Demographics:
Gender: 2/7 female, 2/7male and 3/7 unknown
Underlying diabetes: 3/7 diabetes present, 2/7 unknown, and 2/7 (28.5%) non-diabetic
Age: 3/7age unknown, 4/7 , years of age

Dosage:
3/7 unknown dosage, 1/7 200 mg qd and 3/7 300 mg qd

Duration of Therapy prior to development of AE:
4/7 developed disease within 2 days of starting therapy, 1/7 after 3 weeks and 2/7 after 9 days.

Conclusion with regard to pancreatitis: Very little information was provided with regard to the clinical picture. It appeared as if inflammation of the pancreas developed most commonly within the first 2 days of therapy although the duration ranged from 2 days to 3 weeks. Most affected were patients in the age range, although information was not provided on approximately 40% of the patients. There appeared to be an equal distribution between genders and the presence or absence of underlying diabetes mellitus. Information with regard to the degree of inflammation was not provided on any patient. Overall it became evident that a labeling change was necessary in order to add pancreatitis to the AEs associated with trovafloxacin usage as no cases had been seen previously, however a description of the disease process could not be provided.

Hepatitis Total (N = 31)

Demographics:

Gender: 14/31 (45.2%) female, 9/31 (29%) male, and 8/31 (26%) not reported
Age: 8/31 (32%) > 60 years of age, 9/31 (29%) < 60, 13/31(42%) not reported
Mean 54.25.
Underlying diabetes: 4/31 (13%) diabetic (3 women)
Dosage: 200 –300 mg PO or IV qd (predominantly 200)
Duration of therapy prior to the development of hepatotoxicity: non-specific ranging from 2 days to 4 weeks (the majority 23/30 (77%) within first 10 days: Average 11)
Clinical Picture: variable, all patients complained of fatigue.
Symptomatic Hepatitis (fatigue, fever, abdominal or RUQ pain, jaundice): 8

Laboratory:
Eosinophilia (peripheral or localized to liver): 5/31 (16.1%)
Transaminitis: 13/31 (42%) reported elevated normal 17/31 (55%) not reported and 1/31 (3.2%) within normal limits
Alkaline Phosphatase: 7/31 (22.6%) increased to > 3 x normal - > 10 x normal
Bilirubin: 9/31 (29%) elevated 22/31 (71%) not reported
Hepatitis and Cholestasis: 5/31 (16.1%)
Cholestasis: 8
Cholestasis alone: 3

Determination of Relatedness: N = 24:
Definite: 4
Probable: 9
Possible: 11

From the above, it became apparent that the trovafloxacin-related hepatotoxicity was equally distributed between males and females, that it most commonly appeared in patients aged > 55. Average duration of therapy prior to the development of symptoms or LFT abnormalities was 11 days, much less than that described in the NDA review (4 weeks). Patients appeared to develop either mild symptomatic disease (as

described above) to overt liver failure or to develop a chemical hepatitis alone (LFT elevations without symptoms). Cholestasis also developed in some patients. The clinical and hepatic abnormalities resolved in all patients listed, usually over the course of 6 – 8 weeks. The MO determined that 24 of the cases listed were related to trovafloxacin usage.

Subsequent to the receipt and review of the above, the DSPIDPs requested that Pfizer provide a proposal with regard to a labeling change (June 1998). Pfizer submitted a proposal (see below).

Revised Label as per the sponsor:

Add to Adverse Reactions Section:
Post-Marketing Experience: adverse events reported with trovafloxacin during the post-marketing period for which a causal relationship is uncertain include: anaphylaxis, hepatitis, liver failure (including acute hepatic necrosis with findings of eosinophilic infiltrates), Stevens-Johnson syndrome.

The MO determined that the suggested by the sponsor labeling revision was inadequate and did not provide enough information to adequately guide prescribing MDs with regard to the development of LFT abnormalities and their degree. Additionally, the issue of the development of pancreatitis was not addressed.

Negotiations ensued and on July 9, 1998 a teleconference was held between the FDA and Pfizer and labeling changes were agreed upon. Final changes can be found at the conclusion of this document (page 13). Please refer to the current label (page 3) as needed.

Recommended Regulatory Action:

It is recommended that the TROVAN® label be revised as follows:

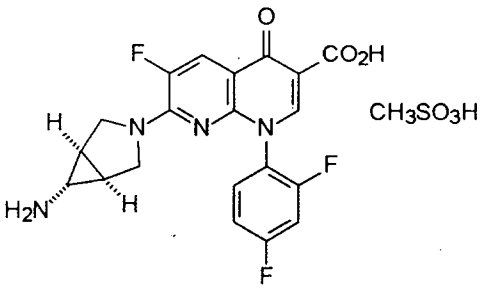
/S/

Regina Alivisatos, MD
DSPIDPs, HFD-590

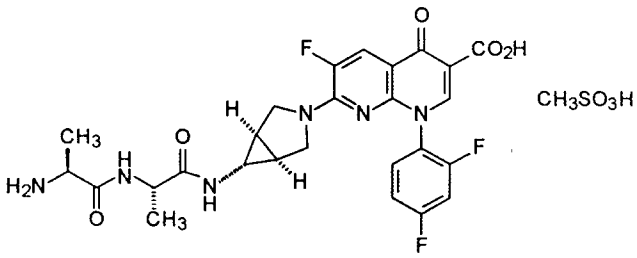
APPEARS THIS WAY
ON ORIGINAL

Cc:
Orig. NDA 20-759
Orig. NDA 20-760
HFD-590
HFD-590/DivDir/MGoldberger /S/
HFD-590/DepDivDir/RAlbrecht
HFD-590/MTL/BLeissa 9/30/98
HFD-590/Biopharm/PGolangeld /S/
HFD-590/Micro/Dionne
HFD-590/Chem/Holbert
HFD-590/Pharm/Hundley
HFD-590/CSO/RAnderson
HFD-725/Biostat/Chakravarty

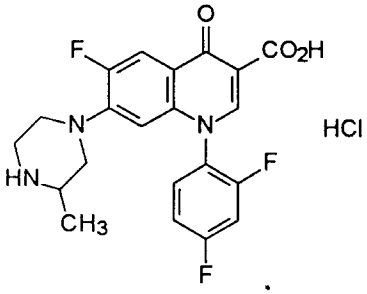
APPEARS THIS WAY
ON ORIGINAL



trovafloxacin mesylate



alatrofloxacin mesylate



temafloxacin hydrochloride

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA

OCT 20 1998

NDA 20-759/20-760
INDICATION: TREATMENT OF ACUTE PELVIC INFECTIONS

DRAFT LABELING EXCERPT:

Abbreviations used in this MOR:

AE = adverse event
AB = antibiotic
BV = bacterial vaginosis
CI = confidence intervals
C/sec = cesarean section
CRF = case report form
DAIDP = Division of Anti-Infective Drug Products
EOS = end of study
EOT = end of treatment
GC = gonococcal **OR** gonorrhea
IV = intravenous
MO = medical officer
MOR = medical officer review
PID = pelvic inflammatory disease **OR** patient identification number
po = by mouth, oral
PPE = postpartum endometritis or endomyometritis

PTC = Points to Consider document
ROM = rupture of (amniotic) membranes
Rx = therapy or treatment
RX = prescription
Sn = sign
STD = sexually transmitted disease
Sx = symptom
TOA = tubo-ovarian abscess
UTI = urinary tract infection

Materials and Literature Reviewed for this Indication:

E-sub from December 1996
Various fax material from the sponsor
E-mails from the sponsor
Large packet of clinical tables mailed 10/30/97

Mandell, Douglas and Dolin, Principles and Practice of INFECTIOUS DISEASES, 4th Edition, 1995.

Sweet, R.L. and Gibbs, R.S., Infectious Diseases of the Female Genital Tract, 3rd Edition, 1995.

Weisenfeld, H.C. and Sweet, R.L., Gynecologic and Obstetric Infections, Chapter 14, 1996.

Casey, B.M. and Cox, S.M., chapter on endometritis, p. 203-22, Infectious Disease Clinics of North America, guest editors Tuomala and Cox, March 1997.

Clinical Background:

Acute pelvic infections constitute a diverse group of both community- and hospital-acquired infections. They are conveniently considered in three categories: infections related to pregnancy; infections following gynecologic surgery; and sexually-transmitted pelvic inflammatory disease (PID). This study included only infections related to postpartum pregnancy, postabortal pregnancy, and gynecological surgery. PID, cervicitis, and certain other specific pelvic infections were excluded per protocol.

