89/107 (83%)

MO Comments continued: Of clinically evaluable subjects, the MO had 11 fewer in the Trovan® and 12 fewer in the control arm primarily because 17 subjects receiving 11 to 14 days therapy were changed to non-evaluable by the MO. The MO also changed the evaluability status of 13 additional subjects as listed in Tables 144.2 and 144.3. The decrease in clinically evaluable subjects automatically decreased the number of bacteriologically evaluable subjects, because this was a subset within the clinically evaluable group. The primary efficacy endpoint was, however, clinical success at EOS, and both the sponsor and the MO showed that Trovan® was statistically comparable to the approved comparator drug regimen.

Final MO Discussion and Recommendations:

Discussion: The severity of illness of the large majority of study patients was judged by the MO to be mild to moderate based on the parameters of temperature elevations, mild severity of signs and symptoms, rapid clearing of such, WBCs and differential counts, early switches to po therapy, and early hospital discharges (120/160=75% of Trovan subjects went home by day #3; 109/160=68% of control subjects went home by day #3). It was of note that the IDSA guidelines talk about a minimum of 4 days of parenteral therapy, when 71.5% of the ITT subjects in this study were home by day 3.

84.7% of all the infections were directly related to pregnancy. Valid conclusions from this study can be drawn only for pregnancy-related pelvic infections including endomyometritis, parametritis and septic abortion.

Following the IDSA/FDA guidelines, the 154-144 study data by itself showed that trovafloxacin was effective in the treatment of pregnancy-related infections and should be approved for the following pathogens:

Enterococcus faecalis
Escherichia coli
Gardnerella vaginalis
Streptococcus agalactiae
Streptococcus anginosis

The initial MO recommendation for the approved label, based solely on data from study 154-144, the MO's analysis, and IDSA/FDA guidelines, was the following:

> **Gynecologic and pelvic infections (mild to moderate), including endomyometritis, parametritis, septic abortion, and post-partum infections** caused by *Enterococcus faecalis, Escherichia coli, Gardnerella vaginalis, Streptococcus agalactiae* and *Streptococcus anginosis.*

Because the subjects in study 154-124 (complicated intra-abdominal infections) were generally more severely ill, had mixed anaerobic and aerobic infections with identical pathogens, and also responded to comparable trovafloxacin dosing, the two reviewing MOs determined that the bacteriological data and clinical conclusions could be combined and extrapolated from the intra-abdominal study to this pelvic infection study. The accepted pathogenicity of *Prevotella* and *Peptostreptococcus* species and **the 154-144 data by itself** supported the clinical and bacteriological efficacy for approval of these two species. The additional 154-124 baseline pathogen data for *Prevotella* spp. (12/16 = 75% cure) and *Peptostreptococcus* spp.(11/14 = 79% cure) provided further support for the inclusion of these two species in the label. See Table 144.13 below for individual study and combined data.

Data from study 154-124 also supported the additional approval of *Bacteroides fragilis* and viridans group streptococci. Both are pathogens associated with acute pelvic infections, and the combined data from the two studies showed an overall cure rate of 92% (22/24) for viridans group streptococci and 85% (29/34) for *Bacteroides fragilis.* Because *Streptococcus anginosis* is a member of the viridans group, it need not be listed separately in the final label. See Table 144.13 below for the combined pathogen data.

Table 144.13
Summary of Clinical Success Rates at EOS
For the Most Frequently Isolated Baseline Pathogens (Clinically Evaluable Subjects)

