Study Design: Study 154-128 was a randomized, double-blind, double-dummy, comparative, multicenter trial of alatrofloxacin (200 mg within 2 hours of surgery and infused over 1 hour), administered intravenously, versus cefotetan (2000 mg within 30-60 minutes of surgical incision and infused over 3-5 minutes), administered intravenously, for the prophylaxis of infection following elective colo-rectal surgery. (NOTE: alatrofloxacin or placebo was infused first followed by the cefotetan or placebo.)

A total of 400 subjects will be enrolled in this study. Each study site should attempt to enroll at least 15 subjects.

APPEARS THIS WAY
ON ORIGINAL

As explained in the protocol introduction to justify the use of TROVAN in this study: In 99,219 distributed well into murine gastric tissue after intravenous administration (tissue to serum ratios of 2.9 for gastric mucosa and 1.7 for gastric tissue), suggesting that 99,219 will be available for treatment of intra-abdominal infections.[1]

Noteworthy Inclusion criteria :

APPEARS THIS WAY
ON ORIGINAL

An "elective" surgery of the colon and/or rectum was defined in the protocol as : those scheduled in advance and those for which there is time to complete preoperative bowel preparation.

Noteworthy Exclusion criteria :

APPEARS THIS WAY
ON ORIGINAL

1. Subjects with any coexisting conditions that will require anti-infective therapy during the course of the study.
2. The following conditions are excluded:

APPEARS THIS WAY
ON ORIGINAL

- **emergency** colo-rectal operations (unscheduled and/or insufficient time for bowel preparation as described in this study)
- decompensated intestinal obstruction
- active inflammatory bowel disease involving the colon
- revision of a previous operation that has involved large bowel resection (e.g. revision of a colostomy and ileorectal anastomosis).

APPEARS THIS WAY
ON ORIGINAL

[1]Polzer RJ, Potchoiba MJ, Renouf DN, West M, Liston TE. Distribution of [^{14}C]CP-99,219 into gastric tissue of Long-Evans rats and Swiss-Webster mice following intravenous administration. ICAAC 1994, Orlando, FL.

3. Subjects with a bacterial infection at the time of surgery or who have been administered an antibiotic within 1 week prior to surgery.

At study entry, investigators were asked to fill out the following information in the Case Report Form for each study subject:

UNDERLYING DISEASE (check all that apply):
- ◊ Diverticulitis
- ◊ Cancer
- ◊ Polyposis
- ◊ Other (specify) _____

INDICATE TYPE OF SURGERY (check all that apply):
- ◊ Ileocecal resection
- ◊ Colic resection
- ◊ Hemicolectomy
- ◊ Colostomy
- ◊ Anterior resection of the rectum
- ◊ Total colectomy with reconstruction
- ◊ Esophagocoloplasty
- ◊ Hartman resection
- ◊ Miles amputation
- ◊ Palliative by-pass
- ◊ Polyp removal by laparotomy
- ◊ Other (specify) _____

Prior to the surgical operation, patients were administered an iso-osmotic oral bowel preparatory, such as GoLYTELY. There was no attempt by the applicant to standardize operative technique among surgeons. However, each study site was asked to standardize the skin preparation method. In addition, Investigators were asked to record whether staples or suture were used for skin closure.

As shown in the following chart, patients were assessed at entry, on each day of hospitalization, and study day 30

Schedule of Study Evaluations
(Copied from the protocol for Study 154-128)

APPEARS THIS WAY ON ORIGINAL

Study day	Pre-surgery	Start of Surgery to Hospital Discharge	Follow-up Day 30
Allowable Window	-48 hours		Day 28-35
Informed consent	X		
Demographic information	X		
Physical examination of the abdomen	X	X[2]	X
Maximum body temperature	X	X[2]	X
Vital signs	X	X[3]	X
Concomitant medication	X	X	X
Bowel preparation	X[4]		
Dosing record	X		
Safety laboratory tests			
• hematology	X	X[5]	abn[6]
• biochemistry	X	X[5]	abn[6]
• urinalysis	X	X[5]	abn[6]
• pregnancy test[7]	X		
Adverse events	X	X	X
Investigator's report of infection history/presence		X[3]	X
Health care resource utilization			X

During the surgery, No antibiotic or antiseptic peritoneal lavage is allowed.

The following post-surgical infection definitions were used:

APPEARS THIS WAY ON ORIGINAL

(A) Primary wound infections

1. Primary surgical site infection diagnosed by purulent exudate (as defined microscopically (≥ 10 PMN/hpf) or by gross inspection), cellulitis requiring antibiotics, or the need to re-open the closed wound. Infection severity will be graded as minor (erythema extends at least 2 cm from the wound in any direction, with or without purulent discharge) or major (a wound with erythema and drainage, a wound with purulent drainage, or a wound that was opened and not re-closed).
2. Intra-abdominal infection defined as an intraperitoneal or a pelvic collection of pus or gastrointestinal contents diagnosed by an imaging study, confirmed by laparotomy, spontaneous discharge (including fistulae), or percutaneous drainage.

APPEARS THIS WAY ON ORIGINAL

[2] once daily
[3] upon hospital discharge only
[4] GoLYTELY (Appendix B) or equivalent
[5] at 48 hours post-surgery and upon hospital discharge
[6] abn = abnormal at previous visit or clinically-significant adverse event
[7] to be done locally for women of child-bearing potential

The investigator should record whether an anastomotic leak or a staple/suture leak has occurred.

(B) Distant site infections

1. Pneumonia diagnosed by a new infiltrate on the chest x-ray and presence of at least one of the following signs and symptoms: fever (defined as body temperature ≥ 38 °C), leukocytosis greater than 12,500 cells/mm^3, increased sputum production with numerous leukocytes, and a predominant bacterial species.
2. Urinary tract infection diagnosed by signs and symptoms of a urinary tract infection and a urine culture with ≥ 100,000 colonies/mL (or ≥ 10,000 colonies/mL if the same bacterial species was isolated from two urine samples at different times).
3. Intravenous catheter infection defined by erythema, swelling, tenderness, and/or the presence of purulent material at the catheter site.
4. Other distant site infections which are clearly unrelated to the primary

(C) Bacteremia

Bacteremia diagnosed by presence of a spiking fever associated with a positive blood culture (at least 2 cultures) of a pathogenic organism. If, in the opinion of the investigator, the source of the bacteremia is known and not associated with the surgical procedure, then the finding of bacteremia in this subject will be considered a distant site infection. Otherwise, if the source of the bacteremia is unknown, or there is clinical suspicion that the source is related to the colo-rectal procedure, bacteremia will be considered a primary wound infection.

(D) Unexplained Fever

Subjects presenting with fever, defined as body temperatures ≥ 38 °C on at least 2 repeated times within an interval of greater than 6 hours, with no immediate explanation will be thoroughly evaluated for an infectious origin. This evaluation will include cultures and a complete physical examination. **If, by the follow-up visit (day 30), the fever remains unexplained and a systemic antibiotic for treatment of this fever was administered, the subject will be considered a failure to prophylaxis.**

Surgical prophylaxis **success** was defined as:

No signs or symptoms of infection at the surgical site (primary site infection). Infection in a distant site (e.g. urinary tract infection, respiratory tract, intravenous catheter) is **not** included as a criterion for success or failure of prophylaxis.