It is important to note that **bacteria classically considered pathogenic may be part of the normal vaginal flora,** so there is debate concerning exactly which bacteria are pelvic pathogens. The normal vaginal flora consists of lactobacilli, various species of streptococci, *Gardnerella vaginalis,* strains of Enterobacteriaceae, and anaerobes. Anaerobes predominate in numbers, with a ratio of 10:1. *Bacteroides fragilis* may be cultured from the normal vagina in approximately 10% of patients, enterococci in 25%, *Clostridium perfringens* in 10%, group B streptococci in , *Gardnerella vaginalis* in , and *Prevotella* spp. (formerly *Bacteroides* spp.) in 25%. In a 11/7/97 talk at NIH, microbiologist Sharon Hillier stated that during pregnancy cultures were positive for enterococci in 33% of asymptomatic women, group B streptococci in 16%, *Gardnerella vaginalis* in 58%, and *Prevotella* spp. in 61%.

Wiesenfeld and Sweet state that **post partum endometritis (PPE)** rarely exceeds 3% of patients post vaginal delivery, but rates post Cesarean section range depending on many different well-established risk factors such as prolonged rupture of membranes, prolonged labor, number of internal exams, socioeconomic data, anemia or the concomitant presence of bacterial vaginosis (BV). There are different clinical diagnoses that are included within the general category of PPE; these **include endomyometritis, parametritis, endoparametritis, and puerperal infection.** PPE is most often **a mixed (polymicrobial) infection of aerobic and anaerobic bacteria.** of PPE cultures grow aerobic *Gardnerella vaginalis, Escherichia coli* & streptococci; grow group B & D streptococci; anaerobic growth is with *Bacteroides* spp., *Prevotella* spp., and *Peptostreptococcus* spp. as the most common. Chlamydia is associated with a late form of PPE, occurring 2 days to 6 weeks after vaginal delivery. Wiesenfeld and Sweet

recommend blood cultures in all patients as will have bacteremia, with group B streptococci and *Gardnerella vaginalis* the most common isolates.

Because these infections are polymicrobial with aerobic and anaerobic organisms, broad spectrum antimicrobial coverage is recommended. Options for more severely ill patients include double or triple antibiotic combinations such as clindamycin or metronidazole + gentamycin +/- ampicillin, or a cephalosporin/penicillin combination such as cefoxitin or cefotetan + ampicillin or amoxicillin. A single agent like cefoxitin, cefotetan, Unasyn®, or Timentin® is appropriate in patients with milder disease or clearly established susceptible microorganisms. Treatment should be continued until the patient is afebrile for 48 hours. If IV therapy is successful, further treatment with oral agents may be unnecessary (Dinsmoor et al., *Obstet. Gynecol.* 77:60-2, 1991).

Failure of antimicrobial therapy usually results from either enterococcal superinfection or inadequate coverage of a multiresistant anaerobe. If fever persists despite apparently appropriate antimicrobial therapy, the differential diagnosis includes a wound or pelvic abscess, ovarian vein thrombosis, septic pelvic thrombophlebitis, ~~or~~ noninfectious fever (e.g., drug fever or breast engorgement).

Postabortion infection is an ascending process and occurs more often in the presence of retained products of conception or operative trauma (induced abortion). The infection typically has its onset within four days of the procedure or spontaneous miscarriage, and is most often caused by an unsuspected sexually transmitted pathogen, or a polymicrobial mixture of anaerobic and aerobic bacteria like those in PPE. Persistent bleeding, sonographic evidence of retained tissue, or persistent infection require curettage in addition to antimicrobial treatment. Many patients are given prophylactic antibiotic coverage at the time of an induced abortion, so a careful history is important when treating these patients.

Postoperative gynecologic infection includes pelvic cellulitis, parametritis, cuff cellulitis, and abscess; these infections are also not well understood in terms of the exact pathophysiology. An endogenous route of infection is most probable with the exception of *Fusobacteria* and *Bacteroides fragilis,* both infrequent members of the normal vaginal flora.

Many factors alter the vaginal flora and may indirectly predispose to postoperative infection. Hospitalization appears to exert a profound effect on the vaginal flora, regardless of surgery or antibiotic prophylaxis, and this change tends to be in the direction of more virulent organisms such as enterococci, *Bacteroides fragilis,* and resistant Enterobacteriaceae. Other common predisposing factors include the use of non-oxynol-9-containing vaginal contraceptives, oral contraceptive hormones, douching, use of the female condom, and the phase of the menstrual cycle. The significance of these factors in relation to infection after gynecologic surgery is unknown.

Many external risk factors for infection after hysterectomy (or any major operative procedure) have been identified such as poor nutrition, lower socioeconomic status, diabetes, anemia, old age, obesity and prolonged surgery. These factors were partially addressed in this clinical trial, and further comments are made later.

The most common infection after hysterectomy is **pelvic cellulitis**. The value of obtaining a culture from the vaginal cuff is controversial in cases of pelvic cellulitis because the infection is within the lower abdominal (pelvic) cavity. Some experts believe that cultures can identify the responsible pathogens, especially when an infection has not responded to the initial antimicrobial therapy. Others argue that contamination with the normal vaginal flora makes such cultures uninterpretable. Pelvic cellulitis usually responds to single-agent parenteral antibiotic therapy. Hager et al. (*Obstet. Gynecol.* 73:326-9, 1989) have shown that oral outpatient antibiotic therapy after successful parenteral therapy for pelvic cellulitis is unnecessary.

Cuff cellulitis is the normal inflammatory process at the margins of the vaginal cuff incision following a hysterectomy; a small percentage of cases will require antibiotics, often as outpatients. **Cuff and pelvic abscess** are the least common of postoperative gynecologic infections; any purulent material recovered should be cultured for aerobic and anaerobic pathogens. Identification of an abscess does not mandate immediate

surgical drainage, as antibiotic therapy alone is often successful in the treatment of this complication. Parenteral antibiotics should be given until the patient is afebrile for at least 24-36 hours.

Regulatory Background:

As noted above in the PDR™ listing of antimicrobial drugs for the general category of gynecological infections, **no quinolones are currently approved specifically for postpartum and postoperative pelvic infections**. Many of the drugs listed are specific for beta-lactamase producing microorganisms, or for *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis,* or for only *Escherichia coli* (Ceptaz®, Fortaz®, Tazicef®, Zosyn®). Several are broad spectrum antimicrobials and cover a much wider range of bacteria, and therefore are approved for a variety of acute pelvic infections as noted above. Study 155-144 was submitted in order to attain approval for acute pelvic infections discussed above in the clinical background section.

The Division of Anti-Infective Drug Products (DAIDP) Points-to-Consider (PTC) document discusses gynecologic infections excluding STDs and acute PID. The PTC recommends that "one statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is needed. At least 50% of the clinically evaluable patients should also be microbiologically evaluable." If there is not a "reasonable mix of various gynecologic infections, such should be noted in the approved labeling by restricting the wording of the Indications and Usage section to just those types of infections actually studied." Furthermore, the PTC document guidelines allow data from a gynecological infections study and a complicated intra-abdominal infection study (such as 155-124) to be used jointly to support an approval for the study drug against specific species of bacteria as long as the extrapolation makes sense clinically and pharmacologically.

> **MO Comment:** Data from both this acute pelvic infections study (154-144) and from the complicated intra-abdominal infections study (155-124) were used in this MOR to draw final conclusions concerning the specific bacteria to be included in the label. The PTC guidelines were closely followed.

Current IDSA/FDA Guidelines (Nov. 1992) devotes an entire section (S41- S52) to "Evaluation of New Anti-Infective Drugs for the Treatment of Acute Pelvic Infections in Hospitalized Women." The following are the recommended evaluability guidelines:

1. the protocol must be followed to assure the potential evaluability of each patient
2. must not miss 2 consecutive doses of antibiotic
3. have clinical categories of failure, improvement, presumptive cure and cure, but improvement is only an interim assessment
4. in the final evaluation, clinical criteria are "much more important than" micro findings, and final evaluation is failure, cure or non-evaluable (indeterminate)
5. patient should be reevaluated 14-28 days after completion of therapy for final (EOS) clinical evaluation
6. pelvic cultures during the last visit are not necessary if patient is clinically cured

The IDSA/FDA document further states that the expected cure rate of acute pelvic infections is ~90% at the EOS visit. Duration of therapy for an evaluable cure should be no less than 4 days and no more than 10 days. Parenteral therapy is recommended for at least the initial four days of therapy, but no specific statement is made about minimal parenteral therapy prior to switching to oral therapy. Use of another antibiotic for the treatment of a pelvic infection because of lack of clinical response is considered a failure.