	Trovan® Arm GYN Study		Control Arm GYN Study		Trovan® Arm CIAI Study		COMBINED Trovan® Data	
PATHOGEN	n/N	%	n/N	%	n/N	%	n/N	%
Gram Positive Aerobes								
Alpha-haemolytic streptococci	N.A.				8/12	67%	8/12	67%
✓ Beta-hemolytic streptococci, Gp. B (= *S. agalactiae*)	13/14	93%	9/13	69%	0/1	0%	13/15	87%
✓ Viridans group streptococci	4/4	100%	0	--	18/20	90%	22/24	92%
✓ *S. anginosus*	11/11	100%	5/5	100%	6/10	60%	17/21	81%
✓ *Streptococcus* sp.	11/11	100%	12/13	92%	26/30	87%	23/24	96%
E. faecium	0/1	0%	0	--	3/4	75%	3/5	60%
✓ *E. faecalis*	25/26	96%	26/30	87%	6/13	46%	31/39	79%
✓ *Enterococcus* sp. (sponsor population)	26/26	100%	22/27	81%	7/10	70%	33/36	92%
✓ *S. aureus*	3/4	75%	9/12	75%	8/11	73%	11/15	73%
Gram Negative Aerobes								
✓ *E. coli*	10/12	83%	14/15	93%	66/77	86%	76/89	85%
E. aerogenes.	1/1	100%	0	--	3/3	100%	4/4	100%
E. cloacae	1/1	100%	0/3	0%	5/7	71%	6/8	75%
✓ *Enterobacter* sp.	0	--	0	--	2/3	67%	2/3	67%
✓ *K. pneumoniae*	2/3	67%	4/4	100%	10/15	67%	12/18	67%
✓ *P. aeruginosa*	0/0	--	3/3	100%	14/16	88%	14/16	67%
Gardnerella vaginalis	8/9	89%	10/10	100%	N.A.		8/9	89%
Gram Positive Anaerobes								
✓ *Peptostreptococcus* sp.	12/14	86%	16/17	94%	11/14	79%	23/28	82%
Clostridium sp.	1/1	100%	0	--	4/5	80%	5/6	83%
✓ *Corynebacterium* sp.	17/20	85%	9/15	60%	3/3	100%	20/23	87%
Gram Negative Anaerobes								
Prevotella buccae	0	--	0	--	1/2	50%		
Prevotella intermedia	3/3	100%	0	--	1/1	100%		
✓ *Prevotella* sp.	16/17	94%	15/16	94%	10/13	77%	31/36	86%
✓ *B. fragilis*	3/3	100%	1/1	100%	26/31	84%	29/34	85%
✓ *B. thetaiotaomicron*	3/3	100%	0	--	11/18	61%	14/21	67%
B. uniformis	1/2	50%	0	--	5/7	71%	6/9	67%
B. vulgatus	0	--	1/1	100%	5/7	71%	5/7	71%
✓ *Bacteroides* sp.	2/3	67%	1/2	50%	7/9	78%	9/12	75%
Fusobacterium necrophorum	3/3	100%	0	--	3/3	100%	6/6	100%
Fusobacterium nucleatum	1/1	100%	0	--	1/2	50%	2/3	67%
✓ *Fusobacterium* sp. (sponsor population)	3/4	75%	0	--	6/7	86%	9/11	82%

✓ = "pathogen" requested in labeling
*Combined data sufficient to add pathogen to approved GYN list of pathogens in the final label.

During labeling negotiations with the applicant, further discussions centered on the MO's initial recommendation that the label included the qualifying words (mild to moderate) concerning the pelvic infections. Although it was true that the majority of subjects in the 154-144 study had mild to moderate pelvic infections, the severity of infection in the 154-124 CIAI study was very different. The subjects were more seriously ill with more complicated infections, had longer IV therapy, longer hospital stays, and more deaths (11 of 201 treated in the Trovan® arm in CIAI, compared to 0 of 160 treated in the Trovan® arm of the pelvic study). Hence, there was a much sicker baseline population in the complicated intra-abdominal study. As noted above, the infections in both studies were often mixed polymicrobial and involved many of the same pathogens, except *Gardnerella vaginalis*. Extrapolation of the overall CIAI clinical and bacteriological data strongly supported omitting any qualifying words from the final approved label, and the MO agreed with this after discussions with the sponsor.

FINAL MO RECOMMENDED INDICATION AND USAGE Label for Study 154-144:

TROVAN® is indicated for the treatment of **Gynecological and pelvic infections, including endomyometritis, parametritis, septic abortion and postpartum infections** caused by: *Escherichia coli, Bacteroides fragilis,* viridans group streptococci, *Enterococcus faecalis, Streptococcus agalactiae, Peptostreptococcus* species, *Prevotella* species, or *Gardnerella vaginalis.*

MO Discussion on Dosage and Administration:

The requested dosage and administration was 300 mg IV followed by 200 mg oral when the patient can tolerate po meds. The total duration of treatment requested was 7-14 days. As explained in this MOR, patients with 11-14 days of therapy were rendered non-evaluable by the MO. Six patients (6/107 = 5.6%) in the sponsor evaluable Trovan® arm received 11-14 days of therapy with a 6/6 (100%) cure rate. These 6 subjects tolerated the longer duration of therapy, did not have any significant AEs, and achieved an excellent (100%) cure rate. For this reason, the MO concluded that the safety and efficacy of Trovan® was adequately demonstrated for a total duration of treatment of 7-14 days.

