

Safety Review:

There were no deaths in this trial and none of the patients discontinued therapy because of an abnormal laboratory value. There were also no patients who temporarily discontinued therapy because of an adverse event.

1/182 (2%) of the trovafloxacin 3-day subjects, 4/182 (2%) of the trovafloxacin 7-day subjects and 4/178 (2%) of the norfloxacin subjects discontinued therapy because of an AE and are presented below: (One patient from each of the above treatment arms discontinued from the study because of an AE.)

Trovafloxacin 3-day (N = 3):

- 50030117: Discontinued after 1 dose because of dizziness, dry heaves, headache, hives, cough, lightheadedness, nausea, tingling, and wheezing.
- 50110366: Discontinued after 2 doses because of dizziness and nausea, did not complete study.
- 54920285: Discontinued after 3 days because of nausea, ringing in ears, and a sensation of skin crawling. Had already completed course of therapy.

Trovafloxacin 7-day (N = 4):

- 50050184: Discontinued treatment because of stomach pain and vertigo after 1 dose
- 50130300: Discontinued after 5 days because of chest pain, palpitations, and tremors not related to the study drug and did not complete the study.
- 56350006: Discontinued after 5 days because of an intestinal virus not related to the study drug and did not complete the study.
- 58210741: Discontinued after 1 dose because of erysipelas in the right leg not related to the study drug and pyrosis which was related.

Norfloxacin (N = 4):

- 50050136: Discontinued after 3 days because of headaches.
- 50410191: Discontinued after first dose because pill lodged in throat.
- 50410248: Discontinued after 1 dose because of a maculopapular rash.
- 56360259: Discontinued after 2 days because of head "swimming."

One patient on each of the trovafloxacin arms had "serious" AEs (< 1%):

- 50130057: anxiety attack requiring hospitalization, the dose was continued unchanged and the attack resolved.
- 56300064: in the post-treatment period this patient suffered a fractured sternum and was hospitalized.

There were 9 (5%) severe AEs reported on the trovafloxacin 3-day regimen, 9 (5%) on the trovafloxacin 7-day regimen, and 3 (2%) on the norfloxacin regimen. The severe AEs that were treatment related were:
Trovafloxacin 3-day:

- 4 episodes of severe headache.
- 2 episodes of nausea.
- 1 fungal infection.

Trovafloxacin 7-day:

- 1 episode of dizziness.
- 3 episodes of headache.
- 1 episode of vertigo.
- 1 episode of thirst.

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Norfloxacin:
None of the severe events were treatment-related.

Within the trovafloxacin 3-day group, the most common severe AEs were headache and nausea.

Within the trovafloxacin 7-day group headache was also the most common AE.

Within the norfloxacin group aggravated allergy, somnolence, and generalized edema were reported most frequently.

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Copied from the Esub and modified by the MO are the sponsor's Tables 6.2, Summary of AEs by Body System: All Causality and Table 6.3, Summary of AE's by Body System, Treatment-Related.

**Table 116.14:
Adverse Events by Body System, All Causality.**

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	Trovafloracin 3-day	Trovafloracin 7-day	Norfloxacin
NUMBER OF SUBJECTS:			
Evaluable for Adverse Events	182 (100%)	182 (100%)	178 (100%)
Subjects With At Least One Event	69 (38%)	61 (34%)	60 (34%)
Subjects Discontinued due to Adverse Event	3 (2%)	4 (2%)	4 (2%)
ADVERSE EVENTS BY BODY SYSTEM:			
Appl./ Inj./ Incision/ Insertion Site	0	1 (<1%)	0
Autonomic Nervous	2 (1%)	1 (<1%)	3 (2%)
Cardiovascular	0	2 (1%)	0
Centr. & Periph. Nerv.	35 (19%)	37 (20%)	23 (13%)
Gastrointestinal	28 (15%)	16 (9%)	21 (12%)
General	13 (7%)	8 (4%)	18 (10%)
Metabolic/ Nutritional	0	1 (<1%)	0
Musculoskeletal	2 (1%)	1 (<1%)	0
Neoplasms	0	0	1 (<1%)
Other Adverse Events	1 (<1%)	0	3 (2%)
Psychiatric	5 (3%)	3 (2%)	3 (2%)
Reproductive	10 (5%)	8 (4%)	5 (3%)
Respiratory	4 (2%)	5 (3%)	2 (1%)
Skin/ Appendages	5 (3%)	4 (2%)	3 (2%)
Special Senses	1 (<1%)	0	1 (<1%)
Urinary System	1 (<1%)	1 (<1%)	1 (<1%)

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**Table 116.15:
Adverse Events by Body System: Treatment-Related.**

	Trova 3-day		Trova 7-day		Norfloxacin	
Evaluable for Adverse Events	182	(100%)	182	(100%)	178	(100%)
Subjects With At Least One Event	42	(23%)	44	(24%)	36	(20%)
Subjects Discontinued due to Adverse Event	3	(2%)	3	(2%)	4	(2%)
ADVERSE EVENTS BY BODY SYSTEM						
Autonomic Nervous	1	(< 1%)	1	(< 1%)	3	(2%)
Cardiovascular	0		2	(1%)	0	
Centr. & Periph. Nerv.	25	(14%)	27	(15%)	13	(7%)
Gastrointestinal	18	(10%)	11	(6%)	18	(10%)
General	5	(3%)	2	(1%)	6	(3%)
Metabolic/ Nutritional	0		1	(< 1%)	0	
Psychiatric	4	(2%)	2	(1%)	2	(1%)
Reproductive	3	(2%)	6	(3%)	2	(1%)
Respiratory	1	(< 1%)	0		0	
Skin/ Appendages	4	(2%)	3	(2%)	2	(1%)
Special Senses	1	(< 1%)	0		0	

The most frequently affected body systems were the CNS and the autonomic nervous systems with 14%, 15%, and 7% of the AEs per arm respectively. This was followed by the gastrointestinal tract with 10%, 6%, and 10%, respectively. These results are similar to those seen in study 103.

**Table 116.16:
Most Common Treatment-Related AEs (All Randomized Patients)**

	Trovafloracin 3-day N= 182		Trovafloracin 7-day N = 182		Norfloxacin N = 178	
Nervous System	25	(14%)	27	(15%)	13	(7%)
Headache	22	12	20	11	15	8
Dizziness	18	10	18	10	8	4
GI System	18	10	11	6	18	10
Nausea	20	11	7	4	12	7
Abdominal Pain	-	-	1	< 1	2	1
Diarrhea	2	1	1	< 1	2	1

*PATIENTS MADE HAVE HAD MORE THAN 1 CONCURRENT AE.