> **MO Comment:** The study protocol allowed 4 to 14 days of therapy and a minimum of one day of parenteral therapy before changing to oral therapy. After careful review of the literature, the IDSA guidelines, the general mild severity of illness in the majority of patients, and the high percentage of prior antibiotic use (as a confounding factor), **the MO elected to use 4 to 10 days of therapy as the evaluable range for cure.** Those patients who received 11 to 14 days of therapy were considered non-evaluable, rather than failures,

because the original protocol did allow up to 14 days of treatment. Patients receiving more than 14 days of the study or control arm antibiotic were considered failures in order to be consistent with the study protocol, as well as IDSA and MO criteria.

Microbiology and Chemistry: copied and modified from page 13 of study report.

Trovafloxacin is a fluoronaphthyridone derivative related to well-known fluoroquinolone antimicrobial drugs such as ciprofloxacin, norfloxacin, and ofloxacin. It has been formulated for human use as the mesylate salt. Trovafloxacin has shown a number of desirable characteristics in preclinical *in vitro* and *in vivo* animal testing. Its mechanism of action is the same as that of the quinolones which act by inhibiting the normal function of the A subunit of DNA gyrase, a bacterial DNA topoisomerase II. Trovafloxacin is selective for bacterial DNA gyrase, and does not significantly affect eukaryotic topoisomerase II.

Trovafloxacin has a broad spectrum of *in vitro* activity, particularly against the common pathogens involved in acute pelvic infections.

MO Comment: The MIC_{90}s of trovafloxacin for some of the pathogens involved in acute pelvic infections are listed in the following MO table with the MIC_{90} data from Sousan Altaie, FDA microbiologist.

Pathogen	MIC_{90} (µg/mL)	
	Range	Median
Bacteroides fragilis		0.5
Enterococcus faecalis (VRE)		8
Enterococcus faecalis (VSE)		2
Escherichia coli		0.06
Gardnerella vaginalis		2
Streptococcus agalactiae		0.25
Streptococcus anginosis		None given
Peptostreptococci spp.		1
Prevotella spp.		1

Pharmacokinetics: modified from the study report.

Trovafloxacin mesylate salt was well-absorbed with an absolute bioavailability in man of approximately 90%. Single and multiple-dose pharmacokinetic studies indicate that systemic exposure increases in a dose-related manner. The peak blood level (C_{max}) of alatrofloxacin at the 300 mg intravenous dose occurred at the end of the recommended 60 minute infusion; in acute pelvic infection subjects it measured ~4.4 µg/mL with a half-life of 10.8 hours. For the oral trovafloxacin, C_{max} was between 1-2 hours, with a range of 30 minutes to 4 hours.

MO Comment: The decreased absorption of trovafloxacin associated with antacid use, especially Bicitra in the surgical prophylaxis study, was determined by Pfizer. The use of antacids did not, however, seem to impact on the results of this gynecologic infections study.

It was also of note that C_{max} levels in general, for a given dose of oral trovafloxacin, were inversely proportional to body weight, irrespective of gender. All subjects in this study were obviously female, but due to their lower weights compared to men, their average peak blood levels were higher than that seen in other studies. This did not, however, impact on the incidence of dizziness or the efficacy of trovafloxacin in this study.

Study No. 154-144

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL ASSESSING THE SAFETY AND EFFICACY OF INTRAVENOUS ALATROFLOXACIN FOLLOWED BY ORAL TROVAFLOXACIN COMPARED WITH INTRAVENOUS CEFOXITIN FOLLOWED BY ORAL AMOXICILLIN/CLAVULANIC ACID FOR THE TREATMENT OF ACUTE PELVIC INFECTIONS.

OBJECTIVES: copied from the study report.

To compare the safety and toleration and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin with the combination of intravenous cefoxitin followed by oral amoxicillin/clavulanic acid in the treatment of subjects with acute pelvic infections.

PRINCIPAL INVESTIGATORS (55)

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5017	John Gezon, MD
	5221	Ashwin Chatwani, MD
	5238	Subir Roy, MD
	5529	Vinod Dhawan, MD
	5601	James McGregor, MD
	5602	Stanley Gąll, MD
	5749	Gregory Fossum, MD
	5750	David Hemsell, MD
	5751	Abner Korn, MD
	5759	Richard Sweet, MD
	5768	Peter Marsh, MD
	5864	Melisa Holmes, MD
	5865	Andrew Kaunitz, MD
	5866	William Koltun, MD
	5867	Robert Nordland, MD
	5868	George Maroulis, MD
	5870	Mary O'Sullivan, MD
	5874	Dale Sundwall, MD
	5875	Michael Valley, MD
	5898	Pamela Berens, MD
	5899	Michael Campion, MD
	5900	Richard Dittrich, DO
	5901	Thomas Garite, MD
	5902	Bruce Mabine, MD
	5906	Dean Coonrod, MD
	5911	Dominic Muzsnai, MD
	5912	Gregory Parker, MD
	5913	Jeffrey Peipert, MD
	5917	Gerardo Carlos, MD
	5922	Daryl Gildenblatt, MD
	5968	Denis Mee-Lee, MD
	5969	Thomas Stovall, MD
	5971	Robert Messer, MD
	5988	Ronald Pruitt, MD
	5994	Richard Hedrick, Jr., MD
	6077	Blane Crandall, MD
Canada	6108	Gilles Murray, MD
	6109	Mark Martens, MD
	6120	Robert Kessler, MD
	6121	Marie Beall, MD

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
	6124	Richard Hansell, MD
	6125	John McGee, MD
	6126	Todd Vanheest MD
	6144	Xavier Pombar, DO
		Howard Strassner, MD
	6148	Lloyd Lewis, MD
	6149	Hugh Miller, MD
	6154	Felix Oyola, MD
	6169	Lamar Ekbladh, MD
	6344	William O'Riordan, MD
	6346	George Harper, MD
	6347	Anthony Smith, MD
	6367	Del Dehart, MD
	6378	Edward Zelnick, MD
Canada	6385	Wendy Wolfman, MD
	6542	Jeanna Piper, MD

DESIGN: copied from the protocol.

Study 154-144 was a randomized, double-blind, double-dummy, multicenter comparative trial conducted at 35 centers from 21 June 1995 to 3 May 1996.

The Phase 3 Protocol stated: Subjects with suspected acute pelvic infections were randomized in a double-blind fashion to receive either a regimen of intravenous CP-116,517 (300 mg/day) and oral CP-99,219 (200 mg/day) or a combined regimen of cefoxitin (2 grams intravenously every 6 hours) followed by amoxicillin/clavulanic acid (500 mg orally every 8 hours) for a maximum of 14 days. Switching from parenteral to oral medication was determined by the investigator when oral intake had been re-established. Double-blind therapy was continued for a minimum of 4 days and terminated after a maximum duration of 14 days, independent of clinical response.

> **MO Comment:** The use of parenteral cefoxitin followed by oral amoxicillin/clavulanic acid was an acceptable comparator for this study. It is an antibiotic regimen that is well-established, commonly used, and recommended by experts in the field of infectious diseases. The dosing used in the comparator arm of this study was the most commonly recommended regimen.

The goal was to obtain at least 300 hospitalized subjects, aged 18 or more, with a medical history and clinical findings consistent with an acute pelvic infection, either post-operative, postpartum, or post-abortion.

Efficacy was evaluated through clinical assessment of signs and symptoms of acute pelvic infections. Safety was assessed throughout the study by recording concomitant medication, vital signs, study drug dosing, adverse events, and laboratory evaluations.

> **MO Comment:** Having a single trial was consistent with the DAIDP PTC document's recommendation that only one trial is required in patients with acute pelvic infections, NOT including sexually transmitted diseases or pelvic inflammatory disease. As noted earlier, the sponsor also conducted a separate clinical trial (study 154-124 to establish the efficacy of trovafloxacin in the treatment of complicated intra-abdominal infections) in order to support this acute pelvic infections trial, as recommended in the PTC document.

PROTOCOL OVERVIEW

Population, visits and procedures:

Copied from the electronic submission, page 30 of the study protocol, is the sponsor's schedule of visits and procedures seen below. Inpatient females who were at least 18 years of age with a preliminary diagnosis of an acute pelvic infection (other than acute PID or another sexually transmitted infection) were eligible for participation in the study.