Surgical prophylaxis **failure** was defined as the occurrence of any of the following during the study period:

- development of infection in the primary operative incision(s).
- development of an unexplained fever requiring systemic antibiotic intervention.
- use of any systemic anti-infective drug during the 30-day post-operative period for treatment of infection (suspected or confirmed) at the primary site.
- any *unexplained* use of anti-infective agents in the 30-day period following the primary operation.
- any drainage procedure at the operative site or in and around the peritoneal cavity for infection.
- need for more than one surgical procedures. However, if the initial surgical procedure is considered inadequate by an independent reviewer, and a subsequent operation is required to correct or reverse the first surgical procedure, then the subject should be considered nonevaluable.

Nonevaluability:

Study subjects were considered nonevaluable if :

a. subjects received less than complete dose of double-blind prophylaxis for reasons other than an adverse event (e.g. administration error, pump failure). Included also will be those situations where the preoperative dose of study drug or control drug is not given, or not given prior to incision, or given not according to protocol

b. subjects received concomitant systemic antibiotic for intercurrent illness or other prophylactic use of an anti-infective agent, not allowed in the protocol (e.g. antibiotics in the lavage procedure)

c. a documented preoperative infection exists that requires antibiotic therapy following surgery (e.g. pre-operative positive urine culture)

d. subjects requiring delayed primary closure

Statistical Considerations

As stated in the protocol : Assuming the response rate of the reference drug is 90% (i.e. a failure rate of 10%), the number of subjects for each treatment group required to ensure with 80% probability that the lower limit of the 95% Confidence Interval for the true difference in efficacy is greater than -10% is 142 subjects per treatment group.

Hence, the planned enrollment of 400 subjects is sufficient to detect differences in equivalence.

Investigators for Study 154-128

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5064	Daniel Buffington, PharmD
	5133	Dennis Mikolich, MD
	5204	Stanley Klein, MD
	5229	Michael Neill, MD
	5429	John Yatsu, MD
	5486	David Borgstrom, MD
	5487	David Canal, MD
	5490	William Friend, MD
	5491	Richard Howerton, MD
	5493	Rama Jager, MD
	5495	George Mueller, MD
	5497	Joseph Wentzky, Jr., MD
	5498	Christine White, MD
	5524	C. Gene Cayten, MD
	5525	David Smith, MD
	5526	Gene Coppa, MD
	5527	John Cunningham, MD
	5529	Vinod Dhawan, MD
	5530	Philip Donahue, MD
	5532	Blaine Enderson, MD
	5533	Michael Esser, MD
	5534	Richard Greenberg, MD
	5537	Luis Jauregui, MD
	5538	Jeffrey Milsom, MD
	5542	Carey Page, MD
	5545	Robert Martindale, MD
	5550	Ronald Simon, MD
	5553	Russell Postier, MD
	5557	William Stahl, MD
	5558	Stephen Vogel, MD
	5559	Jesse Thompson, MD
	5560	Richard Wait, MD
	5563	Robert Beart, MD
		Albert Yellin, MD

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States (continued)	5599	Jefferson Stowers, MD
	5603	John Eggenberger, MD
	5608	Lawrence Nastro, MD
	5610	Jon White, MD
	5611	Paul Harrison, MD
	5612	Leon Josephs, MD
	5613	Peter Krumpe, MD
	5614	Amir Neshat, MD
	5615	Kathaleen Porter, MD
	5616	David Redfield, MD
	5617	Joseph Solomkin, MD
	5742	Yang Chen, MD
	5761	John Mazuski, MD
	5782	Robert Rosser, MD
	5910	Joseph Portoghese, MD
	5931	Carol Kemper, MD
	6005	Marvin Corman, MD
	6012	Corrado Marini, MD
	6044	Alexander Robbins, MD
	6045	Arnold Luterman, MD
	6046	E. Robert Harris, MD
	6047	Joseph Scoma, MD
	6048	Mark Sherman, MD
	6053	Ronald Nichols, MD
	6069	Judith Wolf, MD
	6090	Burke Cunha, MD
	6099	Manual Ramirez, MD
	6100	Vinod Rustgi, MD
	6107	Dana Edwards, MD
	6123	Mahmoud Kulaylat, MD
	6151	Gregory Timberlake, MD
	6170	Eduardo Gonzales, MD
	6246	Michael Hellinger, MD
	6247	Steven Schechter, MD
	6310	Anthony Netterville Brannan, MD
	6317	Susan Galandiuk, MD
	6337	Darell Covington, MD
	6344	William O'Riordan, MD
	6367	Del Dehart, MD
	6369	Renu Sinha, MD
	6379	H. Randolph Bailey, MD
	6421	Raymond Staniunas, MD
	6499	Robert Cohen, MD
Canada	5155	Sylvie Trottier, MD
	5466	Gary Garber, MD
	5826	John Bohnen, MD
	6365	Marvin Gerson, MD
	6368	David Grant, MD
	6384	Jean Ledoux, MD

Summary of Subject Disposition
Study 154-128

	Alatrofloxacin		Cefotetan	
	Number and Percentage (%) of Subjects			
Randomized Subjects	269		249	
Randomized, Not Treated[a]	13		13	
All Treated Subjects	256	(100%)	236	(100%)
Withdrawn from Treatment[b]	7	(3%)	1	(<1%)
Completed Treatment	249	(97%)	235	(>99%)
Withdrawn from Study	10	(4%)	14	(6%)
Withdrawn during Treatment	1	(<1%)	0	
Withdrawn during Follow-Up	9	(4%)	14	(6%)
Completed Study	247	(96%)	223	(94%)
Completed Treatment and Study	240	(94%)	221	(94%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	246	(91%)	236	(95%)
Clinically Evaluable[c]	161	(60%)	156	(63%)
Clinically Evaluable + Subjects Receiving Concomitant Antibiotics for Distant Site Infections	210	(78%)	204	(82%)
Assessed for Safety				
Adverse Events	256	(100%)	236	(100%)
Laboratory Tests	246	(96%)	231	(98%)

a One randomized, not treated subject in each treatment group completed study.
b Of the 7 alatrofloxacin subjects who were withdrawn from treatment, 6 completed study; the 1 cefotetan subject who was withdrawn from treatment completed study.
c Based on End of Study assessment.

Summary of Baseline Characteristics and Underlying Diseases and Syndromes at Baseline
Study 154-128

APPEARS THIS WAY ON ORIGINAL

All Treated Subjects

Baseline Characteristic	Alatrofloxacin 200 mg (N=256)		Cefotetan 2000 mg (N=236)	
	Number and Percentage (%) of Subjects			
Age (years)				
Mean	59.9		59.6	
16-44	38	(15%)	45	(19%)
45-64	116	(45%)	87	(37%)
≥65	102	(40%)	104	(44%)
COPD	27	(11%)	24	(10%)
Diabetes Mellitus	26	(10%)	34	(14%)
Hepatic Disease	10	(4%)	8	(3%)
Congestive Heart Failure	7	(3%)	13	(6%)
Impaired Renal Function	7	(3%)	7	(3%)

COPD = Chronic Obstructive Pulmonary Disease

MO Comment : Baseline populations and characteristics appear similar between the two treatment groups.