Other frequently reported AEs included:

Paresthesias: 2 (1%) of the trovafloxacin 3-day patients.

Flatulence: 2 (1%) of the trovafloxacin 7-day patients.

Fatigue: 3 (2%) of the trovafloxacin 3-day, 2 (1%) of the trovafloxacin 7-day patients, and 4 (2%) of the norfloxacin patients.

Dreaming abnormalities and psychiatric disturbances: 4 (2%) of the trovafloxacin 3-day, 2 (1%) of the trovafloxacin 7-day, and 2(1%) of the norfloxacin patients.

Vaginitis: 3 (3%) trovafloxacin 3-day, and 6 (3%) of the trovafloxacin 7-day patients.

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Rash and skin: 4 (2%), 3 (2%), and 2 (1%) per arm ,respectively.

Clinical Laboratory Abnormalities:

Only 17 subjects on the trovafloxacin 3-day arm and 8 on the norfloxacin arm of this study were evaluable for laboratory abnormalities, due to protocol design. There were 154 evaluable patients on the trovafloxacin 7-day arm.

Of these subjects, 3 trovafloxacin 3-day, 18 trovafloxacin 7-day, and 1 norfloxacin patients had clinically relevant abnormalities.

No subject in any group had significant abnormalities of creatinine, total bilirubin, hemoglobin, or hematocrit.

One patient receiving trovafloxacin 3-day developed an elevated SGOT (#50050179: baseline SGOT _____ and SGPT at baseline _____). This patient had a history of psoriasis and had recently been treated with methotrexate and indomethacin, to which the sponsor attributes the abnormalities.

Subject #54920074, on the trovafloxacin 7-day arm, had increased LFTs at baseline (SGOT _____ and SGPT _____), which increased to 152 and 151, respectively. These values subsequently decreased slightly, on day 39 to 145 and 149, respectively.

Other than these events, no other laboratory abnormalities were deemed to be significant by the MO.

Reviewer's Conclusion:

The MO concluded that trovafloxacin 100 mg PO daily for 3 days is as effective as norfloxacin 400 mg PO bid for 3 days in the treatment of uncomplicated UTI in women with a baseline colony count of CFU/mL *Escherichia coli*. No conclusions could be drawn as to trovafloxacin's effectiveness against other uropathogens.

Among the FDA bacteriologically evaluable subjects at the EOT (TOC), the MO found a bacteriological eradication rate of 101/116 (87.1%) for trovafloxacin 3-day vs. 94/105 (89.5%) for norfloxacin. This was equivalent when a 95% CI was applied. There was also equivalence between the trovafloxacin 7-day arm 105/113(92.9%) and the norfloxacin arm 94/105 (89.5%) but not between the 2 trovafloxacin arms where the 7-day regimen was superior.

At the EOS, the rates decreased to 77/104(74%) trovafloxacin 3-day vs. 69/93 (74.2%) norfloxacin, which were equivalent although, neither 3-day regimen was able to demonstrate equivalence with the trovafloxacin 7-day arm 81/98 (82.7%).

Bacteriologic efficacy analyses by pathogen revealed statistical equivalence between the trovafloxacin 3-day and norfloxacin arms for *Escherichia coli* (88/96 (92%) vs. 75/81 (93%). Equivalence was not demonstrated between the trovafloxacin 3 and 7-day arms (88/96 (92%) vs. 85/90 (93%) in this analysis.

The FDA clinically-evaluable population was the same as the bacteriologically evaluable and there was equivalence between all 3 arms at EOT and EOS (EOT: 113/116 (97.4%) 3-day; 110/113 (97.3%) 7-day; 97/105 (92.4%) norfloxacin; EOS: 91/107 (85%) 3-day; 90/101 (89.1%) 7-day; 81/98 (82.7%) norfloxacin).

The MO analyzed all failures, relapses, recurrences, and superinfections and although the MO determined that there were fewer superinfections on all arms as compared to the sponsor, no real difference between the arms was noted.

The MO's results are similar to the sponsor's results both in terms of all overall efficacy as well as in the separate analyses.

In terms of safety, the MO determined that the most frequently reported AEs were from the CNS and the peripheral nervous systems. This was consistent with the AE profile seen in study 103 with > 15% of the patients complaining of dizziness and headache. In this trial, there was also a large number of patients who complained of nausea.

There were 2 trovafloxacin patients with minor elevations of SGOT or SGPT. This was also seen in study 103.

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Reviewer's Overall Conclusion for the Indication of Uncomplicated UTI:

**Table 116.17
Overview of Efficacy Results/Uncomplicated UTI studies (as per the MO)**

Study #	154- 103	154 - 116
Location	US	US and Europe
Type	Phase II, Double-blind	Phase III, Double-blind
Comparator/Duration	Trovafloxacin 100 bid x 7d Trovafloxacin 100 qd x 7d Ciprofloxacin 250 bid x 7d	Trovafloxacin 100 qd x 3d Trovafloxacin 100 qd x 7d Norfloxacin 400 bid x 3d
# Enrolled	221	560
# MO Evaluable (BT)/EOT	22, 22, and 29	116, 113, and 105
# MO Evaluable (Clinically)/EOT	22, 22, and 29	116, 113, and 105
Bacteriologic Efficacy/Patient EOT/EOS	21/22 (95.5%) 15/21 (75%) 19/22 (86.4%) 18/21 (85.7%) 27/29 (93.1%) 22/27 (81.5%)	101/116 (87.1%) 77/104 (74%) 105/113 (92.9%) 81/98 (82.7%) 94/105 (89.5%) 69/93 (74.2%)
Bacteriologic Efficacy by Pathogen/EOT	21/22 (95.4%) 20/23 (86.9%) 28/30 (89.2%)	109/126 (86.5%) 107/116 (92.2%) 100/111 (90%)
Clinical Efficacy by Patient/EOT	21/22 (95.5%) 16/18 (88.9%) 21/22 (95.5%) 17/19 (89.5%) 28/29 (96.6%) 22/26 (84.6%)	113/116 (97.4%) 91/107 (85%) 110/113 (97.3%) 90/101 (89.1%) 97/105 (92.4%) 81/98 (82.7%)
Eradication EOT <i>Escherichia coli</i>	19/19 (100%) 17/18 (94.4%) 21/21 (100%)	88/96 (92%) 85/90 (93%) 75/81 (93%)
Conclusion	Underpowered and Phase II. Trovafloxacin 100 qd appeared numerically comparable to ciprofloxacin for 7 days.	Trovafloxacin 3 days equivalent to norfloxacin 3 days. Trovafloxacin 7 days was superior to trovafloxacin 3 days but equivalent to norfloxacin 3 days for BT efficacy at EOT. Neither 3 day was equivalent to 7 day at EOS. Same results by pathogen. Clinical efficacy revealed equivalence between all 3 arms.
Adverse Events all causality	CNS 26 (36%) 21 (28%) 18 (24%)	35 (19%) 37 (20%) 23 (13%)

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Overall, trovafloxacin appeared safe and effective in the treatment of uncomplicated urinary tract infections caused by *Escherichia coli*, predominantly in women, and the sponsor's request for this indication should be approved at a dose of 100 mg PO daily for 3 days.