FINAL MO RECOMMENDED DOSAGE AND ADMINISTRATION for Study 154-144:

The recommended dosage for Trovan® Tablets or Trovan® IV for the treatment of infections is 300 mg IV followed by 200 mg oral when the patient can tolerate po meds. Doses of Trovan® are administered once daily. Patients whose therapy is started with Trovan® IV may be switched to Trovan® Tablets when clinically indicated at the discretion of the physician. The total duration of treatment is 7-14 days.

/S/

Daniel Davis, MD, MPH
Medical Officer, HFD-590

/S/

Concurrence: HFD-590/Div. Dir./MGoldberger
HFD-590/MTL/BLeissa /S/

cc:
Orig. NDA #20-759
Orig. NDA #20-760
HFD-590 Division Files
HFD-590/Dep. Dir./RAlbrecht
HFD-590/MO/RAlivisatos
HFD-590/Pharm/AEllis
HFD-590/Biopharm/PColangelo
HFD-590/Biostat/Silliman
HFD-590/CSO/RAnderson
HFD-590/LEISSA

OCT 20 1998

MEDICAL OFFICER' S REVIEW OF NEW DRUG APPLICATIONS
NDA's 20-759 and 20-760

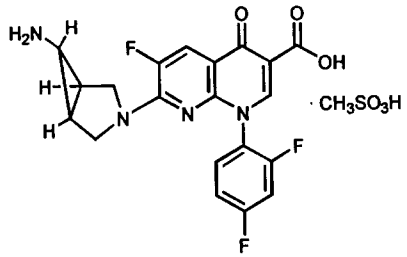
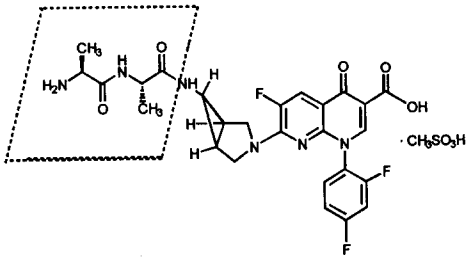
Applicant Name and Address:	Pfizer Central Research, Medical Research Laboratory Eastern Point Road Groton, Connecticut 06340
Date of Submission:	27 December 1996
CDER Stamp Date:	30 December 1996
Date Submissions Received by Reviewer:	4 June 1997
Date Review Begun:	1 July 1997
Date Review Completed:	11 December 1997
Generic Name:	Trovafloxacin mesylate(tablets) Alatrovafloxacin mesylate (solution for injection)
Proposed Trade Name:	Trovan
Chemical Name:	**Tablet**: 100 mg, 200 mg (1α, 5α, 6α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate.
	Solution: 5 mg/ml (1α, 5α, 6α)-L-alanyl-*N*-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]-L-alaninamide, monomethanesulfonate.
Chemical Structure:	
	
Molecular Formula:	$C_{20}H_{15}F_3N_4O_3 \bullet CH_3SO_3H$
	$C_{26}H_{25}F_3N_6O_5 \bullet CH_3SO_3H$
Molecular Weight:	512.46
	654.62
Pharmacologic Category:	Fluoronaphthyridone
Dosage Forms:	Tablets (NDA 20-759) Solution (NDA 20-760)
Routes of Administration:	Oral (NDA 20-759) Parenteral (NDA 20-760)

TABLE OF CONTENTS

A. General Information

1. Proposed Indication

(Verbatim from proposed labeling by applicant)

The following is the proposed indication, with regards to skin and skin structure infections, as it appears in the proposed label:

> **"SKIN AND SKIN STRUCTURE INFECTIONS** (uncomplicated and complicated, including diabetic foot infections) caused by *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Staphylococcus haemolyticus, Streptococcus agalactiae, Pseudomonas aeruginosa, Enterococcus faecalis, Escherichia coli, Proteus mirabilis, Corynebacterium* species, *Klebsiella pneumoniae, Klebsiella oxytoca, Streptococcus equisimilis, Enterobacter cloacae, Staphylococcus simulans, Staphylococcus hominis,* or *Peptostreptococcus* species."