Summary of High Risk Factors for Post-Operative Infection Study 154-128				
Number and Percentage (%) of Clinically Evaluable Subjects with High Risk Factors				
	Alatrofloxacin 200 mg (N=161)		Cefotetan 2000 mg (N=156)	
Subjects with ≥1 High Risk Factor	78	(48%)	67	(43%)
High Risk Factor				
Surgery Time >215 Minutes	20	(12%)	33	(21%)
Surgical Procedure Rectal	49	(30%)	37	(24%)
Age >75 Years	21	(13%)	19	(12%)

MO Comment : Cefotetan recipients appeared more likely to undergo prolonged surgery times compared to alatrofloxacin recipients.

Summary of Other Risk Factors Study 154-128				
Number and Percentage (%) of Clinically Evaluable Subjects with Other Risk Factors				
	Alatrofloxacin 200 mg (N=161)		Cefotetan 2000 mg (N=156)	
Other Risk Factors				
Type of Closure Other Than Stitches/Staples	5	(3%)	6	(4%)
Surgical Drain Present	48	(30%)	41	(26%)
Albumin ≤2 g/dL	0		0	
Diabetes Present	17	(11%)	21	(13%)
Health Insurance None	11	(7%)	10	(6%)

MO Comment : Other risk factors appeared comparable between treatment groups.

APPEARS THIS WAY
ON ORIGINAL

PROPHYLACTIC EFFICACY:

Summary of the Applicant's Assessment of Clinical Response
Study 154-128

	Hospital Discharge		End of Study	
Clinically-Evaluable Subjects				
	Alatrofloxacin 200 mg (N=161)	Cefotetan 2000 mg (N=156)	Alatrofloxacin 200 mg (N=161)	Cefotetan 2000 mg (N=156)
	Number and Percentage (%) of Subjects			
Success[a]	127 (79%)	128 (82%)	116 (72%)	113 (72%)
Failure	34 (21%)	28 (18%)	45 (28%)	43 (28%)
Clinically-Evaluable Subjects Plus Subjects Receiving Concomitant Antibiotics for Distant Site Infection				
	Hospital Discharge		End of Study	
	Alatrofloxacin 200 mg (N=210)	Cefotetan 2000 mg (N=204)	Alatrofloxacin 200 mg (N=210)	Cefotetan 2000 mg (N=204)
Success[a]	165 (79%)	158 (77%)	152 (72%)	139 (68%)
Failure	45 (21%)	46 (23%)	58 (28%)	65 (32%)

a No signs or symptoms of a primary infection.

Corrected 95% CI for clinically-evaluable population at EOS: (-11%, 10%)

Corrected 95% CI for clinically-evaluable population including those being treated for distant site infection at EOS: (-5%, 14%).

MO Comment : Alatrofloxacin demonstrates similar prophylactic efficacy relative to cefotetan.

The IDSA Guidelines for colorectal prophylaxis imply that based on historical controls, one would expect infection rates of for parenteral cephalosporins -- which may be less effective than that for the typical oral bowel preparations

In this study, the infection rate was >20% in the TROVAN arm (albeit comparable to the cefotetan arm); 21% at hospital discharge and 28% at EOS.

The applicant was asked to provide an explanation as to why the infection rate (for both study arms) was so much higher than that of historical controls, and therefore, why this should be considered adequate in light of the lower numbers seen with historical controls.

Pfizer Response (11/25/97 e-mail): "The overall infection rate of intestinal origin (28%) was somewhat higher than that found with historical controls. Because there was no difference in failure rate between treatment groups, the patient population, study design, and risk factors for failure were likely the causes of difference in outcome from previous studies. A significant proportion of patients (86/317, 27%) underwent surgical procedures associated with a higher risk of failure, i.e., abdomino-perineal resection and low anterior resection (1-3). Other studies with a similar profile of procedures had higher than typical failure rates). There was a 60%

increase in failure rate associated with these procedures compared with the remaining patient population. A surgical time in excess of 3.5 hours has also been identified as a risk factor for failure to prophylaxis (1,2). In the current study, 53 patients (53/317, 17%) had surgical times >215 minutes; these patients had a failure rate of 49% compared with an incidence rate of 23% in patients who had surgical times ≤ 215 minutes. Thus, approximately one-half of the patients in the current study had risk factors known to be associated with failure to prophylaxis (i.e., more difficult procedures, surgical time > 215 minutes) which may inflate the overall incidence of failure compared with literature values (3).

"The protocol also adopted a conservative approach to the definition of failure to prophylaxis. Culture-negative minor wound infections or inflammatory responses that were treated with an antibiotic were considered failures. If a subject was given a concomitant antibiotic for bacteremia from an unknown source, unexplained fever, or unexplained use, then the clinical response was considered failure to prophylaxis. If a subject had no post-baseline assessments, then the clinical response was considered failure to prophylaxis. Further, a subject was a failure to prophylaxis if he/she required any unplanned drainage procedure at the operative site or in and around the peritoneal cavity, whether for infection or exploratory. Intra-abdominal infections were also considered failures to prophylaxis. The incidence rate of intra-abdominal infections in this study (4%) is consistent with previous reports (7,8) and was not different between treatment groups.

"Nonetheless, the failure rate to prophylaxis of alatrofloxacin was equivalent when compared with the accepted prophylactic regimen of intravenous cefotetan given as a single preoperative 2-gram dose."

Pfizer referenced literature:

1. Coppa GF, Eng K. Factors involved in antibiotic selection in elective colon and rectal surgery. *Surgery* 1988;104:853-858.
2. Gorbach SL. Antimicrobial prophylaxis for appendectomy and colorectal surgery. *Rev Infect Dis* 1991;13(Suppl 10):S815-S820.
3. Gorbach SL, Condon RE, Conte JE, Jr., *et al.* Evaluation of new anti-infective drugs for surgical prophylaxis. *Clin Infect Dis* 1992;15(Suppl 1):S313-S338.
4. Periti P, Mazzei T, Tonelli F. Single-dose cefotetan *vs.* multiple-dose cefoxitin - antimicrobial prophylaxis in colorectal surgery. *Dis Colon Rectum* 1989;32:121-127.
5. Periti P, Tonelli F, Mazzei T, *et al.* Antimicrobial chemoimmunoprophylaxis in colorectal surgery with cefotetan and thymostimulan: Prospective, controlled multicenter study. *J Chemother* 1993;5:37-42.
6. Walker AJ, Taylor EW, Lindsay G, *et al.* A multicentre study to compare piperacillin with the combination of netilmicin and metronidazole for prophylaxis in elective colorectal surgery undertaken in district general hospitals. *J Hosp Infect* 1988;11:340-348.
7. Hershman MJ, Swift DTR, Logan WA, *et al.* Prospective comparative study of cefotetan with piperacillin for prophylaxis against infection in elective colorectal surgery. *J R Coll Surg Edinb* 1990:35:29-32.