SCHEDULE OF STUDY VISITS AND PROCEDURES

Study day Allowable Window: Treatment Period Day 1 to Day 14[a] Follow-up period Day 15 to Day 42	Day 1 -48 hours	Day 3 Day 2-4	Day 5[e] Day 5-7	Day 14[a] Day 5-14	Day 30 Day 28-42
Informed consent	X				
Demographic information	X				
Maximum body temperature[b]	X----------			----------X	
Targeted physical exam	X	X	X	X	X
Vital signs	X	X		X	X
Clinical signs & symptoms	X	X	X	X	X
Concomitant medication	X----------			----------X	X
Dosing record	X----------			----------X	
Microbiology culture & sensitivity[c]					
• pelvic areas	X	X[d]		X[d]	X[d]
• blood	X	X[d]		X[d]	X[d]
• urine	X	X[d]		X[d]	X[d]
Safety laboratory tests					
• hematology	X	X		X	abn
• biochemistry	X	X		X	abn
• urinalysis	X	X		X	abn
Adverse events	X----------			----------X	X
Investigator's assessment of clinical response[c]		X		X	X
Health care resource utilization	X----------			----------X	X

[a]or end of double-blind therapy if sooner
[b]performed daily during the hospitalization period
[c]and to be done at the time of discontinuation, if applicable
[d]only if clinically indicated (e.g., time of discontinuation, previously positive culture, or time of the determination of drug failure)
abn = to be done only if abnormal at previous visit or if subject experiences a clinically-significant adverse event

[e] *only if subject remains hospitalized* (June 29, 1995 Amendment)

The study consisted of a minimum of 4 subject evaluation visits, with clinically evaluable subjects having clinical and laboratory assessments at Day 1 (baseline), Day 3 (after 48 hours of therapy, allowable window days 2-4), Day 14 or earlier (end of double-blind therapy, designated EOT), and Day 30 (the final assessment, day 28 to 42, designated EOS). Targeted physical examinations and signs and symptoms (assessed during the baseline visit) were also assessed at Day 5 (allowable window days 5-7) only if the subject was still hospitalized (June 29, 1995 Amendment) after initiation of double-blind therapy.

> **MO Comment:** Only 11 Trovan® and 11 control arm patients remained hospitalized on Day 5 and therefore potentially received clinical and laboratory assessments during the 5-7 day window. Also a large number did not have EOT assessments. This was acceptable to the MO because the test of cure (TOC) was based on the findings at the EOS visit. The MO also accepted a larger allowable window of up to day 52 for the "Day 30 final assessment" (EOS) evaluation.

The study consisted of inpatient followed by outpatient therapy for a minimum of 4 days to a maximum of 14 days. All subjects were randomized to receive intravenous medication initially, regardless of their ability to take oral medications. Thus, subjects were assigned single intravenous infusions of Alatrofloxacin or cefoxitin as the first treatment regimen in a double-blind fashion. NO subject was allowed to receive oral double-blind medication initially. Thereafter, based upon clinical impressions, the investigator could switch the subject from intravenous to oral medication. Each subject received two oral tablets once daily (morning dose) and 10 ml of oral suspension 3 times daily, every 8 hours (morning, afternoon, and evening), for a maximum total double-blind double-dummy treatment period of 14 days. A switch back to intravenous therapy was allowed at the investigator's discretion. Also, subjects could remain on intravenous therapy for the entire 14-day study period.

> **MO Comment:** It is of note that of the 160 treated subjects in the trovafloxacin arm, 46 received only 1 day IV therapy and 52 received only 2 days IV therapy (this totals 61% (98/160) of the trovafloxacin arm). Of the 156 treated subjects in the cefoxitin arm, 18 received only 1 day IV therapy and 56 received only 2 days IV treatment (74/156 = 47% of the control arm). Therefore, the majority of the entire study population (172/316 = 54%) received only 1 or 2 days of IV therapy.

Day 1 (baseline) Visit- within 48 hours prior to the start of therapy (copied from page 17 of the protocol).

"The baseline assessment included collection of demographic information, concurrent diseases, antibiotic therapy within the last 7 days, concomitant medication use, vital signs (pulse, respiration, blood pressure, and body temperature), and a targeted physical examination. Signs and symptoms consistent with the diagnosis of an acute pelvic infection (e.g., fever [body temperature ≥ 38 °C], leukocytosis [WBC ≥ 12,500 cells/mm^3]) should be documented on the subject's Case Report Form.

Diagnosis of cuff cellulitis, pelvic cellulitis, or pelvic abscess, where applicable, should be noted on the subject's Case Report Form. In the event that the acute pelvic infection was secondary to incomplete abortion, the nature of the abortion (spontaneous, elective, or self-induced) should be noted on the subject's Case Report Form.

Blood and urine samples for laboratory safety testing should be obtained. Sites of infection were cultured for both aerobic and anaerobic bacteria; samples were obtained within 48 hours prior to initiation of therapy. Each probable pathogen will be identified to the species level."

> **MO Comment:** The protocol did not clarify that testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* should be performed in all cases of septic abortion and possible

PID; a positive result would render the subject non-evaluable because this study excluded subjects with either pathogen.
The protocol did state that each probable pathogen should be identified to the species level, although this was not done consistently by the individual study sites.

"For subjects with the diagnosis of *endometritis*, *endomyometritis*, or *septic abortion*, a sample from the endometrial cavity will be obtained with a protected culture device. For subjects with *pelvic cellulitis* or *cuff cellulitis*, a sample will be obtained from the supravaginal space using a protected sterile swab. For subjects with *pelvic abscesses*, a sample will be obtained from the supravaginal space (abscess cavity) with a protected sterile swab or by suction (needle or syringe, computed tomography-directed drainage, or surgical drainage). Blood cultures (more than 1) for both aerobic and anaerobic cultures were obtained in all subjects. Isolates from blood cultures were sent to the central laboratory for testing.

A urine sample should be obtained by either the clean-catch method or by catheterization for culture in all subjects."

MO Comment: Upon MO request, the sponsor clarified the use of "a protected culture device;" a specific commercial device was recommended and used in order to minimize the chances of contaminating endometrial samples with "normal vaginal flora." This was an important requirement in the protocol because contamination of endometrial samples has been a common problem in accurately diagnosing the pathogens in pelvic infections.

Although important to rule out a primary or concomitant UTI in these subjects, the value of a "clean-catch" urine sample for culture in a postpartum patient was debatable in light of contamination due to the recent delivery or surgery, the heavy discharge, and normal post-op or postpartum bleeding.

Days 1 to 14 (Double-blind therapy)- copied from page 19 of the study protocol.

"Clinical response to therapy will be assessed by the investigator after 48 hours (day 3, allowable window: days 2-4) of double-blind therapy.

MO Comment: As Day 1 was the first day of treatment in this study, assessment of clinical response after 48 hours was an appropriate time for an early evaluation, but this would not have included Day 2. However, many patients were discharged from the hospital on days 1, 2, and 3; therefore, the MO accepted a window of days 2-4 for this second potential assessment.

The daily maximum body temperature will be recorded on the subject's Case Report Form. Targeted physical examinations and signs and symptoms (assessed during the baseline visit) will be assessed 48 hours (day 3, allowable window: days 2-4) and 120 hours (day 5, allowable window: days 5-7 *if still hospitalized*) after initiation of double-blind therapy. The battery of blood and urine safety tests and vital signs (respiration, blood pressure, and pulse) performed at baseline will also be repeated 48 hours after initiation of double-blind therapy, or if at any time the subject is experiencing a clinically significant event.

Other procedures to be performed throughout the hospitalization period are recording of concomitant medications, study drug dosing, and adverse events volunteered by the subject or observed by the investigator.

The decision to stop double-blind therapy will be made by the investigator based upon his/her assessment of a successful outcome. Typically, drug therapy continues until the subject is afebrile for a period of 24 to 48 hours. However, the determination to discontinue double-blind therapy either

based upon the determination of a successful outcome, because of an adverse experience, or due to the determination of failed drug therapy will be based upon the clinical assessment of the investigator. Under no circumstances will the subject remain on double-blind therapy after 14 days.

Blood and/or urine cultures are to be repeated at 48 hours after initiation of double-blind therapy only if the baseline blood and/or urine cultures were positive. If available and clinically-indicated, pelvic cultures should be obtained at 48 hours after initiation of double-blind therapy."

Day 14 or Earlier (End of double-blind therapy, also designated EOT)- page 20 of printed protocol.

"A targeted physical examination will be performed at the end of double-blind therapy. Vital signs, including body temperature, will be recorded at the end of double-blind therapy. Signs and symptoms assessed during the baseline visit will be re-evaluated at the EOT.

The battery of blood and urine safety tests performed at baseline will be repeated at the end of double-blind therapy, or if the subject is experiencing a clinically significant event.