The sponsor submitted 2 clinical trials in support of this indication. The first study, 154-103, was a Phase II trial that compared 7 days of trovafloxacin 100 mg/day, trovafloxacin 100 mg/bid and ciprofloxacin 250 mg/bid for 7 days. Although 221 patients were enrolled, the MO determined that only 22, 22, and 29 patients per arm respectively, were evaluable. The MO differed from the sponsor in the inclusion of patients with colony counts $\leq 10^5$ CFU/mL and as to the timing of the TOC analysis. The MO considered evaluable only those patients with colony counts of $\geq 10^5$ CFU/mL and the TOC visit had to be at least 5 days after the completion of therapy.

Statistically significant results could not be obtained from this underpowered study. The MO found an overall bacteriologic eradication rate at the EOT of 21/22 (95.5%), 19/22 (86.4%), and 27/29 (93.1%) per arm respectively.

Bacteriologic efficacy by pathogen for the most commonly isolated baseline pathogen, *Escherichia coli* was 19/19 (100%), 17/18 (94.4%), and 21/21 (100%) per arm respectively.

Clinical efficacy at EOT was also comparable for all 3 arms, with cure rates of 21/22 (95.5%), 21/22 (95.5%), and 28/29 (96.6%) per arm respectively.

The second study, 154-116, was considered pivotal by both the sponsor and the MO. It was a Phase III trial comparing trovafloxacin 100 mg/qd for 3 days (the proposed dose), with trovafloxacin 100 mg/qd for 7 days, and norfloxacin 400 mg/bid for 3 days. Norfloxacin is currently approved for uncomplicated UTI at the dose utilized in this trial.

The MO concluded that trovafloxacin 100 mg PO daily for 3 days was as effective as norfloxacin 400 mg PO bid for 3 days in the treatment of uncomplicated UTI in women with a baseline colony count of $\geq 10^5$ CFU/mL *Escherichia coli*. No conclusions could be drawn as to the effectiveness against other organisms.

Among the FDA bacteriologically evaluable subjects at the EOT (TOC), the MO found a bacteriological efficacy rate of 101/116 (87.1%) for trovafloxacin 3-day vs. 94/105 (89.5%) for norfloxacin. This was statistically-equivalent when a 95% CI was applied. There was also equivalence between the trovafloxacin 7-day arm 105/113 (92.9%) and the norfloxacin arm 94/105 (89.5%) but not between the 2 trovafloxacin arms where the 7-day regimen was superior.

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Bacteriologic efficacy analyses by pathogen revealed equivalence between the trovafloxacin 3-day and norfloxacin arms for *Escherichia coli* (88/96 (92%) vs. 75/81 (93%). Equivalence was not demonstrated between the trovafloxacin 3 and 7-day arms (88/96 (92%) vs. 85/90 (93%) in this analysis.

Equivalence was found in terms of clinical cure between all 3 arms at EOT and EOS (EOT: 113/116 (97.4%) 3-day; 110/113 (97.3%) 7-day; 97/105 (92.4%) norfloxacin; EOS: 91/107 (85%) 3-day; 90/101 (89.1%) 7-day; 81/98 (82.7%) norfloxacin).

The MO's results are similar to the sponsor's results both in terms of all overall efficacy as well as in the separate analyses.

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In terms of safety (study 116), the MO determined that the most frequently reported AEs were from the CNS and the peripheral nervous systems. This was consistent with the AE profile seen in study 103 with > 15% of the patients complaining of dizziness and headache. In this trial, there was also a large number of patients who complained of nausea.

**Recommended Regulatory Action:
Indications and Usage:**

The following statement can be added to the labeling:

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BY [unclear]

/S/

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Regina Alivisatos, MD
Medical Officer, DSPIDPs

- Orig. NDA #20-759
- Orig. NDA #20-760
- HFD-590
- HFD-590/Div. Dir./MGoldberger /S/
- HFD-590/Dep. Dir./RAlbrecht
- HFD-590/MTL/BLeissa /S/ 12/18/97
- HFD-590/MO/RAlivisatos
- HFD-590/CSO/PFogarty
- HFD-725/Biostat/Silliman
- HFD-344/Thomas

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**CONTAINED TRADE
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INFORMATION**

Bacterial Prostatitis:

The proposed indication as it will appear in the labeling, if approved is:

Bacterial Prostatitis caused by *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, or coagulase-negative staphylococci.

The proposed dose is 200 mg PO daily for 28 days.

In support of this indication, the sponsor submitted one double-blind, comparative trial of the efficacy and safety of trovafloxacin at the proposed dose compared to ofloxacin 300 mg PO BID for 6 weeks (42 days).

The MO located other documents within the electronic submission related to the pharmacokinetics and microbiological properties of trovafloxacin. These are summarized in the MOR.

Oral Antimicrobial Agents Currently Approved for this Indication:

Ofloxacin: (*Escherichia coli*)

Norfloxacin: (*Escherichia coli*)

Carbenicillin: (*Escherichia coli*, *Enterococcus faecalis*, *Proteus mirabilis*, and *Enterobacter* spp.)