8. Jensen LS, Anderson A, Fristrip SC, *et al.* Comparison of one dose *versus* three doses of prophylactic antibiotics, and the influence of blood transfusion, on infectious complications in acute and elective colorectal surgery. *Br J Surg* 1990;77:513-518.

During the NDA review, Pfizer was also asked to assess prophylaxis outcome for low versus high risk subjects. On 12/11/97, Pfizer responded via e-mail with the following analysis:

Colorectal Surgical Prophylaxis Outcome (Success Rate) and Risk Factors at EOS (Clinically Evaluable)		
	Alatrofloxacin	Cefotetan
Low Risk	110/124 (89%)	107/122 (88%)
High Risk	19/32 (59%)	20/30 (67%)

APPEARS THIS WAY ON ORIGINAL

MO Comment : Although prophylaxis efficacy may be less in the high risk population, numbers are too small to conclude this.

APPEARS THIS WAY ON ORIGINAL

Summary of the Most Common Primary Wound Infections[a]
Study 154-128
(Investigator Assessment)
(Clinically Intent-to-Treat Subjects)

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

	Alatrofloxacin 200 mg (N=246)		Cefotetan 2000 mg (N=236)	
	Number and Percentage (%) of Subjects			
Hospital Discharge				
Primary Wound Infections	49	(20%)	41	(17%)
Primary Surgical Site Infection	42	(17%)	37	(16%)
Major	22	(9%)	21	(9%)
Minor	22	(9%)	14	(6%)
Wound Dehiscence	7	(3%)	12	(5%)
Intra-Abdominal Infection	5	(2%)	5	(2%)
Intraperitoneal Focus	5	(2%)	4	(2%)
Bacteremia	4	(2%)	5	(2%)
Unexplained Fever	7	(3%)	1	(<1%)
End of Study				
Primary Wound Infections	26	(11%)	30	(13%)
Primary Surgical Site Infection	22	(9%)	24	(10%)
Major	13	(5%)	12	(5%)
Minor	7	(3%)	11	(5%)
Wound Dehiscence	6	(2%)	7	(3%)
Intra-Abdominal Infection	4	(2%)	5	(2%)
Anastomotic Leak	2	(<1%)	4	(2%)

a ≥2% of subjects in either treatment group.

MO Comment : The two treatment groups appeared similar.

Summary of the Most Common Distant Site Infections[a]
Study 154-128

(Investigator Assessment)
(Clinically Intent-to-Treat Subjects)

	Alatrofloxacin 200 mg (N=246)		Cefotetan 2000 mg (N=236)	
	Number and Percentage (%) of Subjects			
Hospital Discharge				
Distant Site Infections	19	(8%)	24	(10%)
Pneumonia	5	(2%)	7	3%)
Urinary Tract Infection	11	(4%)	16	(7%)
End of Study				
Distant Site Infections	16	(7%)	12	(5%)
Urinary Tract Infection	11	(4%)	12	(5%)
Other Infection	5	(2%)	1	(<1%)

a ≥2% of subjects in either treatment group.

MO Comment : The two treatment groups appeared similar.

Summary of the Most Common Pathogens Associated with Primary and Distant Site Infections[a] Study 154-128

(Clinically Intent-to-Treat Subjects)

	Alatrofloxacin 200 mg (N=246)		Cefotetan 2000 mg (N=236)	
	Number and Percentage (%) of Subjects			
Number of Subjects with a Primary and/or Distant Site Infection and an Isolated Pathogen	93	(38%)	87	(37%)
Wound Site Pathogen				
Abdominal Wound				
E. faecalis	0		5	(2%)
Blood				
P. aeruginosa	4	(2%)	0	
Surgical Wound Discharge				
B. fragilis	5	(2%)	9	(4%)
Bacteroides sp.	3	(1%)	5	(2%)
B. thetaiotaomicron	1	(<1%)	4	(2%)
Coagulase-Negative *Staphylococcus*	8	(3%)	10	(4%)
Corynebacterium sp.	7	(3%)	3	(1%)
E. faecalis	2	(<1%)	6	(3%)
Enterococcus sp.	3	(1%)	8	(3%)
E. coli	2	(<1%)	8	(3%)
Peptostreptococcus sp.	4	(2%)	0	
P. aeruginosa	4	(2%)	4	(2%)
S. aureus	6	(2%)	2	(<1%)
S. epidermidis	6	(2%)	7	(3%)
Staphylococcus sp.	2	(<1%)	6	(3%)
Streptococcus sp.	1	(<1%)	4	(2%)
S. viridans	4	(2%)	6	(3%)
Urine				
E. faecalis	0		9	(4%)
Enterococcus sp.	6	(2%)	12	(5%)
E. coli	2	(<1%)	9	(4%)
K. pneumoniae	2	(<1%)	5	(2%)
P. aeruginosa	2	(<1%)	4	(2%)

a ≥2% of subjects in either treatment group.

BEST POSSIBLE COPY

MO Comment : For unknown reasons, more enterococcal infections (wound site and urinary tract) were seen in the cefotetan arm compared to alatrofloxacin.

Perhaps a difference in spectrum. The cephalosporin one is not very good for enterococci. It has not been shown to me that the in vitro activity is clinically useful.

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

SAFETY:

Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically-Significant Laboratory Values Study 154-128 (According to applicant)

	Alatrofloxacin 200 mg		Cefotetan 2000 mg	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	156/256	(61%)	135/236	(57%)
Treatment-Related Adverse Events	26/256	(10%)	6/236	(3%)
Discontinuations from Treatment Due to Adverse Events[a]	5/256	(2%)	0/236	
Clinically Significant Laboratory Abnormalities	191/246	(78%)	184/231	(80%)

a - All were treatment-related.

MO Comment : Approximately three-times as many treatment-related adverse events were reported with alatrofloxacin compared with cefotetan. However, all causality AEs were comparable between treatment arms.

APPEARS THIS WAY
ON ORIGINAL

A Summary of the Most Commonly Reported Adverse Events[a,b] by Body System - All Causalities Study 154-128 (All Treated Subjects)

	Alatrofloxacin 200 mg IV (N=256)		Cefotetan 2000 mg IV (N=236)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	156	(61%)	135	(57%)
BODY SYSTEM WHO Term				
APPL./INJ./INCISION/INSERTION SITE	66	(26%)	51	(22%)
Appl./Inj./Incision/Insert. Infection/Inflammation	30	(12%)	26	(11%)
Appl./Inj./Incision/Insertion Site Pain	10	(4%)	5	(2%)
Appl./Inj./Incision/Insertion Site Reaction	19	(7%)	5	(2%)
Appl./Inj./Incision/Insertion/Device Complication	20	(8%)	19	(8%)
CARDIOVASCULAR SYSTEM	29	(11%)	20	(8%)
Tachycardia	8	(3%)	4	(2%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	19	(7%)	15	(6%)
Confusion	7	(3%)	5	(2%)
Headache	8	(3%)	5	(2%)
GASTROINTESTINAL SYSTEM	49	(19%)	48	(20%)
Diarrhea	3	(1%)	6	(3%)
Ileus	7	(3%)	10	(4%)
Nausea	27	(11%)	27	(11%)
Vomiting	19	(7%)	14	(6%)
GENERAL	34	(13%)	24	(10%)
Fever	17	(7%)	13	(6%)
PSYCHIATRIC	15	(6%)	10	(4%)
Insomnia	7	(3%)	4	(2%)
RESPIRATORY SYSTEM	23	(9%)	31	(13%)
Atelectasis	7	(3%)	9	(4%)
Pneumonia	6	(2%)	6	(3%)
SKIN/APPENDAGES	24	(9%)	14	(6%)
Pruritus	13	(5%)	9	(4%)
URINARY SYSTEM	30	(12%)	38	(16%)
Urinary Retention	8	(3%)	9	(4%)
Urinary Tract Infection	11	(4%)	14	(6%)

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

MO Comment : Overall, causality safety was comparable between treatment groups. However, more insertion site reactions were reported with alatrofloxacin.