Other procedures to be performed at the end of double-blind therapy are recording of concomitant medications, study drug dosing, and adverse events volunteered by the subject or observed by the investigator. Also, the investigator is to provide an evaluation of clinical response, as described in Section 8.1 of the protocol.

Blood and/or urine cultures are to be repeated only if the previous blood and/or urine cultures were positive. If available and clinically-indicated, pelvic cultures should be obtained at the EOT."

Day 30 (day 28 to 42- the final assessment)

All signs and symptoms identified at all the previous evaluations, as well as new signs or symptoms since the last visit, should be assessed.

Other procedures to be performed at the day 30 evaluation are recording of vital signs (including body temperature), concomitant medication, and adverse events volunteered by the subject or observed by the investigator. The battery of blood and urine safety tests performed at baseline needs to be repeated only if an abnormality was present at the end of double-blind therapy, or if the subject is experiencing a clinically-significant adverse event.

At this visit the investigator is to provide a final evaluation of clinical response.

> **MO COMMENT:** There were very limited requirements to obtain follow-up pelvic cultures. As per protocol, pelvic cultures should be done only "if available and clinically-indicated." Follow up cultures were not strictly required in all subjects because the most important parameter for a cure in acute gynecologic infections was the clinical evaluation at end of study (EOS). The MO agreed with this approach.

Protocol Deviations: copied from the study report page 34.

Deviations from protocol were noted for 27 subjects, four of whom had more than one deviation, during the study. These deviations were categorized as follows:

1. Inclusion criteria deviations included subjects who: did not have an infection (endomyometritis/endometritis/myometritis, parametritis, phlegmon, and/or abscess, pelvic infection following hysterectomy, or septic incomplete abortion) requiring anti-infective therapy (4 subjects), were <18 years of age (10 subjects), were not permanently sterilized or were not using an accepted clinical means of contraception (2 subjects), did not sign an updated informed

consent to include nursing mothers (2 subjects), did not sign the informed consent (1 subject), and did not have physical examination findings consistent with an acute pelvic infection (1 subject).

2. Exclusion criteria deviations included subjects who had: a history of seizures or epilepsy (5 subjects), evidence of drug or alcohol abuse or dependence (4 subjects), received chronic treatment with known immunosuppressive drugs (2 subjects), and a known or suspected hypersensitivity or intolerance to any quinolone, penicillin, or β-lactam antibiotic (1 subject).

None of the five subjects (2 Trovan® and 3 control arm) who had a history of seizure or epilepsy prior to enrollment in the study had seizure activity or neurological adverse events at any time during the study. With the exception of the four subjects (2 Trovan® and 2 control arm) with inappropriate baseline diagnoses who were not evaluable, none of the subjects was considered to be nonevaluable due to protocol deviations.

MO Comment: The MO agreed with the sponsor's analysis.

Compliance:

This study was conducted in compliance with local and central Institutional Review Board (IRB) and informed consent regulations.

Protocol Amendments: copied from page 17 of study report.

The protocol was amended on June 29, 1995, as detailed below:

1. The minimum age for enrollment was changed from 18 to 16 years.
2. Signs and symptoms and targeted physical examinations were to be performed at Day 5 *only* if the subject was still hospitalized.
3. Outpatient women requiring intravenous antibiotic therapy were eligible for enrollment.
4. Procedures for collection of breast milk were specified.

The protocol was amended on August 18, 1995, as detailed below:

1. Discontinuation from study procedures were modified to specifically address subjects discontinued from study therapy because of clinical failure and adverse events.
2. Clinical failure criteria were modified to exclude subjects who stopped double-blind therapy due to the onset of a significant adverse experience.

The protocol was amended on December 1, 1995, as detailed below:

1. The minimum age for enrollment was changed from 16 to 18 years.
2. Statistical Methods section was updated.
3. Outpatient subjects who initially require IV therapy may be enrolled in the study.

MO Comment: The June 29, 1995 Amendment changed the minimum age of enrollment to 16: 10 patients in the study were < age 18, and 2 were age 14 or 15. Obstetrical patients under the age 18 are common and in fact are at risk for at least three of the indications in this study: septic abortion, Cesarean section delivery and postpartum endometritis. The

December 1, 1995 Amendment changed this back to age ≥ 18 years. Additionally, outpatients who required intravenous antibiotic therapy were also made potentially eligible. The December amendment did not clarify why the enrollment age changed back to ≥ 18; according to the sponsor, however, this was because the FDA expressed safety concerns about the use of quinolones in patients under 18 ("pediatric" population). All patients < 18 years old who were already enrolled were still included as potentially evaluable for safety and efficacy. The MO agreed with these above amendments.

The December 1995 amendment allowing outpatient subjects was an acceptable change in light of today's managed care and continuing pressure on the healthcare industry for increased outpatient treatments and procedures.

Concomitant Medications: modified from the study report.

The investigator documented all concomitant medications and any therapeutic interventions at each visit. Other antimicrobials were allowed if it was felt that they would not impact in any way on the pelvic infection. In such cases, however, in order to ensure that the subject remained evaluable, final efficacy assessments were to be performed prior to starting new antibiotic treatment. If another microbial was used that might influence the outcome of the pelvic infection, then the patient was classified as a treatment failure.

The concomitant use of no more than 10 mg/day prednisone or equivalent was allowed. The use of any other investigational drug or immunosuppressive therapy was prohibited. Mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, or magnesium-based antacids were not to be taken within (before or after) two hours of dosing.

MO Comment: Not allowing the concomitant use of certain minerals, vitamins, and antacids was important as it was demonstrated that they would adversely affect the absorption of oral doses of trovafloxacin, and potentially affect its efficacy.

Discontinuation of Therapy: copied and modified from page 17 of study report.

The investigator was to discontinue study therapy in the event of a serious or severe AE, limiting side effects or significant lab abnormalities. The reasons for discontinuation were to be recorded on the CRF, and all severe AEs were to be reported to the Pfizer monitor immediately.

Precautions:

Subjects were instructed not to donate blood during the study or for 6 weeks after the end of the study.

Inclusion/Exclusion Criteria of Note:

Inclusion: copied from page 11 of protocol.

Inpatient *or outpatient* women *requiring intravenous antibiotic therapy*. Subjects must not become pregnant both during the study and for a one month period after the end of the study.

Subjects who were found to have one of the infections listed below requiring anti-infective therapy. Subjects had to have physical examination findings consistent with an acute pelvic infection (e.g., new onset of lower abdominal, pelvic, back, and/or leg pain) as well as systemic evidence of inflammation (e.g., fever [body temperature ≥ 38 °C], elevated white blood cell count). Where appropriate, imaging studies could support signs and symptoms of an acute pelvic infection.

The following diagnoses were acceptable:

1. endomyometritis. Subjects must have had a recent cesarean or vaginal delivery, symptoms of pelvic pain and uterine tenderness, and at least one oral temperature of ≥ 38 °C.

2. parametritis, phlegmon, and/or abscess. The criterion for abscess inclusion was a palpable mass located laterally in a parametrial area, anteriorly under the bladder flap, or in the posterior pelvis. Where possible, identification should be confirmed by sonography or other noninvasive testing. This diagnosis could be associated with a delivery, abortion, or hysterectomy.

> **MO Comment:** There were 23 subjects with a diagnosis of parametritis; the MO requested further information concerning additional diagnoses in this group of patients. The parametritis was related to 1 abortion, 1 salpingo-oophorectomy, 8 vaginal deliveries, 7 Cesareans, and 6 unspecified diagnoses.
>
> There were only 3 sponsor-evaluable (1 MO evaluable) subjects with a pelvic abscess in the entire study.

3. pelvic infection (cuff cellulitis or pelvic cellulitis) following hysterectomy. Subjects must have symptoms of pelvic, abdominal, and/or back pain with tenderness in the lower abdomen and the vaginal cuff, parametria, and/or adenexa within 1 to 3 days after the procedure. A recurrent elevation in body temperature (≥38 °C oral or equivalent) should have persisted for approximately 24 hours after the procedure.

4. septic incomplete abortion (spontaneous or induced). This infection was diagnosed in a patient with amenorrhea or abnormal uterine bleeding who had a positive pregnancy test, a temperature of ≥38 °C (oral or equivalent) on two consecutive occasions, and lower abdominal and/or pelvic pain and uterine cramping associated with a tender uterus (and parametrium). The internal cervical os was usually open. The nature of the abortion (elective, spontaneous, or self-induced) will be noted on the subject's Case Report Form.