2. Proposed Dosage and Administration

(Verbatim from proposed labeling by applicant)

Skin and Skin Structure Infections, Complicated, including diabetic foot infections
200 mg oral or 200 mg I.V. followed by 200 mg oral for 10-14 days duration

Skin and Skin Structure Infections, Uncomplicated
100 mg oral for 7-10 days duration

3. Approved agents

The following agents have been approved for treatment of skin and skin structure infections:

Skin and Skin Structures

Amoxicillin/clavulanate potassium (Augmentin ™)
caused by beta-lactamase-producing strains of *S. aureus*, *E. coli*, and *Klebsiella* spp.

Cefamandole: *S. aureus* (penicillinase- and non-penicillinase-producing), *S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae, E. coli, Enterobacter* sp, and *P. mirabilis.*

Ceftazidime: *Pseudomonas aeruginosa*; *Klebsiella* spp.; *Escherichia coli*; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*; *Enterobacter* spp.; *Serratia* spp.; *Staphylococcus aureus* (methicillin-susceptible strains); and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

Cefuroxime:
Zinacef ™ *S. aureus* (penicillinase- and non-penicillinase-producing strains), *S. pyogenes, E. coli, Klebsiella* spp., and *Enterobacter* spp.
Kefurox ™ *S. aureus* (penicillinase- and non-penicillinase-producing strains), *S. pyogenes, E. coli, Klebsiella* spp., and *Enterobacter* spp.

Cephalexin:
Keflex ™ Staphylococci and/or streptococci.
Keftab ™ *S. aureus* and/or beta-hemolytic streptococci.

Cefpodoxime: *S. aureus* (including penicillinase-producing strains) or *S. pyogenes.*

Imipenem

Intramuscular preparation: including abscesses, cellulitis, infected skin ulcers and wound infections caused by *Staphylococcus aureus* including penicillinase-producing strains; *Streptococcus pyogenes**; Group D streptococcus including *Enterococcus faecalis*; *Acinetobacter* species* including *A. calcoaceticus**; *Citrobacter* species*; *Escherichia coli; Enterobacter cloacae; Klebsiella pneumoniae**; *Pseudomonas aeruginosa** and *Bacteroides* species* including *B. fragilis**.
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Intravenous preparation: *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis, Acinetobacter* species, *Citrobacter* species, *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Morganella morganii, Proteus vulgaris, Providencia rettgeri**, *Pseudomonas aeruginosa, Serratia* species, *Peptococcus* species, *Peptostreptococcus* species, *Bacteroides* species *including B. fragilis, Fusobacterium* species*.
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Piperacillin: It is approved for treatment of skin infections due to the following organisms (however, there is no specification as to whether the infections are to be complicated or uncomplicated): *E. coli*, *Klebsiella* sp, *Serratia* sp, *Acinetobacter* sp, *Enterobacter* sp, *Pseudomonas aeruginosa*, indole-positive *Proteus* sp, *Proteus mirabilis*, *Bacteroides* sp, including *B. fragilis*, anaerobic cocci, and enterococci.

Uncomplicated

Azithromycin: *S. aureus, S. pyogenes,* or *S. agalactiae.*

Clarithromycin: *S. aureus*, and *S. pyogenes.*

Dirithromycin: *S. aureus* (methicillin-susceptible strains).

Cefaclor: *S. aureus* (methicillin-suscpetible strains).

Cefepime: *S. aureus* (methicillin-susceptible strains only) or *S. pyogenes.*

Cefprozil: *S. aureus* (including penicillinase-producing strains) and *S. pyogenes.*

Cefuroxime:
Ceftin™ *S. aureus* (including beta-lactamase-producing strains), and *S. pyogenes.*

Loracarbef: *S. aureus* (including penicillinase-producing strains) or *S. pyogenes.*

Piperacillin/Tazobactam: Piperacillin resistant, beta-lactamase producing strains of *S. aureus.*

Levofloxacin: *S. aureus* or *S. pyogenes.*

Ciprofloxacin: *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus aureus,* (methicillin susceptible), *Staphylococcus epidermidis*, or *Streptococcus pyogenes.*
(Note: Ciprofloxacin's label has a table listing dosages guidelines per indication and it has an entry under Skin and Skin Structure for "Severe/Complicated." It is believed that the use of the term "complicated" in this label is different than how it is presently intended in the Points to Consider document, as it precedes the existence of the document.)