Ciprofloxacin: (*Escherichia coli* and *Proteus mirabilis*; chronic bacterial prostatitis)

Abbreviations used in this section:

Ofloxacin = Floxin®, Oflox

UTI = urinary tract infection

VB1 = voided bladder specimen 1, (first 5 - 10 ml of voided urine = urethral specimen)

VB2 = voided bladder specimen 2, midstream urine

VB3 = voided bladder specimen 3, the urine voided after prostatic massage

EPS = prostatic secretions expressed by massage

V1 = visit one or baseline visit on study day 1

V2 = visit 2, window = study days 3 - 5

V3 = visit 3, study day 18 - 22

V4 = visit 4, EOT visit for the trovafloxacin-treated patients, study days 33 - 37, window = days 25 - 42

V5 = visit 5, EOT visit for the ofloxacin patients and the second follow-up visit for the trovafloxacin patients, study days 47 - 51, window = study days 43 - 59

V6 = visit 6, EOS visit for all patients, study days 63 - 84, window = study days 60 - 90

EOT = End of Therapy

EOS = End of Study

TOC = Test of Cure

AE = Adverse Event

PTC = Points to Consider

Background:

The term prostatitis is a clinical term, used to describe a large group of adult men with a variety of complaints from the lower urogenital tract. Classification of these patients can be made into 4 subgroups: acute bacterial prostatitis, chronic bacterial prostatitis, nonbacterial prostatitis, and prostatic pain. This subdivision is based on careful bacteriologic assessment of sequential urine cultures obtained during urination (technique of Meares and Stamey). Specifically, VB1, VB2, and VB3 are the sequential urines obtained in addition to the expressed prostatic secretion culture (EPS). The diagnosis of bacterial prostatitis requires that the colony count in the VB3 specimen or the EPS exceed that in VB1, or VB2 by 10-fold. In patients with chronic prostatitis, there are only small numbers of bacteria in the prostate and often this technique is not helpful in establishing a pathogen.

The syndromes of acute and chronic bacterial prostatitis are distinct. Additionally, acute prostatitis does not usually lead to chronic disease and chronic disease is not usually preceded by acute disease.

Acute bacterial prostatitis is an acute localized infectious process, characterized by the development of local heat, tenderness, and fever. Other symptoms of disease include chills, perineal pain, back pain, dysuria, increased frequency, and urgency. The prostate gland is warm, swollen, and tender to palpation. Gram stain specimens of EPS reveal polymorphonuclear leukocytes and bacteria.

Chronic disease usually produces fewer symptoms to none at all, related to the prostate, which serves as a nidus of a low-grade infection. Patients with chronic disease often have symptoms such as low back pain, perineal pressure, low-grade fever, or difficulty urinating during an acute phase but often can be asymptomatic. Chronic bacterial prostatitis, however, is the most common cause of relapsing UTI in men. Rectal examination is not notable during the chronic phase in these patients. This entity is very difficult to cure because of poor penetration of most antimicrobials into the noninflamed prostate and additionally the nidus of the infectious process may be small calculi. Relapses occur frequently.

From the standpoint of bacterial etiology, most cases of acute prostatitis are caused by Gram (-) enteric organisms. In the past, *Neisseria gonorrhoeae* was common but now is seen less frequently. Chronic disease is most commonly caused by *Escherichia coli*, but also by *Klebsiella* spp., *Enterobacter* spp., *Proteus mirabilis* and enterococci. Coagulase-negative staphylococci such as *Staphylococcus epidermidis* as well as *Staphylococcus aureus* and diptheroids are often isolated in EPS specimens but there is debate as to their role as true pathogens as opposed to their presence as urethral commensals.

In terms of therapy, current recommendations suggest that only lipid-soluble and basic compounds are capable of entering the acidic environment of the prostate and exerting a therapeutic effect. Trimethoprim and the fluoroquinolones diffuse into the prostate tissue in high concentrations. Acute disease usually responds well to antimicrobial therapy and following a favorable initial clinical response, therapy should be continued for 4 – 6 weeks. Chronic disease, as stated above, is difficult to cure and often requires surgical intervention. Prior to this however, antimicrobial therapy is used and duration of treatment can be anywhere from 1 – 3 months. Cure rates approximate 33% in these patients. If therapy is unsuccessful, the management approach suggested is either the treatment of acute exacerbations in a traditional manner or the use of chronic suppressive therapy using low daily doses of the aforementioned antimicrobials.

Mandell, Douglas and Bennett's principles and Practice of Infectious Diseases, Fourth edition, pages 680, 681, 1080, 1081.

Other sources that enabled the MO to ascertain current thought as to the bacterial etiology of prostatitis included:

Urinary Tract Infections, Molecular Physiology and Clinical Management, HLT Mobly and John Warren, MD, 1996, page 39: "Acute prostatitis is generally associated with UTI and is caused most commonly by Gram (-) bacilli (*Escherichia coli*, *Klebsiella* spp., and *Proteus* spp., among others). Acute prostatitis is associated with increased number of WBCs per high-power field in prostatic fluid. Gram-positive cocci, including *Enterococcus* spp. and *Staphylococcus aureus* are much less frequently associated with acute prostatitis. Prostatitis due to *Staphylococcus aureus* is often the consequence of catheter use. Infection of the prostate may also occur with *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma* spp. or rarely trichomonads.

Chronic prostatitis can be associated with either relapsing UTI or the persistence of a pathogen within the prostate gland."

Current IDSA Guidelines (Clinical Infectious Diseases, Vol. 15, supplement 1, Nov. 1992, pages S219 – S224), state that "Acute uncomplicated UTI in men, analogous to that occurring in women, is quite uncommon. It should be assumed that any UTI in a man > 40 years of age, is associated with bacterial invasion of the prostate and/or kidney."

"The differentiation in most men between bacterial prostatitis and bacterial UTI is artificial and inaccurate. This distinction should be eliminated for the purposes of clinical trials and all UTIs in men should be regarded as complicated."

"Some men have persistent symptomatic or asymptomatic infection of the prostate even after eradication of bladder bacteruria. This persistence is frequently the cause of recurrent infection with the same microorganism."

In terms of trial design, the IDSA suggests that patients be characterized as having acute disease if they had been free of symptoms of UTI for > 6 months and as having chronic UTI if they have had symptomatic infection with the same organism at least once in the 6 months before enrollment. The schedule of visits is the same in all complicated UTIs including prostatitis. An entry visit followed by V1 at 3 -5 days after the start of therapy, followed by a TOC visit 5 -9 days after therapy is completed are suggested. A second follow-up visit, 4 - 6 weeks after completion of therapy is recommended and should encompass at least 50% of the evaluable patients. It is expected, that in acute disease, > 90% of patients will have improvement at V1 and that > 75% will have microbiological suppression and clinical improvement at the EOT, (5- 9 days post R/x visit). If > 50 % of patients are seen at the 4 -6 week follow-up visit, it is expected that > 50% of these patients will continue to have clinical improvement and microbiological suppression (that is a final outcome of cure).

The current Guidance for Evaluability Criteria of the DAIDP has not recently addressed the issue of bacterial prostatitis. The only available guidance is from the DAIDP's Points to Consider document, which states that for acute prostatitis "one statistically adequate and well controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. In this infection, an evaluable patient should be both clinically and microbiologically evaluable."