> **MO Comment:** There were a total of 5 Trovan® and 8 control arm subjects with a septic abortion. It was not clear how many of these patients received a D&C in addition to the study antibiotic as part of their therapy <u>during</u> the study. This information was important because a D&C for retained tissue with a septic abortion would often be indicated. A D&C would render the subject non-evaluable by the MO because it would be a confounding factor in determining efficacy (was the cure due to the D&C, the antibiotic therapy, or both?).

Duration of the treatment of the acute pelvic infection is anticipated to be at least 4 days ("72 hours of continuous therapy").

> **MO Comment:** The above statement was clear for the Trovan® arm of the study because of the q 24 hour IV dosing: it meant at least 4 IV doses <u>or</u> therapy over 72 hours. It was much more confusing for the control arm because of the q 6 hour IV dosing changing to q 8 hour po dosing. For example, a subject who received a 10PM dose on Day 1, 4 doses on Day 2 and 3, and 1 or 2 doses on Day 4 would have received insufficient (< 72 hours of) continuous control arm therapy over the course of 4 different study days, but enough of the Trovan® drug (4 doses on 4 different days).

Exclusion: copied from pages 12-13 of the protocol.

Pregnant women (determined by history of the subject by the principal investigator) or nursing mothers.

Known or suspected hypersensitivity or intolerance to any quinolone, penicillin, or ß-lactam.

Subjects with any of the following disease states:

1. abdominal incision infection after cesarean section or hysterectomy
2. vulvar abscess
3. Bartholin gland abscess
4. pyometra
5. pelvic inflammatory disease
6. cervicitis
7. infection with *Chlamydia trachomatis* which requires treatment.

MO COMMENT: The exclusion criteria were standard and acceptable to the MO. It is of note that two of the excluded infections (PID and Chlamydia infections) were covered by separate Trovan® studies for additional specific indications in this NDA.

Subjects previously enrolled in this protocol.

Subjects with any infections that require treatment with an anti-infective agent other than the study drugs.

Subjects with any of the following conditions:

1. known acquired immunodeficiency syndrome (AIDS)
2. neutropenia, defined as a total white blood cell count < 2,500 leukocytes/mm^3 or an absolute neutrophil count < 1000 neutrophils/mm^3
3. immunosuppressive therapy, defined as chronic treatment with known immuno-suppressant medications (including treatment with greater than 10 mg/day prednisone or equivalent)
4. prior history of seizures or epilepsy
5. terminal illness, defined as subjects who are expected to expire within 48 hours
6. severe renal failure (creatinine clearance < 10 mL/minute/1.73 m^2 defined by the Cockcroft-Gault equation)

Treatment with another investigational drug within 4 weeks prior to the baseline visit, or requiring investigational drug therapy throughout the study period.

Treatment with any systemic antibiotic for 24 hours or longer within 2 weeks prior to entry into the study, unless there is documented evidence of clinical failure. Single dose or standard regimen antibiotics administered for prior surgical prophylaxis are allowed.

MO Comment: Sponsor Table 7 "Listing of Prior Antibiotics Taken at Study Entry", found in Appendix V, listed 157 patients (157/317 represented 49.5% of the entire study subjects). Overall the MO agreed with the sponsor's listing of the clinical evaluability status of these subjects. More than 90% of the prior antibiotics were for prior surgical prophylaxis, which was allowed by protocol, but which was certainly a confounding factor.

Nowhere in the protocol or study report was it clear to the MO exactly what was an acceptable regimen for "prior surgical prophylaxis," and in fact many different antibiotics were used. Close review by the MO of the different prophylactic antibiotic combinations showed, however, that they were commonly-used (acceptable) regimens.

Table 2.4 "Listing of Concomitant Antibiotics Taken During Study" (Appendix I) listed 139 subjects. Closer analysis shows that there was duplication between this Concomitant Antibiotic list and the Prior Antibiotic list, and that at least 47/139 (34%) of these subjects received the antibiotic(s) as surgical prophylaxis. These 47 patients were considered evaluable by the MO if there was evidence that the "concomitant antibiotics" had failed to prevent or treat the patient's infection.

Evidence of recent drug or alcohol abuse or dependence.

Evaluability Criteria

Patients were considered **clinically evaluable by the sponsor** if the following general conditions were met (modified and bolding by MO, from pages 24-5 of study report):

1. they met the inclusion and exclusion criteria;
2. completed between 4-14 days of the therapy;
3. no other systemic anti-infective medications were taken at any time from Day 1 to EOS;
4. completed the study visits and were compliant according to the protocol.

MO Comment: Patients were considered **clinically evaluable by the MO** if the above sponsor criteria were used, except as noted below:

1. patient completed at least 4 days or 72 hours of continuous Rx, and no more than 10 days of Rx;
2. patient could be reevaluated 14 - 52 days after completion of therapy for final clinical evaluation;
3. eliminated patients that could also have had acute PID (from the CRF the MO could not tell if most of the parametritis patients were post op or postpartum or neither); upon request, the sponsor provided further information by email on 11/4/97 on the 23 patients diagnosed with "parametritis". The sponsor provided data on underlying causes, chlamydia and gonorrhea cultures, and prior antibiotic treatment or prophylaxis. MO analysis showed that 17 "parametritis"patients clearly had acceptable associated diagnoses such as PPE or septic abortion; 6 had unspecified diagnoses.
4. allowed 20% of clinically evaluable patients to be evaluated by follow up phone contact, as opposed to an actual visit, under extenuating circumstances (transportation, child care or social problems);
5. required that all patients must have had at least one post-baseline clinical assessment, unless considered a clinical failure or given another antibiotic for insufficient response or unknown reason (after Day 1) at any time during the study; and
6. patient had no intercurrent illness to confound the clinical evaluation.

Patients were considered **clinically non-evaluable by the sponsor** if any of the following were present at the end of study (modified from pages 24-5 of study report):

1. Insufficient Therapy: A subject who discontinued study medication, for any reason other than insufficient therapeutic effect, before completing 3 days of active double-blind therapy (IV and/or oral) was not evaluable.
2. Prior Antibiotic Usage: A subject who took an antibiotic for 1 or more calendar days within 14 calendar days before Day 1 and the baseline pathogens were susceptible to the prior antibiotic were not evaluable unless there was documented evidence of clinical failure or unless the subject had a pelvic abscess and/or phlegmon at baseline. This excluded any antibiotic which began on Day 1 and any prophylaxis before start of the study. If a prior antibiotic started and stopped on Day 1 prior to administration of study medication, that antibiotic was not considered concomitant.
3. Concomitant Antibiotics Given for Intercurrent Illness: A subject who was prescribed a concomitant antibiotic during the course of active treatment for indications other than the primary diagnosis was not evaluable. Additional antibiotics given after the end of active double-blind treatment did not render the subject not evaluable for efficacy assessment unless the antibiotic was given before the End of Study assessment for longer than 1 day. The use of concomitant antibiotic therapy due to insufficient therapeutic effect of the study medication or unknown reason was not a reason for exclusion from the Clinically Evaluable Subjects subset. A prior antibiotic use that ended on Day 1 was not considered concomitant.
4. Intercurrent Illness: A subject who developed an intercurrent illness whose clinical course confounded the clinical evaluation of the subject's clinical response was not evaluable. The sponsor determined intercurrent illnesses that caused a subject to be not evaluable for this reason.
5. No Post-Baseline Clinical Assessments: A subject with no post-baseline investigator clinical assessments was not evaluable unless given an antibiotic for insufficient response or discontinued due to inadequate response any time during the study, up to and including the last day of the End of Study analysis window.

MO Comment: Patients with the following were considered non-evaluable as per the MO.

1. Received 11 to 14 days of double-blind therapy (7 Trovan® and 11 control arm patients);
2. Received less than 4 days or 72 hours of the study double-blind therapy and were not a clinical failure;
3. Discontinued the study antibiotic because of side effects;
4. Non-compliance with the study protocol;
5. Had an uncertain baseline diagnosis (e.g., possible PID, UTI, ruptured cyst, appendicitis);
6. Had an additional infection and/or antibiotic that would interfere with the study evaluation; or
7. Had a concomitant medical or surgical condition that would interfere with the study evaluation (e.g., one subject had acute cholecystitis and another had TTP during the study time).

Endpoints

Primary efficacy endpoint- from page 31 of Phase 3 Protocol.

"The primary efficacy endpoint will be *sponsor defined* (December 1, 1995 Amendment) clinical response at follow-up (day 30). Clinical response will be determined by the sponsor and evaluated after 48 hours of double-blind therapy, at the end of double-blind therapy, and at the end of the follow-up period (day 30). Clinical response will be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. The investigator will classify the clinical presentation of the subject at the evaluation time point (without regard to factors that may have influenced the presentation) using the criteria that follow:

Cure

"The investigator defined complete resolution of all signs and symptoms as cure. The final assessment of cure was made at follow-up (day 30) by the investigator.