Ofloxacin: *S. aureus, S., pyogenes,* and *P. mirabilis.*

Complicated
Piperacillin/Tazobactam: piperacillin resistant, beta- lactamase producing strains of *Staphylococcus aureus.*

4. Material Reviewed

This review was done utilizing an electronic submission provided by the applicant as a stand-alone network server. The application was on an electronic search and retrieval system which contained the results of the statistical analyses, case report forms, and submission documents (study reports, study protocols, safety reports, etc.). The documents were stored in Portable Document Format (PDF) files, as well as Microsoft Word word processing software format. The application supported full text search through a World Wide Web interface (Netscape Navigator).

5. Regulatory Background

The original IND for the trovafloxacin mesylate tablets . The IND for the intravenous formulation, alatrovafloxacin mesylate.

There were several protocol amendments submitted for each of the studies. Please refer to the NDA submission for details.

There were no Phase II/III Clinical issues that were contested regarding the protocols for the indications addressed in this review. The protocols attempted to follow the guidelines suggested by the Division's Point to Consider Document with respect to these indications. In particular, that document, which became available in 1992, specifically mentioned the following points regarding trials design for study of skin and skin structure infections:

Uncomplicated Skin and Skin Structure Infections

1. One statistically adequate and well-controlled muilticenter trial which establishes equivalency or superiority to an approved product.
2. In order for this general claim to be granted, there should be at least 20% each of the following: simple abscesses, impetiginous lesions, furuncles, and cellulitis.
3. Inclusions/exclusion criteria, evaluability criteria, and outcome definitions should be clearly stated in the protocol.
4. At least 50% of the clinically evaluable patients should be microbiologically evaluable. Of the microbiologically unevaluable, the majority should be patients with "cellulitis" as the diagnosis, where low pathogen recovery is expected. Growth of transient or resident skin flora should not be considered a microbiologically evaluable patient.
5. Analyses should include stratification by the presence or absence of therapeutic surgical interventions.
6. Analyses should establish a correlation between clinical cure and bacterial eradication. Further, the direction of the independent 95% confidence interval testing of the successful outcome rates between the overall clinically evaluable, and the clinically and bacteriologically evaluable subsets should be confirmatory.
7. Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of clinical effectiveness should be provided.

Complicated Skin and Skin Structure Infections

The recommendations were very similar to the points mentioned above, and only the differences will be noted below:

1. Diagnoses under this heading include infected ulcers, burns, and major abscesses or other skin structure infections that require significant surgical intervention in addition to antimicrobial therapy.
2. At least 70% of the clinically evaluable patients should be microbiologically evaluable.

In addition, the general discussion section of the document indicates that only those microorganisms considered to be an etiologic agent (pathogen) in at least 10%, or 10 total cases, whichever is higher, of the evaluable cases of the specific infection should be included in the INDICATIONS AND USAGE section of the product labeling. These cases should meet both the clinical and microbiological evaluability criteria. Furthermore, the eradication rate of the pathogen accomplished by the investigative agent should be clinically acceptable.

However, it may be possible to include other organisms in this section of the label, even if they number of cases do not meet the numerical threshold described above. The following criteria, reproduced from the Points to Consider document, should be met:

"(1) generally accepted as pathogens at the site of infection under investigations (however in numbers less than 10%) and the number of such infections studied in the clinical trials is consistent with the percentage of such infection due to these pathogens in the general population,

(2) for which in vitro activity is at least similar to that of other pathogens more substantially evaluated in the clinical trials,

(3) for which the mechanism(s) of resistance is similar to other pathogens more substantially evaluated in the clinical trials, and

(4) for which there are no scientific data suggesting any differences in the management of the infection due to these pathogens or in the prognosis of patients with the infection due to these pathogens."

6. Foreign Marketing Experience

These applications are the first marketing applications for alatrofloxacin and trovafloxacin. The applicant indicated that they were planning on submitting registration dossiers to the European Medicines Evaluation Agency in 1997, as well as to the Canadian Health Protection Branch.