"It is assumed that the compound would have also established effectiveness in complicated UTI and that the majority of pathogens are similar. Clearly some potential pathogens such as species of *Chlamydia*, should be evaluated on their responses in this study."

Based on the above, the MO concluded that bacterial prostatitis, although apparently a well-defined clinical entity, has not been dealt with separately by IDSA. Additionally, there is no concurrence between the currently available guidance documents and the medical literature as to the true bacterial etiology of this disease. The current submission as well as previously reviewed NDAs, cited below, have not adequately defined acute and chronic disease, thus all populations studied, appear to have included patients with both acute and chronic disease.

NDA 19-735/Ofloxacin for bacterial prostatitis:

This review resulted in the approval of ofloxacin for the treatment of bacterial prostatitis due to *Escherichia coli*. As per the Division Director's review, the study submitted (in accordance with the PTC Guidance document), utilized the following as minimal evaluability criteria:

- clinical signs and symptoms of prostatitis pretreatment
- expressed prostatic secretion culture positive for a recognized pathogen, prior to the initiation of treatment
- treatment with the drug product for approximately 6 weeks unless a clinical failure
- EPS culture obtained 5 - 9 days after stopping therapy (for those patients treated for approximately 6 weeks; clinical failures not cultured post-treatment, or cultured while still on therapy were considered presumed bacterial persistences)
- clinical signs and symptoms assessed at 5 - 9 days post-therapy and approximately 4 - 6 weeks post-therapy
- no concurrent antimicrobials during the treatment period or follow-up time period (if given, patients were judged to be clinical failures)

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Ofloxacin had a clinical cure rate of 79% at long-term follow-up compared to a 53% clinical cure rate for carbenicillin. Cure plus improvement resulted in an overall cure rate of 86% for the ofloxacin-treated patients and 78% for the carbenicillin-treated patients at the EOT. The eradication rates at the first post-therapy visit were 75% for ofloxacin versus 67% for carbenicillin. There was a 0% and 11% reinfection rate per arm, respectively.

All patients on the ofloxacin arm of the study had an infection with a single organism. The most commonly isolated pathogen was *Escherichia coli* (15/33), followed by *Proteus mirabilis* (4/33), and *Pseudomonas aeruginosa* (4/33). The respective numbers for the carbenicillin patients were 14/33, 5/33, and 1/33. *Enterococcus faecalis* was also seen in 4/33 of the carbenicillin patients and none of the ofloxacin patients. Coagulase-negative staphylococci were considered evaluable in 1/33 isolates on each arm.

The MO determined that the overall trial design of this study was very similar to that reviewed in this NDA. However, although coagulase-negative staphylococci were not excluded, they represented an extremely small percentage of the "pathogens." No differentiation was made in regards to chronicity of disease.

MOR NDA 19-384/S-020/Norfloxacin:

The sponsor submitted 2 studies comparing the efficacy and safety of norfloxacin to carbenicillin. One study was domestic and the other foreign. At the request of the reviewing MO, the sponsor also submitted data demonstrating adequate penetration into prostatic tissue as well as tissue levels. Overall trial design was similar to that described for the ofloxacin NDA with the exception that the late post-therapy follow-up was performed 9 - 12 weeks after the EOT.

One of the per protocol exclusion criteria in these studies was that patients were excluded if they had an organism isolated that had "a high probability of being a urethral colonizer," including *Staphylococcus epidermidis*, diphtheroids, and nonenterococcal streptococci. Eradication rates were higher overall for norfloxacin-treated patients (14/15) as compared to carbenicillin-treated patients (12/15). Recurrence rates were higher for the carbenicillin-treated patients. *Escherichia coli* was the most commonly isolated pathogen (11/15) norfloxacin, (8/15) carbenicillin. The remainder of the isolates were Gram (-) organisms. These results applied to the US study only.

In the foreign trial there were 49 and 26 evaluable patients per arm, respectively. Information was provided at the request of the MO as to the number of previous episodes of prostatitis the patients had had. 32/48 evaluable norfloxacin and 22/26 evaluable carbenicillin patients had had one or more episodes in the past. The status of the remaining patients was unknown. The MO determined, based on this information, that most of the patients had chronic prostatitis as opposed to acute disease. Clinical cure rates (including improved patients) were 48/48 and 25/26 per arm, respectively.

Eradication rates were 40/50 and 14/26 per arm, respectively. Relapse rates were comparable. The pathogen most commonly isolated was *Escherichia coli* (21/50 norfloxacin isolates compared to 6/26 carbenicillin isolates). Gram (-) organisms accounted for the remainder of the evaluable pathogens. *Staphylococcus aureus* was isolated in 6 norfloxacin and 10 carbenicillin patients but was not considered evaluable. Pooled efficacy data revealed a clinical cure rate of 66/67 (98.5%) norfloxacin versus 38/40 (95%) carbenicillin. Bacteriologic efficacy was 57/68 (83.8%) norfloxacin versus 26/41 (63.4%) carbenicillin. There were 3 relapses on the norfloxacin arm and 5 of the carbenicillin arm.

Despite the chronicity of the infections studied, the MO recommended and norfloxacin was approved for the treatment of "prostatitis due to *Escherichia coli*."

Overall trial design was similar to that in the current submission. However, non-enterococcal Gram (+) isolates were not considered evaluable. Additionally, the protocol allowed the investigator to provide the number of previous episodes that occurred in the last 6 months, thus allowing the ROM to analyze the patients for acute and chronic disease.

MOR NDA 19-537/SE1-021/Ciprofloxacin:

Although the applicant submitted this supplement in order to obtain the indication of prostatitis, the RMO requested that the indication be changed to "chronic bacterial prostatitis." The 2 pivotal trials were conducted in the US and Germany and included treatment for 28 days

Follow-up evaluations were performed at 3 days, 3 months, and 6 months after treatment. Evaluable pathogens were either Gram (-) rods or *Enterococcus faecalis* only. *Escherichia coli* was the most common pathogen (56/104 evaluable isolates), followed by *Proteus mirabilis* (12 evaluable isolates). No Gram (+) organisms with the exception of enterococci and *Enterococcus faecalis* (8/10 evaluable pathogens), were considered evaluable. Bacterial eradication rate for ciprofloxacin was 72/89 (80.8%) versus 16/23 (69.5%) TMP-SMX versus 17/20 (85%) carbenicillin. Specific pathogens: *Escherichia coli*: 49/56 (87.5%) and *Proteus mirabilis*: 12/12 (100%).