APPEARS THIS WAY
ON ORIGINAL

8.2 Study 154-146

Protocol Title: "A randomized, double-blind, multicenter trial of the efficacy and safety of a single oral dose of trovafloxacin (99,219) compared with intravenous cefoxitin for the prophylaxis of infection following elective abdominal or vaginal hysterectomy."

8.2.1 Protocol Overview:

Study Objectives: To compare the safety and efficacy of a single oral dose of trovafloxacin with a single intravenous dose of cefoxitin in the prophylaxis of post-operative infection following elective abdominal or vaginal hysterectomy.

Study Dates: 18 January 1996 - 11 June 1996

Study Design: Study 154-146 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin, administered orally, versus cefoxitin administered intravenously, for the prophylaxis of infection following elective abdominal or vaginal hysterectomy.

Pre-operative Administration:

Oral trovafloxacin or its matching placebo tablets are to be administered 45 (±15) minutes prior to the estimated time of surgical incision. Trovafloxacin should therefore not be administered less than 30 minutes, or more than 60 minutes, prior to the estimated time of the surgical procedure. Only a minimal volume of water (~50 mL) should be provided to assist administration.

Trovafloxacin will not be available to subjects at the conclusion of the study.

Cefoxitin or its matching placebo I.V. solution is to be infused over 10 (±5) minutes. Completion of the infusion should occur no earlier than 30 minutes prior to, and no later than the time of, surgical incision. While intravenous cefoxitin or its matching placebo is being injected, it is advisable to temporarily discontinue administration of any other solutions at the same site.

Second Administration Of I.V. Study Drug Regimen: Should the duration of surgery extend beyond four hours, or, if there is greater than a 1500 mL blood loss, a second dose should be provided as follows:

Placebo for cefoxitin (0.1 mL MVI in solution for injection) OR cefoxitin (2 grams in solution for injection)

Second Dose Administration:

If a second dose is indicated, cefoxitin or its matching placebo I.V. solution is to be infused over 10 (±5) minutes. The infusion should be given within 4-6 hours of the initiation of surgery. While intravenous cefoxitin or its matching placebo is being injected, it is advisable to temporarily discontinue administration of any other solutions at the same site.

Noteworthy Inclusion criteria:

Women scheduled to undergo elective abdominal or vaginal hysterectomy for non-malignant disease processes (e.g., dysplasia, abnormal bleeding, uterine prolapse, leiomyomas).

Noteworthy Exclusion criteria:

1. Subjects undergoing emergency hysterectomy and/or hysterectomy for malignant disease processes.
2. Subjects with significant gastrointestinal or other conditions which may have affected study drug absorption; known acquired immunodeficiency syndrome (AIDS); neutropenia; or immunosuppressive therapy (including treatment with >10 mg per day of prednisone); prior history of seizure or epilepsy; significant renal impairment (Cr_s >2.5 mg/dL).
3. Subjects with any coexisting condition(s) that would require anti-infective therapy during the course of the study.
4. Subjects with signs and symptoms of infection at the time of surgery or subjects who had been administered an antibiotic within 1 week prior to surgery.

At study entry, investigators were asked to fill out the following information in the Case Report Form for each study subject:

PRIMARY REASON FOR HYSTERECTOMY (check one only):

◊ Leiomyomas
◊ Endometriosis
◊ Chronic pelvic pain
◊ Cervical dysplasia
◊ Recurrent dysfunctional uterine bleeding
◊ Other (specify) _____

Definition of infections

Symptoms and physical findings of any infections found during the 30-day study period will be recorded on the case report form and cultures will be obtained as previously described. Upon verification of a positive culture in the local laboratory, all potentially pathogenic isolates will be sent to the central laboratory.

Primary infections

1. Surgical site infection (Abdominal surgical wounds only). Diagnosed as present if any one or more of the following are present:

   -purulent exudate (as defined microscopically *(≥ 10 PMN/hpf)* or by gross inspection) with or without positive culture, or

   -non-purulent drainage from the wound with a positive culture and signs/symptoms of infection at the wound site (hyperemic, hyperthermic, indurated and/or the presence of tenderness/ pain), or

   -cellulitis requiring antibiotic therapy, or

   -the need to re-open the closed wound.

2. Pelvic Cellulitis

   General findings are infection in the extraperitoneal space extending to parametrial tissue with signs and symptoms of pelvic, back, and/or lower abdominal pain and tenderness on deep palpation in the lower abdominal wall. *Vaginal cuff should be tender to palpation*. Tenderness into parametrial tissue and engorgement without masses present should be evident on bimanual examination. Purulent discharge from the vaginal incision may or may not be present. Specific criteria are as follows: a) body temperature $\geq 101^0$ F on a single occasion or $\geq 100.4^0$ F on two separate occasions at least 6 hours apart (following the initial 24 hour post-operative period) *and b) one or more of the following: tachycardia (bmp ≥ 100), leukocytosis (WBC ≥ 2 x baseline or > upper limit of normal), or left shift (≥ 10% bands).*

3. Pelvic Abscess or Infected Hematoma. Palpation of a *new* mass in the parametrial or adnexal region in addition to signs and symptoms of generalized pelvic inflammation and tenderness specified in (2) above *or, supportive imaging studies.*

4. Severity Grading For Primary Infections[8](Abdominal surgical wounds only).
   0=no erythema or discharge at surgical site
   1=cellulitis present at surgical site without purulent exudate

[8] Jensen LS, Andersen A, Fistrup SC, Holme JB, Hvid HM, Kraglund K, Rasmussen PC, Toftgaard C. Comparison of one dose *versus* three doses of prophylactic antibiotics, and the influence of blood transfusion, on infectious complications in acute and elective colorectal surgery. *Br J Surg* 1990: **77**:513-518.

2=cellulitis present at surgical site with purulent exudate
3=infection throughout surgical site or evidence of pelvic cellulitis/abcess

Distant infections

1. Pneumonia. Diagnosed by *an* infiltrate on chest x-ray and presence of at least one of the following signs and symptoms: fever (defined as body temperature ≥ 100.4^0 F following the initial 24 hour post-operative period), leukocytosis *(WBC ≥ 2 x baseline or > upper limit of normal), left shift (≥ 10% bands)*, increased sputum production with numerous leukocytes, or a predominant bacterial species on culture.
2. Urinary tract infection. Diagnosed by signs and symptoms of a urinary tract infection and a urine culture with ≥ 10^5 colonies/mL (or ≥ 10^4 colonies/mL if the same bacterial species was isolated from two urine samples at different times). Signs and symptoms of urinary tract infection include at least one of the following: dysuria, frequency, urgency or suprapubic pain.
3. Intravenous catheter infection. Diagnosed by the presence of erythema, swelling, tenderness, and/or the presence of purulent material at the catheter site.
4. Other distant site infection. Other infections with associated signs and symptoms that are not classified above and are clearly unrelated to the operative procedure. The case report form will specify the type of infection.