Typically, cure was characterised by resolution of:

1. signs and symptoms of an inflammatory response (e.g., fever [body temperature ≥ 38.5 °C], elevated white blood cell count [WBC ≥ 12,500 cells/mm^3]),

2. signs and symptoms of acute pelvic distress. Therapy is typically continued for at least 24 hours after body temperature falls below 37.8 °C in those subjects with relatively uncomplicated acute pelvic infections. In subjects who develop phlegmon or abscess, therapy often continues for 48 hours after temperature returns to normal.

Regardless of which parameters were used, the opinion of the investigator determined cure of the acute pelvic infection in each subject.

Improvement

"Improvement was defined as partial resolution of fever, abdominal pain, and/or other signs and symptoms of acute pelvic infection that were identified during the baseline period prior to initiation of double-blind therapy and no requirement for additional antibiotic.

Failure

"Failure was defined by one or all of the following conditions:

1. lack of resolution of any signs and symptoms of an acute pelvic infection as defined above and a need for additional antibiotic.
2. the need for greater than 14 days of double-blind therapy.
3. the need for surgical intervention. An exception is allowed when the initial diagnosis is made at the time of a surgical procedure.
4. death of the subject as a result of the infectious process.

The occurrence of any of the following conditions will supersede the evaluation of response as cure, improvement, or failure and will result in the reassignment of outcome by the sponsor as follows:

1. for subjects who were previously assessed as failures, the outcome will always be failure at subsequent time points.
2. for subjects who were given a concomitant systemic antibiotic prior to an evaluation time point, response will be classified as failure if the concomitant antibiotic was given for incomplete clinical response or failure.
3. for subjects who stopped double-blind therapy because of no apparent response, response will be classified as failure (August 18, 1995 Amendment).

MO Comment: The MO agreed with these 3 definitions of clinical response.

Bacteriological Response- from page 33 of the protocol.

"Bacteriological response was determined by the sponsor and evaluated (if applicable) after 48 hours of double-blind therapy (day 3), at the end of double-blind therapy, at the end of follow-up (day 30), and at the time of discontinuation due to lack of clinical response.

Definition of bacteriological response was as follows:

Bacteriologic evaluable patient subgroup: from page 33-4 of the protocol.

All subjects with positive pelvic and/or blood cultures at baseline were considered for bacteriologic evaluability.

The following subjects were considered as having **indeterminate outcomes** and excluded from bacteriologic evaluability:

1. relevant post-baseline cultures are not obtained, unless it is a result of the absence of adequate purulent culture material or concomitant antibiotic use due to bacteriologic persistence
2. the subject was not considered clinically evaluable.

The occurrence of any of the above conditions will preclude the evaluation of response as being any of those found below:

Eradication: Elimination of the original causative organism(s) from the same site (e.g., pelvic dead space, abscess, or blood) during or upon completion of therapy.

Presumed Eradication: Absence of adequate culture material (i.e., tissue or abscess) for evaluation because the subject was clinically improved and there was no need to collect any further samples.

Persistence: Failure to eradicate the original causative organism at completion of therapy from sites previously cultured, whether signs of infection are present or not. Also included are the subjects given concomitant antibiotics for bacteriologic persistence at a prior time point.

Superinfection: Emergence of new pathogens during therapy or within 3 days after treatment had been completed, either at the original site of infection or at a distant site.

Presumed Microbiological Persistence: Use of concomitant antibiotic therapy due to continued clinical symptoms of the infection at study entry in the absence of microbiological data.

MO COMMENT: The MO agreed with the above.

Statistical Considerations

The primary efficacy endpoints were clinical response at Day 30 , and bacteriological response if it was evaluable. Clinical response was based on the percent of patients showing a clinical response of cure or improvement at or about day 30 after the first day of antibiotic therapy. The bacterial response was based on the percent of patients showing a bacterial response of "eradication" or "presumed eradication".

The objective of this study was to demonstrate that trovafloxacin was as effective as standard therapy (intravenous cefoxitin and oral amoxicillin/clavulanic acid) in the treatment of acute pelvic infections in women.

The definition of equivalence was that the lower 95 % confidence limit for the difference in response rates is greater than -10% when the true satisfactory response rate of the reference drug is 90 % or better.

A computer-generated, blinded randomization list was provided by the sponsor to the investigators in the study. The treatment groups were randomly assigned with each center and are balanced in a ratio of 1:1.

> **MO COMMENT:** The MO agreed with the above, except to note that a continuity correction factor (CCF) was used by the MO or FDA statistician in calculating each 95% confidence interval (CI). Furthermore, the allowable delta (δ) used in the 95% CI calculation varied with the higher percentage rate of the two treatment groups being compared. The two treatments were considered statistically similar if the lower limit of the 95% CI for the difference in the overall success rates (trovafloxacin minus comparator arm) exceeded a specified value (δ). The specified value was $\delta = -10\%$ if the larger of the two overall success rates was equal to or exceeded 90%; $\delta = 15\%$ if the larger of the two overall success rates was between 80% and 89% (inclusive).

Evaluability: modified from the study report.

As per the sponsor, there were 320 randomized subjects with a signed consent, of which 3 were withdrawn because of an inappropriate baseline diagnosis, leaving 317 treated subjects (see Table below). One other subject was withdrawn, leaving 316 in the clinical ITT group. Of the 317 randomized subjects, 160 received Trovan® and 157 the control arm regimen. 113 Trovan® subjects and 128 control arm subjects completed treatment, and 141 Trovan® subjects and 139 control arm subjects completed study. 66% (107/161) of the Trovan® and 75% of the control arm subjects were clinically evaluable. 55% (88/161) of the Trovan® and 58% (93/159) of the control arm subjects were bacteriologically evaluable. 100% of all treated subjects were evaluated for adverse events, and 146/160 (91%) of Trovan® and 152/157 (97%) of control arm patients were assessed for safety by laboratory testing.

> **MO Comment:** The above percent of bacteriologically evaluable patients met the PTC criteria of at least 50%. The primary efficacy variable, however, was the clinically evaluable population at the end of study (EOS).

The Sponsor's Table A. of Summary of Subject Disposition: from the study report page 31:

Table A. Summary of Subject Disposition per Applicant

	Alatrofloxacin ↓ Trovafloxacin		Cefoxitin ↓ Amoxicillin/Clavulanic Acid	
	Number and Percentage (%) of Subjects			
Randomized Subjects	161		159	
Randomized, Not Treated[a]	1		2	
ALL TREATED SUBJECTS	**160**	(100%)	**157**	(100%)
Withdrawn from Treatment[b]	**47**	(29%)	**29**	(18%)
Completed Treatment	113	(71%)	128	(82%)
Withdrawn from Study	**20**	(13%)	**18**	(11%)
Withdrawn during Treatment	17	(11%)	10	(6%)
Withdrawn during Follow-Up	3	(2%)	8	(5%)
Completed Study	141	(88%)	139	(89%)
Completed Treatment and Study	**110**	**(69%)**	**120**	**(76%)**
EVALUATED FOR EFFICACY				
Clinical Intent-to-Treat	159	(99%)	157	(99%)
Clinically Evaluable	**107**	**(66%)**	**119**	**(75%)**
Bacteriologically Intent-to-Treat	132	(82%)	122	(77%)
Bacteriologically Evaluable	**88**	**(55%)**	**93**	**(58%)**
Assessed for Safety				
Adverse Events	160	(100%)	157	(100%)
Laboratory Tests	146	(91%)	152	(97%)

a One randomized, not treated subject (Subject 5221-0474) in the alatrofloxacin/trovafloxacin group received one dose of placebo and completed study.

b Of the 47 alatrofloxacin/trovafloxacin subjects who were withdrawn from treatment, 30 completed study; of the 29 cefoxitin/amoxicillin/clavulanic acid subjects who were withdrawn from treatment, 19 completed study.

Ref.: Tables 1.1 and 1.2

MO Comment: The two arms were comparable with respect to the numbers of treated subjects who were bacteriologically evaluable and assessed for safety. They differed, however, in terms of the number of subjects who were clinically evaluable, withdrew from treatment, and completed treatment. The difference was primarily due to the 43/161 Trovan® subjects (27%) who withdrew from the treatment after only 1 to 3 days of therapy for reasons other than failure of the treatment (40 of these subjects received only IV therapy) and became clinically non-evaluable. In the control arm there were 33/159 subjects (20.7%) who withdrew after 1 to 3 days of therapy for reasons other than failure of the treatment. See study discontinuation section for further analysis of the subjects who withdrew early in the study.