Although trial design differed as opposed to that of the current NDA, ciprofloxacin was briefly reviewed in order to demonstrate the change in the requested indication. Ciprofloxacin was ultimately approved for chronic bacterial prostatitis caused by Escherichia coli and Proteus mirabilis. The RMO did not provide the numbers of previous infections per patient in the MOR and therefore this reviewer could not ascertain the basis for the characterization of the studied population as one of chronic prostatitis.

Literature Review:

The MO was unable to find many recent, (last 10 years), references pertaining to the bacterial etiology of prostatitis. The following were noted:

- Ten years experience with chronic prostatitis in Africa; Magocha et al; East Afr. J. of Med; 1996 March; 73 (3) 176-8.
73 men were prospectively evaluated. 58 had prostatitis of a non-bacterial etiology. 11 (73.3%) of those patients with an isolate were found to have *Escherichia coli*.
- Bacterial infection in prostatic prostatic; Lowentritt et al; Dept. of Urology, Tulane, Journal of Urology 1995, October 154 (14) 1378-81.
22 patients and 16 controls. 9 patients had positive cultures from prostatic secretions.

Coagulase-negative staphylococci were the most common isolate (68%). The authors concluded that these organisms appear to play an increasing role in the bacterial etiology of chronic bacterial prostatitis.

- Bacteriology of patients with chronic bacterial prostatitis: Fernandez-Milian et al: Programs and Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 33 (0). 1993

A group of 156 men with symptoms of chronic bacterial prostatitis were evaluated using the 4 glass segmental urine test. 142 patients had cultures from all 4 segmented urines. 51 patients (36%) were culture-positive with a total of 62 bacterial strains. The organisms most frequently recovered were coagulase-negative staphylococci (15/62), *Escherichia coli* (6/62), enterococci (3/62), 2 each *Morganella*, *Pseudomonas*, *Staphylococcus aureus*, *Citrobacter*, and *Proteus*. 1 strain of *Enterobacter* was recovered.

- Coagulase-negative *Staphylococcus* in Chronic Prostatitis; Nickel J.C. et al, University of Calgary, Canada, Journal of Urology 1992, February, Vol. 147, 398 –401.

3 patients with a clinical history of prostatitis with coagulase-negative staphylococci in EPS were studied after failing antimicrobial therapy. Biopsies were performed in addition to cultures and the authors concluded that "Coagulase-negative staphylococci may be implicated in the pathogenesis of chronic bacterial prostatitis." They suggested that the biofilm surrounding these bacteria keeps them from being eradicated by antibiotics.

- Kunin Calvin M.: Urinary Tract Infections, Detection, Prevention, and Management. Fifth edition, 1997.

"Acute bacterial prostatitis is a suppurative process characterized by fever, chills, leucocytosis, and acute perineal and low back pain. In more severe cases there may be bacteremia, shock, and DIC. Blood cultures are often positive with the same microorganism found in the urine. *Escherichia coli* and other uropathogens are considered to be the etiologic agents."

"Chronic bacterial prostatitis may be asymptomatic or characterized by a sensation of perineal fullness, low back pain, dysuria, and pyuria. Fever is less common. The hallmark of this process is the presence of the same microorganism with each recurrent episode of UTI. This is the most important cause of recurrent UTI in the adult male and difficult to eradicate because of the presence of prostatic calculi. The microorganisms are the same uropathogens as found in UTIs. Coagulase-negative staphylococci, alpha-hemolytic streptococci, and diphtheroids are part of the normal flora of the male urethra and only rarely cause infections."

"Prostodynia is a noninflammatory condition of unknown origin, encountered most often in young men and characterized by a sense of fullness or pressure in the perineum, testicles and low back. The EPS secretions are sterile."

MO Conclusion: From the information provided above, the MO determined that the sponsor provided a well-designed clinical trial in order to assess the efficacy of trovafloxacin in the treatment of bacterial prostatitis. However, the MO elected not to accept the sponsor's evaluability criteria (listed in the protocol review), as applied in the data analysis because they are inconsistent with the Points-to-Consider guidelines, the medical literature, and IDSA. The evaluability criteria that the MO imposed are:

- Strict adherence to the lower limit of the window of evaluation at the EOT visit, which is also, the TOC visit. As per protocol this was at 5 – 9 days post-therapy. The sponsor widened out this window to a range of study days 25 – 42 (from study days 33 – 37) for the trovafloxacin-treated patients and to study days 43 – 59 (from study days 47 – 51) for the ofloxacin-treated patients. Because of the pharmacokinetics of trovafloxacin and its long half-life of 11 hours, the MO did not consider as an evaluable cure, any patient who was seen before study day 33 (or day +5 post-therapy) for the trovafloxacin-treated patients or study day 47 (day +5 post-therapy) for the ofloxacin-treated patients.

Initially, the MO imposed no such restrictions on the upper limit of the window or at any side of the final (V6) visit. However, after reviewing the sponsor's evaluability criteria and prior to reviewing the data, the MO in conjunction with the MTL, Dr. Brad Leissa, determined that the sponsor in setting up the evaluability windows did not provide for an equal comparison between the 2 arms. Specifically, the trovafloxacin TOC or V4 was set at 25 - 42 days post-therapy which would be anywhere from 3 days before the EOT (28 days) to 14 days or 2 weeks after. The analogous timepoint for the ofloxacin-treated patients (V5) was set at study days 43 - 59 or anytime 1 day post-therapy up to 17 days post-therapy. The sponsor set V6 at study days 60 - 90 for both groups, which represents +5 - +8 weeks post-therapy for the trovafloxacin-treated patients and +3 - +6 weeks post-therapy for the ofloxacin-treated patients. Because this analysis was performed prior to unblinding, it became apparent, that potentially an unfair comparison was being made and that the trovafloxacin-treated patients would technically have had 2 timepoints at which they could have been called a recurrence. However, the same was not true for the ofloxacin-treated patients, where a patient could have only been called a recurrence at V6.

The MO elected to modify the windows for the MOR of the data in the following manner:

V4: Trovafloxacin TOC: Days 33 - 53 (+5 - +25)
 V5: Ofloxacin TOC: Days 47 - 67 (+5 - +25)
 V6: Recurrence assessment: Trovafloxacin: Study days 54 - (+) 4 weeks (= approximately 6 - 10 weeks post-therapy or days + 26 - + 84)
 Ofloxacin: study days 68 - (+) 4 weeks (= approximately 3 - 7 weeks post-therapy or days + 26 - 90).