Febrile Morbidity

Defined as subjects presenting with fever (≥ 101°F on a single occasion or ≥ 100.4°F on two separate occasions at least 6 hours apart) following the first 24 hour post-operative period for whom their is neither clinical or microbiological evidence of infection as specified above.

Clinical Response

For both evaluable and intent-to-treat subjects, sponsor-defined subject clinical response was based primarily on the investigator's documented evidence or history of infection.

1. Success: No signs or symptoms of a primary infection. Infection in a distant site alone (e.g., urinary tract infection, respiratory tract, or intravenous catheter) was not included as a criterion for success or failure of prophylaxis.
2. Failure: If the investigator's assessment was primary site infection at any time, then the sponsor-defined subject clinical response was failure at all subsequent visits.
3. Failure: If a subject was given a concomitant antibiotic at any time for primary surgical site infection or unexplained use, then the sponsor-defined subject clinical response was failure at all subsequent assessments.
4. Failure: If a subject had no post-baseline assessment, then the sponsor-defined clinical response was failure at both the Hospital Discharge and End of Study.

5. Failure: If a subject needed any significant drainage procedure at the operative site or in and around the pelvic cavity for infection, then the sponsor-defined subject clinical response was failure at all subsequent assessments.

Statistical Considerations

As stated in the protocol: The definition of equivalence, as suggested by some regulatory agencies, is that the 95% confidence interval for the difference in response rates is within 10% when the true satisfactory response rate of the reference drug is 90% or better.

Assuming the response rate of the reference drug is 90 to 95% (i.e., a failure rate of 5 to 10%), the number of subjects for each treatment group required to ensure with 80% probability that the lower limit of the 95% confidence interval for the true difference in efficacy is greater than -10% is ; per treatment group (for 5% and 10% failure, respectively). Hence, the planned enrollment of 350 subjects is sufficient to detect differences in equivalence assuming 80% of subjects are evaluable.

Schedule of Study Evaluations
(Copied from the protocol for Study 154-146)

Study day	Pre-surgery	Start of Surgery to Hospital Discharge	Follow-up Day 30
Allowable Window	-72 hours		*Day 24-36*
Informed consent	X		
Demographic information	X		
History & Physical (including pelvic)	X		
Examination for signs and symptoms of infection with abdominal/perineal exam	X	X[a]	X
Oral body temperature	X	X[b]	X
Vital signs	X	X[b]	X
Concomitant medication	X	X	X
Dosing record	X		
Safety laboratory tests			
• hematology	X	X[c]	abn[d]
• biochemistry	X	X[c]	abn[d]
• urinalysis	X	X[c]	abn[d]
Adverse events	X	X	X
Investigator's assessment of infection		X	X
Health care resource utilization			X

[a] once daily during post-op hospital course
[b] q 4-6h
[c] at 48 hours post-op or at hospital discharge (whichever is earlier)
[d] only if clinically significant abnormality was present at time of most recent determination

Investigators for Study 154-146

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5238	Subir Roy, MD
	5601	James Mcgregor, MD
	5748	David Baker, MD
	5750	David Hemsell, MD
	5766	Sebastian Faro, MD
	5770	Joseph Pastorek, MD
	6003	John Larsen, Jr., MD
	6109	Mark Martens, MD
	6126	Todd Vanheest, MD
	6390	Lane Mercer, MD
	6470	David Godwin, MD
	6471	Stephen Gordon, MD
	6474	Maurizio Maccato, MD
	6475	Mark Pearlman, MD
	6476	Campbell Skokos, MD
	6478	David Soper, MD
	6479	Neil Wolfson, MD
	6567	Nicholas Lindberg, MD

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Summary of Subject Disposition Study 154-126

	Trovafloxacin		Cefoxitin	
	Number and Percentage (%) of Subjects			
Randomized Subjects	196		191	
Randomized, Not Treated[a]	8		16	
All Treated Subjects	188	(100%)	175	(100%)
Withdrawn from Treatment[b]	5	(3%)	0	
Completed Treatment	183	(97%)	175	(100%)
Withdrawn from Study	6	(3%)	1	(<1%)
Withdrawn during Treatment	1	(<1%)	0	
Withdrawn during Follow-Up	5	(3%)	1	(<1%)
Completed Study[c]	185	(98%)	181	(103%)[c]
Completed Treatment and Study	178	(95%)	174	(>99%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	183	(93%)	185	(97%)
Clinically Evaluable	133	(68%)	127	(66%)
Clinically Evaluable + Subjects Receiving Concomitant Antibiotics for Distant Site Infections	163	(83%)	162	(85%)
Assessed for Safety				
Adverse Events	188	(100%)	175	(100%)
Laboratory Tests	179	(95%)	172	(98%)

a Three randomized, not treated subjects in the trovafloxacin group completed study and seven randomized, not treated in the cefoxitin group completed study. No subject received placebo.
b Of the five trovafloxacin subjects who were withdrawn from treatment, four completed study.
c Includes seven subjects who were randomized but not treated and who completed study.

BEST POSSIBLE COPY

APPEARS THIS WAY ON ORIGINAL

Summary of Baseline Characteristics and Underlying Diseases and Syndromes at Baseline Study 154-146

All Treated Subjects

	Trovafloxacin 200 mg (N=188)		Cefoxitin 2000 mg IV (N=175)	
Baseline Characteristic	**Number and Percentage (%) of Subjects**			
Age (years)				
Mean	42.9		42.5	
Minimum	(b)(4)			
Maximum				
16-44	107	(57%)	103	(59%)
45-64	75	(40%)	68	(39%)
≥65	6	(3%)	4	(2%)
Anemia	40	(21%)	26	(15%)
Hypertension	39	(21%)	33	(19%)
Diabetes Mellitus	14	(7%)	13	(7%)
COPD	3	(2%)	2	(1%)
Congestive Heart Failure	1	(<1%)	1	(<1%)
Hepatic Disease	0		1	(<1%)
Impaired Renal Function	1	(<1%)	0	

COPD = Chronic Obstructive Pulmonary Disease

APPEARS THIS WAY ON ORIGINAL

Summary of High Risk Factors Study 154-146

	Trovafloxacin 200 mg (N=133)		Cefoxitin 2000 mg IV (N=127)	
Number and Percentage (%) of Clinically Evaluable Subjects with High Risk Factors				
Subjects with ≥1 High Risk Factor	89	(67%)	88	(69%)
High Risk Factor				
Abdominal Procedure	73	(55%)	73	(57%)
Age >50 Years	17	(13%)	14	(11%)

MO Comment : The two treatment arms appeared similar at baseline.