7. Summary of Clinical Development Program

The following table is a summary of the clinical trials which support the indications cited in this review. For each indication, a pivotal study enrolling U.S. patients was performed.

Clinical Trials

Study	Countries	Pivotal vs. Supportive	Blinding	Evaluations	Controlled	Number of Patients
Complicated Skin and Skin Structure Infection						
154-131	United States	Pivotal	Blinded	Clinical/bac-teriological	Yes	287
154-132	United States, Costa Rica, Canada	Supportive	Unblinded	Clinical/bac-teriological	No	214
154-139	United Kingdom, Ireland, Italy, Spain, Belgium, United States, Germany	Supportive	Unblinded	Clinical/bac-teriological	Yes	323
Uncomplicated Skin and Skin Structure Infection						
154-130	United States, Costa Rica	Pivotal	Blinded	Clinical/bac-teriological	Yes	446
154-129	United Kingdom, Belgium, Ireland, Germany	Supportive	Blinded	Clinical	Yes	280

B. Evaluation of Efficacy and Safety by Indication and Study

1. Complicated Skin and Skin Structure Infection

1.1 Study 154-131

Title: A randomized, multicenter, investigator/subject-blind (double-blind) trial comparing intravenous alatrofloxacin (CP-116,517) followed by oral trovafloxacin (CP 99,219) and intravenous piperacillin sodium/tazobactam (Zosyn™) followed by oral cefpodoxime proxetil (Vantin™) for the treatment of complicated infections of the skin and skin structure.

Study Dates
27 June 1995 - 28 May 1996

1.1.1 Study Design and Objectives

A randomized, double-blind, double-dummy, comparative, multicenter trial. The duration of treatment was 10-14 days. The treatment groups were:

1. Alatrofloxacin, 200 mg/day, intravenously, for 2 to 7 days, followed by oral trovafloxacin, 200 mg/day, orally, for a maximum total treatment duration of 10 or 14 days.

2. Zosyn™, 3.375 g, intravenously qid, for 2 to 7 days, followed by oral Vantin™, 400 mg bid, orally, for a maximum total treatment duration of 10 or 14 days.

Medical Officer Comment
The choice of comparators were discussed with the applicant during the End of Phase II meeting, and were considered appropriate.

The safety and efficacy measurements were performed as per the schedule summarized in the table on the following page, which is adapted from Appendix A of the Study Protocol in the applicant's submission:

Visit number Study day Allowable window	1 Day 1 (~48 hours)	2 Day 4 (Day 3-7)	3 End Rx Day + 1 (Day 11-16)	4 Day 30 (Day 28-35)
Treatment period	Day 1 to Day 10 or Day 14			
Follow-up period			Day 11 or 15 to Day 35	
Informed consent	x			
Demographic information	x			
Physical examination	x			
Concomitant medication	x	x	x	x
Vital signs	x	x	x	x
Dosing record		x	x	
Clinical signs & symptoms	x	x	x	x
Bone X-ray of infected area	x[2]			
Microbiology				
exudate (or other specimen) culture & sensitivity	x	x	x	x[3]
blood culture	x	x[4]	abn	
Safety laboratory tests				
hematology	x	x	x	abn
biochemistry	x	x	x	abn
urinalysis	x		x	abn
Pregnancy test [1]	x			
Adverse events				
routine events		x	x	x
serious adverse events		x	x	x
Investigator's evaluation of clinical response[5]		x	x	x

abn = abnormal at previous visitor clinically significant adverse event
[1] to be done by local site for women of childbearing potential
[2] to be done if the skin and skin structure infection is proximal to bone to rule out contiguous osteomyelitis
[3] to be done if clinically indicated
[4] to be done in all subjects with a positive baseline blood culture and in those who discontinue because of clinical failure
[5] to be done at time of discontinuation, if applicable

The objective of the study was to assess the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin compared to intravenous piperacillin sodium/tazobactam sodium (Zosyn™) followed by oral cefpodoxime proxetil (Vantin™), in the treatment of subjects with complicated infections of the skin and skin structure. The infections were to have been of such severity that the patient was to have been assessed as initially requiring inpatient intravenous antimicrobial therapy.