The MO determined that this modification would ensure a fair comparison and that although staggered it allowed for a clearer assessment of clinical efficacy (cures, failures, or recurrences) and bacteriologic efficacy (eradication, persistence, partial eradication, and presumed persistence).

The MO points out that all evaluable failures were carried forward and that in the sponsor's analysis, the increased range of the window, (against protocol requirements), was effected by the sponsor, post-study and prior to unblinding, in order to capture an increased number of patients.

- The MO did not clearly determine from the literature review or the review of previous NDAs the appropriateness of accepting Gram (+), coagulase (-) organisms as true pathogens in this disease. The MO communicated this to the sponsor on June 19, 1996 in a Telecon. The MTL, Dr. Leissa was present. During the discussion, the MO requested that the sponsor provide information that would justify the inclusion of Gram (+) cocci, other than enterococci, in the group of evaluable pathogens. Additionally, it was requested that the sponsor also provide information pertaining to the acceptability of mixed specimens of this type of organism. The MO stated that she was willing to consider as evaluable only those coagulase-negative staphylococci that were sole pathogens and that meet the other requirements imposed by the sponsor, that is that in order for an organism to be classified as a pathogen in bacterial prostatitis, it is required that the colony count in the VB3 specimen or the EPS exceed by 10-fold that in VB1 or VB2. A consultant's opinion would also have been acceptable if their opinion could be backed up by literary sources. The MO recognized that trovafloxacin, if approved for this organism, has the potential for use in patients where it does not represent a true pathogen but a contaminant.
- The MO was not able to classify the patients into those with acute, chronic, and acute exacerbations of chronic disease. The MO concluded from the literature review that these are indeed different clinical entities but that the bacteriology is similar as is the duration of antimicrobial therapy. Certainly, the relapse rate is expected to be higher for those patients with chronic recurring disease, who may require surgical removal of calculi or other procedures. The sponsor did not provide the investigators with the ability to differentiate these patients in the CRF. Nor was any information provided on the number of recurrences in the last 6 months, as was done in the norfloxacin review. The sponsor did provide the duration since the onset of the primary diagnosis for each patient. The mean duration for the 108 sponsor-evaluable trovafloxacin patients was 73.4 days with a range of 1 - 1042 days, and

42.3 days for the 111 ofloxacin-treated, sponsor-evaluable patients with a range of 1 - 437 days. No real conclusions could be drawn from this information because, as per Dr. Johnson on June 13, 1997, the investigators reported 2 different things in this section, either the duration of the current episode or the duration of the underlying disease. Based on this information, the MO concluded that this study is compromised of a mixed population of patients who most likely were suffering from "acute exacerbation" of chronic prostatitis. The MO points out that true "acute prostatitis" is characterized by toxicity including high fever, and frequent bacteremias necessitating hospitalization and intravenous antimicrobial therapy. EPS can often aggravate this state and many physicians, based on current standard of care, are reluctant to perform this exam on patients. It is therefore relatively unlikely that many patients in this study had true acute disease.

Additionally, the bacteriology associated with this submission was more consistent with that of chronic prostatitis as opposed to acute prostatitis. Consideration should be given to the granting of the indication as "acute exacerbation of chronic prostatitis" or as "chronic prostatitis."

- The MO requested that in the reanalysis of the data, the sponsor adhere strictly to IDSA and Divisional policy in terms of the verification of the bacterial etiology of prostatitis by colony counts. In other words the MO required adherence to the protocol, that in order for a pathogen to be considered evaluable, it had to be present in an amount 10-fold than that which was present in VB1 and VB2. The sponsor did not adhere to this in their analysis but instead, elected to use the standard of "greater than" as opposed to 10-fold.

Toxicity Issues:

The initial IND associated with this NDA was submitted in 7/92. The RMO expressed concern over increased LFTs found in 2/8 dogs studied (increased serum LFTs at 2 months and histologic findings at 6 months). The MO re-reviewed this study (93-783-16) in the MOR of Supplemental Preclinical information, submitted on April 1, 1994. 8 dogs received 50mg/kg of the study drug daily for 6 months. The abnormalities were associated with findings consistent with hepatic necrosis on the microscopic exam. The lesions consisted of centrilobular hepatocellular vacuolar degeneration and necrosis of moderate degree in a male dog and marked in a female. The associated LFT abnormalities were from 2 to 16 times those of the control animals. The RMO provided a comparison of animal and human drug exposure and stated that if this comparison was performed on a mg/m² basis, the conversion factor from dogs to humans is 1/2 (NCI). Using this factor, the human dose that is equivalent to the dog dose is 25 mg/kg/day, for 180 days or if a 60 kg person were used, the daily comparative dose would be 1500 mg. This was compared to the 200 mg daily dose that was ultimately used in the prostatitis study. The MO concluded that there was a safety factor of at least 5 with regards to daily dosage and an additional factor of 12 if duration was considered.

The RMO also provided a comparison of serum blood levels and concluded that a human dose of 300 - 600 mg/day would correspond to the dosage in dogs that had caused hepatotoxicity. This would mean that the safety factor was much lower as only 1 to 2 times the proposed dosage caused problems in dogs. The RMO requested that clinical studies be limited to 14 days duration.

This study (94-783-23), was performed and 4/16 dogs were found to have increased LFTs (primarily ALT), which returned to baseline after treatment discontinuation on days 67 to 89. There was microscopic correlation, that is findings of hepatocellular necrosis and periportal infiltration in 3 of the animals. The histologic changes were all found to be reversible at necropsy. This was at a 50 mg/kg dose for 6 months. The prostatitis study was allowed to proceed after this data was provided but limited to 4 weeks for the trovafloxacin-treated patients. Additionally, the RMO revised the protocol to provide for laboratory reevaluations at day 21 of the study and weekly thereafter.

In addition to the above, the sponsor also performed a phase I study, #154-007, which was an open study, comparing safety, tolerance, and pharmacokinetics in patients with chronic hepatic insufficiency and normal subjects. No abnormalities of significance, attributable to the trovafloxacin were found in patients with Class A impairment at the 100 mg dose daily for 7 days and permission was given to the sponsor to

study patients with class B impairment at a 200 mg daily dose for 7 days. Weight adjusted mean values of AUC than in normal subjects at both dose levels. On multiple dosing, weight adjusting gave the class B subjects the highest dose-adjusted AUC (20.6 mcg-hr/mL), followed by the class A subjects (15.2 mcg-hr/mL). The values for the Class B and A controls were 12.6 mcg-hr/mL and 10.3 mcg-hr/mL, respectively.