APPEARS THIS WAY
ON ORIGINAL

PROPHYLACTIC EFFICACY:

Summary of the Applicant's Assessment of Clinical Response
Study 154-146

	Hospital Discharge		End of Study	
All Clinically Evaluable Subjects				
	Trovafloxacin 200 mg (N=133)	Cefoxitin 2000 mg IV (N=127)	Trovafloxacin 200 mg (N=133)	Cefoxitin 2000 mg IV (N=127)
	Number and Percentage (%) of Subjects			
Success[a]	128 (96%)	122 (96%)	111 (84%)	117 (92%)
Failure	5 (4%)	5 (4%)	22 (16%)	10 (8%)
Clinically Evaluable Subjects: Excluding Subjects who Received BICITRA®				
	Hospital Discharge		End of Study	
	Trovafloxacin 200 mg (N=103)	Cefoxitin 2000 mg IV (N=97)	Trovafloxacin 200 mg (N=103)	Cefoxitin 2000 mg IV (N=97)
	Number and Percentage (%) of Subjects			
Success[a]	99 (96%)	93 (96%)	91 (88%)	88 (91%)
Failure	4 (4%)	4 (4%)	12 (12%)	9 (9%)
Infection types of failures			12	9
Surgical site			3	4
Pelvic cellulitis			5	3
Pelvic cellulitis, abscess or infected hematoma			2	2
Vaginal cuff infection			1	0
Missing			1	0
Subjects who failed requiring rehospitalization or prolonged hospitalization			4	5
Clinically Evaluable Subjects: Excluding Subjects who Received BICITRA® By Type of Hysterectomy				
			End of Study	
			Trovafloxacin 200 mg (N=103)	Cefoxitin 2000 mg IV (N=97)
			Number and Percentage (%) of Subjects	
Abdominal			(n=55)	(n=59)
Success[a]			48 (87%)	53 (90%)
Failure			7 (13%)	6 (10%)
Vaginal			(n=48)	(n=38)
Success[a]			43 (90%)	35 (92%)
Failure			35 (10%)	3 (8%)
Clinically Evaluable Subjects Plus Subjects Receiving Concomitant Antibiotics for Distant Site Infection: Excluding Subjects who Received BICITRA®				
	Hospital Discharge		End of Study	
	Trovafloxacin 200 mg (N=131)	Cefoxitin 2000 mg IV (N=130)	Trovafloxacin 200 mg (N=131)	Cefoxitin 2000 mg IV (N=130)
Success[a]	123 (94%)	126 (97%)	112 (85%)	118 (91%)
Failure	8 (6%)	4 (3%)	19 (15%)	12 (9%)

a No signs or symptoms of a primary infection.

FDA 95% CI for ALL clinically-evaluable patients at EOS: (-17%, 0%)

FDA 95% CI for clinically-evaluable patients (excluding BICITRA® recipients) at EOS: (-12%, 7%)

FDA 95% CI for clinically-evaluable patients (including distant site infections BUT excluding BICITRA® recipients) at EOS: (-14% ,3%)

MO Comment : Trovafloxacin appeared to be less effective than cefoxitin in preventing surgical infections. However, in a *post hoc* analysis, Pfizer determined that if patients who received Bicitra orally were excluded, the treatment arms are comparable with regard to preventing surgical infections post hysterectomy. In addition, there efficacy was comparable for both abdominal or vaginal hysterectomy.

During the NDA review, Pfizer was also asked to assess prophylaxis outcome for low versus high-risk subjects. On 12/12/97, Pfizer responded via e-mail with the following analysis for hysterectomy:

"We did the analysis and the efficacy was not different between the "high risk" population (67 and 69% for Trovan and comparator, respectively - clinically evaluable with or without Bicitra) and those not considered at high risk by treatment arm."

In addition, Pfizer submitted the following analysis on 12/15/97 by e-mail:

Hysterectomy Surgical Prophylaxis Outcome (Success Rate) with/without Risk Factors AND including/excluding Bicitra at EOS (Clinically Evaluable)		
	Trovafloxacin	Cefoxitin
Including Bicitra		
No risk factors	36/44 (82%)	36/39 (92%)
At least 1 risk factor	75/89 (84%)	81/88 (92%)
Excluding Bicitra		
No risk factors	32/35 (91%)	26/29 (90%)
At least 1 risk factor	59/68 (87%)	62/68 (91%)

MO Comment : The MO is satisfied that prophylacitc efficacy was comparable between the two treatment arms depending with no risk factors or with at least 1 risk factor (with or without Bicitra).

Summary of Pathogens Associated With Primary Site Infection (Clinical Intent-to-Treat Subjects Excluding Subjects who Received BICITRA®) Study 154-146		
	Trovafloxacin 200 mg (N=149)	**Cefoxitin 2000 mg (N=150)**
Number of Subjects with a Primary Site Failure	19	17
Number of Subjects with a Primary Site Infection and an Isolated Pathogen	10	3
Gram Positive Aerobes		
S. agalactiae	4	1
S. anginosus	1	0
S. mitis	0	1
Staphylococcus sp.	4	1
Gram Negative Aerobes		
E. coli	0	1
P. mirabilis	1	1
P. aeruginosa	0	1
Gram Positive Anaerobes		
Lactobacillus sp.	1	0
Peptostreptococcus sp.	3	0
Propionibacterium sp.	1	0
Gram Negative Anaerobes		
Bacteriodes sp.	1	0
Gardnerella vaginalis	2	1
Prevotella sp.	2	0

MO Comment : Overall, the number of subjects with a primary site prophylaxis failure were similar between treatment groups. When a primary site failure occurred, more pathogens were isolated from trovafloxacin recipients.

APPEARS THIS WAY
ON ORIGINAL

SAFETY:

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values Study 154-146

	Trovafloxacin 200 mg		Cefoxitin (2000 mg IV)	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	114/188	(61%)	97/175	(55%)
Treatment-Related Adverse Events	0/188		2/175	(1%)
Discontinuations From Treatment Due to an Adverse Event	1/188[a]	(<1%)	0/175	
Clinically Significant Laboratory Abnormalities	110/179	(61%)	95/172	(55%)

a Rash developed during infusion of drug-free placebo (PID 5766-0177).

MO Comment : All causality adverse events were similar between treatment groups. Unlike to colorectal prophylaxis study, no treatment-related AEs were reported with trovafloxacin.