Evaluability by Center: Table 144.1 below was created by the MO from study report data.

Table 144.1
By Center Evaluability, as per the Applicant

			Trovafloxacin Arm			Control Arm		
		Total Rx'd	Treated # N	Eval. # n	% Eval. = n/N	Treated # N	Eval. # n	% Eval. = n/N
Sponsor Totals ⇒		**317 (% of total)**	**160**	**107**	**67%**	**157**	**119**	**76%**
Center	**Location**							
5221	Philadelphia, PA	23 (7.3%)	12	6	50%	11	10	91%
5238	Los Angeles, CA	100 (31.5%)	51	39	76%	49	42	86%
5529	Los Angeles, CA	3 (0.9%)	1	1	100%	2	2	100%
5601	Denver, CO	3 (0.9%)	1	0	0%	2	2	100%
5602	Louisville, KY	4 (0.3%)	2	1	50%	2	1	50%
5750	Dallas, TX	7 (2.2%)	4	3	75%	3	3	100%
5751	San Francisco, CA	1 (0.3%)	0	0	0%	1	1	100%
5759	Pittsburgh, PA	3 (0.9%)	1	1	100%	2	2	100%
5768	Tacoma, WA	1 (0.3%)	1	1	100%	0	0	0%
5864	Charleston, SC	12 (3.8%)	6	5	83%	6	4	67%
5865	Jacksonville, FL	20 (6.3%)	11	4	36%	9	5	56%
5866	San Diego, CA	29 (9.1%)	14	12	86%	15	12	81%
5870	Miami, FL	2 (0.6%)	1	0	0%	1	1	100%
5875	Oklahoma Cty, OK	6 (1.9%)	3	1	33%	3	1	33%
5898	Houston, TX	7 (2.2%)	3	1	33%	4	2	50%
5899	Philadelphia, PA	2 (0.6%)	1	1	100%	1	1	100%
5900	Philadelphia, PA	15 (4.7%)	7	5	71%	8	5	63%
5901	Orange, CA	3 (0.9%)	2	1	50%	1	1	100%
5902	Philadelphia, PA	6 (1.9%)	3	2	67%	3	3	100%
5911	Sylmar, CA	6 (1.9%)	3	1	33%	3	1	33%
5912	Charlotte, NC	1 (0.3%)	0	0	0%	1	1	100%
5968	Honolulu, HI	5 (1.6%)	2	2	100%	3	2	67%
5988	Nashville, TN	1 (0.3%)	1	0	0%	0	0	0%
6077	Naples, FL	1 (0.3%)	1	0	0%	0	0	0%
6108	Quebec, Canada	1 (0.3%)	1	0	0%	0	0	0%
6109	Minneapolis, MN	26 (8.2%)	13	7	54%	13	9	69%
6125	New Orleans, LA	1 (0.3%)	1	1	100%	0	0	0%
6126	Detroit, MI	9 (2.8%)	4	2	50%	5	3	60%
6144	Chicago, IL	4 (1.3%)	2	0	0%	2	2	100%
6148	Tampa, FL	1 (0.3%)	1	1	100%	0	0	0%
6154	Fort Meyers, FL	5 (1.6%)	3	2	67%	2	0	0%
6344	San Diego, CA	1 (0.3%)	0	0	0%	1	1	100%
6347	Philadelphia, PA	3 (0.9%)	2	2	100%	1	0	0%
6385	Toronto, Ontario	1 (0.3%)	0	0	0%	1	1	100%
6542	San Antonio, TX	4 (1.3%)	2	2	100%	2	1	50%
35 Centers	**Applicant TOTALS**	**317**	**160**	**107**	**67%**	**157**	**119**	**76%**
	MO TOTALS**	**317**	**160**	**96**	**60%**	**157**	**107**	**68%**

** MO totals are listed here for comparison, but discussed later in the MOR.

MO Comment: There were 55 centers of which 35 enrolled patients for this study. The distribution of subjects was uneven with center #5238 in Los Angeles enrolling 100/317 patients (31.5%). Next, in descending order, there were 7 centers collectively with 134/317, or 42.3% of the subjects: 29 (9.1%), 26 (8.2%), 23 (7.3%), 20 (6.3%), 15 (4.7%), 12 (3.8%), and 9 (2.8%) patients. 20 of the centers enrolled a total of 41 patients (1 to 4 subjects per center), and the 20 centers that enrolled 0 patients are not listed above. **TOTAL: 317 patients treated.**

The MO's 203 evaluable patients totaled 23 less than the sponsor's number of 226 . The distribution of these 23 patients was relatively equally split with 11 from the trovafloxacin arm and 12 from the control arm. The listing of the MO changes in evaluable patients can be found in Tables 144.2 and 144.3 shown later in the MOR.

Exclusions from Evaluation: modified from the study report.

Of the 161 Trovan® randomized subjects and 159 control arm subjects, 2 and 1 respectively had an inappropriate baseline diagnosis and were excluded from all analyses. In addition, one subject in the control arm had a perforated appendix and was excluded. This left 159 Trovan® and 157 control arm subjects. 52 in the Trovan® group and 38 in the control group were not clinically evaluable. Therefore 107 and 119 subjects were evaluable. The most common reason for exclusion was concomitant antibiotic therapy for intercurrent illness in 33/161Trovan® (20%) subjects and 12/159 control arm (8%) subjects. Other reasons were lack of follow-up assessments, insufficient therapy, and antibiotic use for > 24 hours within 2 weeks prior to study entry.

Table 2.1.1 copied below from the E-sub presented demographic characteristics of all patients enrolled in both arms of the study. There were obviously no males, only 2 subjects < 16 years old, 7 "older" subjects age 45 to 64, and one age > 64. Per the applicant, "the two treatment groups were generally comparable with respect to age, race and weight. Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects."

Table 2.1.1
Demographic Characteristics
Treated Subjects according to Applicant
Trovafloxacin Protocol 144

	Alatrofloxacin 300 mg -> Trovafloxacin 200 mg mg t.i.d.			Cefoxitin 2000mg q6h -> Amoxicillin/Clavulanic acid 500		
	Male	Female	Total	Male	Female	Total
Number of Subjects		160	160		157	157
Age (yr)						
14-15	0	2 (1%)	2 (1%)	0	0	0
16-44	0	154 (96%)	154 (96%)	0	153 (97%)	153 (97%)
45-64	0	3 (2%)	3 (2%)	0	4 (3%)	4 (3%)
>=65	0	1 (<1%)	1 (<1%)	0	0	0
Mean		27.8	27.8		27.4	27.4
Minimum						
Maximum						
Race						
ARABIC	0	1 (<1%)	1 (<1%)	0	0	0
ASIAN	0	6 (4%)	6 (4%)	0	7 (4%)	7 (4%)
ASIAN INDIAN	0	1 (<1%)	1 (<1%)	0	0	0
BLACK	0	53 (33%)	53 (33%)	0	62 (39%)	62 (39%)
HAWAIIAN	0	1 (<1%)	1 (<1%)	0	2 (1%)	2 (1%)
HISPANIC	0	72 (45%)	72 (45%)	0	69 (44%)	69 (44%)
NATIVE AMERICAN	0	0	0	0	2 (1%)	2 (1%)
WHITE	0	26 (16%)	26 (16%)	0	15 (10%)	15 (10%)
Weight (kg)						
Mean		76.9			78.0	
Minimum						
Maximum						
Missing		3			6	

Percentages may not add to 100 due to rounding.
Source Data: APPENDIX V TABLE 3 Data Extract: 09/09/96 14:45 Table Generation: 09/09/96 14:52

MO COMMENT: It was of note that 96 and 97% of the 160 and 157 treated patients were age 16 to 44, and 97 and 98% of the 107 and 119 clinically evaluable patients in the two study arms (Trovan® and control arm, respectively) were age 16 to 44. Obviously this is the age category for post-partum and post-abortion women, but not necessarily for post-operative gynecological surgery patients. Furthermore, there is discussion in the literature about differences in the vaginal/pelvic flora in pre- and post-menopausal women, as well as differences in the risk of infection in these two groups. This study had only 8/317 subjects (2.5%) over the age of 44.

The MO also noted that the ethnic distribution between the two arms was very similar, with the Trovan® treated arm having a 4% Asian, 16% White, 33% Black, and 45% Hispanic ethnic distribution, and the comparable control arm having a distribution of 4% Asian, 10% White, 39% Black, and 44% Hispanic.