APPEARS THIS WAY
ON ORIGINAL

A Summary of the Most Commonly Reported Adverse Events[a,b] by Body System - All Causalities
Study 154-146
(All Treated Subjects)

APPEARS THIS WAY ON ORIGINAL

	Trovafloxacin 200 mg (N=188)		Cefoxitin 2000 mg IV (N=175)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	114	(61%)	97	(55%)
BODY SYSTEM WHO Term				
APPL./INJ./INCISION/INSERTION SITE	37	(20%)	23	(13%)
Appl./Inj./Incision/Insertion Site Infection Inflammation	6	(3%)	3	(2%)
Appl./Inj./Incision/Insertion Site Edema	6	(3%)	1	(<1%)
Appl./Inj./Incision/Insertion Site Pain	9	(5%)	8	(5%)
Appl./Inj./Incision/Insertion/Device Complication	16	(9%)	13	(7%)
CENTRAL AND PERIPHERAL NERVOUS	15	(8%)	13	(7%)
Dizziness	6	(3%)	4	(2%)
Headache	8	(4%)	8	(5%)
GASTROINTESTINAL	23	(12%)	21	(12%)
Constipation	1	(<1)	6	(3%)
Nausea	14	(7%)	10	(6%)
Vomiting	7	(4%)	4	(2%)
GENERAL	47	(25%)	38	(22%)
Cellulitis, other than Injection Site	7	(4%)	2	(1%)
Fever	32	(17%)	32	(18%)
PSYCHIATRIC	8	(4%)	7	(4%)
Insomnia	5	(3%)	5	(3%)
SKIN/APPENDAGES	20	(11%)	22	(13%)
Pruritus	14	(7%)	18	(10%)
URINARY SYSTEM	14	(7%)	17	(10%)
Urinary Tract Infection	8	(4%)	10	(6%)

a ≥3 % of subjects in any treatment group.
b Includes data up to 7 days after last dose of active study medication

MO Comment : When specifc AEs are assessed, there appeared to be more injection site complications reported in the trovafloxacin arm (placebo, since trovafloxacin was administered orally) compared with cefoxitin.

Time of Drug Dosing for Optimal Surgical Prophylaxis

For effective surgical prophylaxis, the optimal dosing strategy is to time drug administration such that peak antimicrobial peak drug concentrations are present at the time of first surgical incision.

For oral TROVAN, the T_{max} is 1-2 hours. During the NDA review, Pfizer was asked to provide a rationale for why they chose a 30-60 minute oral dosing prior to surgical incision for the hysterectomy study.

Pfizer Response (11/25/97 e-mail): "The package insert for cefoxitin states that it must be administered 30-60 minutes before surgical incision. To preserve double-blinding, the protocol stated that both drugs (trovafloxacin and cefoxitin) would be administered at the same time. Further, standard surgical practice is such that prophylaxis drugs are administered within 30-60 minutes of the surgical incision. Other antibiotics approved for prophylaxis, such as cefoxitin and cefotetan, are administered intravenously such that the T_{max} is upon completion of the administration, and elimination half-lives are too short to permit a longer window for drug administration. We wanted to test trovafloxacin under the same standards of practice to be assured that it was effective if used according to the practices for other prophylactic antibiotics. According to its pharmacokinetics, there would be adequate concentrations when administered 30-60 minutes before surgical incision, and the long elimination half-life allows for delays in surgical start times as well as prolonged complicated cases."

In addition, Pfizer was asked to examine the impact of the start of infusion relative to the timing of surgical incision and its impact on effective colorectal prophylaxis in study 154-128. Although the protocol stipulated that prophylaxis be administered within 2 hours of surgery, Pfizer requested that a "Single dose within 4 hr before surgery" be included in the DOSAGE & ADMINISTRATION section of product labeling. Indeed, many patients received their first dose of alatrofloxacin ≥2 hours prior to incision.

Pfizer submitted the following analysis on 12/9/97:

Surgical Prophylaxis Success Rates Based on Time of Start of Infusion Relative to Time of Surgical Incision (154-128) ***Clinical ITT Population***			
Hospital Discharge			
Timing of infusion start prior to surgical incision	Alatrofloxacin	Cefotetan	95% CI (w/ continuity correction)
≤2 hrs	102/130 (79%)	100/126 (79%)	-12%, 10%
>2 and <4 hrs.	77/97 (79%)	70/94 (75%)	-8%, 18%
<4 hrs	179/227 (79%)	170/220 (77%)	-7%, 10%
End of Study (EOS)			
≤2 hrs	93/130 (72%)	89/126 (71%)	-11%, 13%
>2 and <4 hrs.	72/97 (74%)	61/94 (65%)	-5%, 24%
<4 hrs	165/227 (73%)	150/220 (68%)	-4%, 13%

Surgical Prophylaxis Success Rates Based on Time of Start of Infusion Relative to Time of Surgical Incision (154-128) ***Clinically Evaluable Population***			
End of Therapy (EOT)			
Timing of infusion start prior to surgical incision	Alatrofloxacin	Cefotetan	95% CI (w/ continuity correction)
≤2 hrs	75/94 (80%)	73/86 (85%)	-17%, 7%
>2 and <4 hrs.	52/67 (78%)	55/70 (79%)	-16%, 14%
<4 hrs	127/161 (79%)	128/156 (82%)	-13%, 6%
End of Study (EOS)			
≤2 hrs	67/94 (71%)	66/86 (77%)	-19%, 8%
>2 and <4 hrs.	49/67 (73%)	47/70 (67%)	-11%, 23%
<4 hrs	116/161 (72%)	113/156 (72%)	-11%, 10%

MO Comment : Alatrofloxacin appeared comparable to cefotetan when dosing began as long as 4 hours prior to surgical incision.

Pfizer also stated on 12/9/97:

APPEARS THIS WAY
ON ORIGINAL

"The protocol for the elective colorectal study (154-128) and the elective hysterectomy study (154-146) stipulated windows of 2 hours and 30-60 minutes, respectively, for TROVAN dosing. As with all studies, we reviewed the dosing window while still blinded to treatment during our review of the evaluability listings. Many subjects (approx. half the clinically evaluable subset in the 128 study but far fewer [<5] subjects in the 146 study) were rendered not clinically evaluable due to dosing occurring

outside the 2-hour window. Reasons for the noncompliance in adhering strictly to the dosing window were largely due to delays in surgery starts (OR scheduling conflicts, surgeon timetables, etc.). Since clinical outcome was not different when one looked at a 2-hour window or a 4-hour window, we applied the 4-hour window for clinical evaluability. In so doing, we are able to assess the drug in a clinically realistic environment (i.e., where operating room and surgical incision times are difficult to standardize).

"In summary, all 128 and 146 subjects who received study drug within 4 hours of the surgical incision were included in efficacy analysis."

The MO is satisfied that the phrase, "Single dose within 4 hr before surgery" may be included for both colorectal and hysterectomy prophylaxis.

9. Conclusions:

TROVAN is safe and effective in preventing infections associated with elective colorectal and abdominal/vaginal hysterectomy.

The applicant has adequately demonstrated that TROVAN can be administered up to 4 hours prior to the surgical procedure. However, because the concept of attaining peak serum concentrations at the time of surgical incision remains important, TROVAN should not be administered any earlier than 30 minutes prior to incision. (This is consistent with labeling for other products.)

The applicant has adequately demonstrated that trovafloxacin should NOT be administered orally within 2 hours of Bicitra®. Bicitra® causes decreased bioavailability of oral trovafloxacin when the two are co-administered.

10. Recommendations:

APPEARS THIS WAY
ON ORIGINAL

TROVAN should be approved with the following product labeling:

/S/

Brad Leissa, MD
Medical Officer/HFD-590

cc: Orig. NDA
Division file
HFD-590/MO/Leissa
HFD-590/MO/Alivisatos
HFD-590/MO/Cox
HFD-590/CSO/Kimzey

Concurrence only: DivDir/Goldberger

/S/

APPEARS THIS WAY
ON ORIGINAL