The MO provided the above information as background material. This information was of import because of its implications on the duration of therapy and how the protocol was ultimately designed.

Safety issues that developed during this study were reviewed in the safety section of this review.

Microbiology:

In support of the effectiveness of trovafloxacin against the requested pathogens, the sponsor submitted table G.39.1 from the microbiology section of the electronic submission. This table, entitled "Trovafoxacin MICs at Baseline versus Clinical Response and Pathogen Outcome at the EOT for Subjects Treated with Trovafoxacin in Prostatitis Studies," showed the MICs of the pathogens isolated versus trovafloxacin. These are listed below for the requested organisms:

Escherichia coli: $\leq .03$ mcg/mL - $\leq .06$ mcg/mL
Enterococcus faecalis: .12 - .25 mcg/mL
Staphylococcus epidermidis: $\leq .03$ - 8 mcg/mL
Staphylococcus haemolyticus: $\leq .03$ - 4 mcg/mL

Pharmacokinetics:

The sponsor provided a study entitled, "An Open Randomized Study in Patients to Determine the Penetration of Trovafoxacin into Prostatic Tissue Following Multiple Dosing with Trovafoxacin (200 mg QD)"/ protocol 154-041. The pharmacokinetics reviewer reviewed this study, however, for the purposes of this review, it was also mentioned here.

This was an open, randomized study to determine trovafloxacin concentrations in prostatic tissue relative to serum at corresponding timepoints. Thirty-two (32) male subjects scheduled to undergo elective trans-urethral resection of the prostate, ranging in age and in weight entered and completed the study. Subjects received trovafloxacin 200 mg daily, beginning at least 3 days before their scheduled surgery. If the surgery was delayed, an additional (fourth) dose could have been administered. Subjects had their scheduled surgery within one of the following time intervals: 2 to 6 hr, >6 to 12 hr, or >12 to 30 hr after the last dose of trovafloxacin. Two samples of prostate tissue were collected during surgery. At the same time that the first tissue sample was taken, a venous blood sample was also taken for the purpose of determining serum trovafloxacin levels.

Trovafoxacin concentrations in serum and prostatic tissue were generally greater than 1 μ g/mL and 1 μ g/g, respectively, at 3 to 10 hours post-dose. This was many times higher than the MIC 90 of trovafloxacin *in vitro* against *Escherichia coli* (0.06 μ g/mL). The mean tissue concentrations were 0.96 ± 0.63 mcg/mL, the mean serum concentrations were 1.0 ± 0.6 mcg/mL. Both prostatic tissue and serum trovafloxacin concentrations peaked rapidly and then declined in parallel. Trovafoxacin penetrated well into prostatic tissue, with a mean prostatic tissue/ serum concentration ratio of 1.0 ± 0.3 .

The sponsor did not provide information about tissue or serum concentrations beyond 30 hours after the last dose, however, the MO determined previously that it was appropriate to set the lower limit of the first post-therapy evaluability window, at 5 days post-therapy in order to ensure that there was no residual drug in concentrations that would inhibit bacterial growth.

Study 154-119

TITLE: A Randomized, Multicenter, Double-blind, Double-dummy, Comparative trial of Trovafloxacin and Ofloxacin for the Treatment of Bacterial Prostatitis.

List of Principal Investigators:

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	5631	Stacy Childs, MD
	5634	Steven Bull, MD
	5638	Scott Cinel, MD
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	5647	Robert Feldman, MD
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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
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Study dates: July 17, 1995 - May 30, 1996

Objective: The primary objective of this study was to compare the safety and efficacy of trovafloxacin and ofloxacin as treatment for bacterial prostatitis.

Study Design: This was a randomized, multicenter, double-blind, double-dummy, comparative trial of trovafloxacin (200 mg daily), administered orally for 28 days versus ofloxacin (300 mg twice daily), administered orally for 42 days.

Protocol Overview:

Copied below from the electronic submission, appendix A of the study report is the sponsor’s schedule of visits and procedures:

SCHEDULE OF STUDY VISITS AND PROCEDURES

STUDY DAYS

	Screening Day -5	On Therapy				EOT ^a Day 42	Post-Therapy	
		Baseline Day 1	Visit 2 (3-5) ^b Day 4	Visit 3 (18-22) Day 20	Visit 4 (33-37) Day 35	Visit 5 (47-51) Day 49	Visit 6 Day 63-84	
Treatment		X						X
Compliance Checks			X	X	X			X
Informed Consent	X							
Demographic Information	X							
Targeted Physical Examination	X							
Concomitant Medication	X		X	X	X		X	X
Vital signs	X		X	X	X		X	X
Assessments								
Clinical	X		X	X	X		X	X
Laboratory								
1. Hematology	X		X	X	X		X	(X) ^c
2. Serum Chemistry	X		X	X	X		X	(X) ^c
3. Urinalysis	X		X	X	X		X	(X) ^c
4. Fractionated Urine Cultures ^d	X				X		X	X
5. Urine Culture			X	X				
Adverse Events	X		X	X	X		X	

^a End of therapy (double-blind dosing)

^b Window for visit

^c To be done only if there is/are significant abnormality(ies) at visit 5

^d VB₁-Initial 5-10 mL of urinary stream

VB₂-Clean-catch midstream urine Specimen

EPS-Expressed prostatic secretions by digital massage after midstream urine Specimen

VB₃-First 5-10 mL of urinary stream immediately after prostatic massage

As noted from this schedule, within 5 days of starting study drug (screening visit), all subjects were to have a presumptive diagnosis of bacterial prostatitis characterized by one or more signs and symptoms from each of the following two groups:

- APPROX THIS WAY
ON ORIGINAL
- Disturbances of urination, including frequency, urgency, dysuria, and/or lower urinary tract obstruction.
 - Perineal or low back pain, fevers chills, and/or a tender, tense prostate on palpation.

If the screened patients met the above criteria, as well as the inclusion and exclusion criteria, they were considered eligible for evaluation. At this visit they also underwent collection of demographic information, medical history, targeted physical examination, concomitant medication use, and vital signs (pulse, respiration, blood pressure, and body temperature). Hematology, serum chemistry, and urinalysis determinations were performed for safety testing. The investigator confirmed the diagnosis of bacterial prostatitis by quantitative bacteriological cultures (processed by the local laboratory), of the following fractionated urine and prostatic secretion specimens obtained within 5 days before initiation of therapy:

- Voided bladder 1 (VB₁) - Initial 5-10 mL of urine specimen.
- Voided bladder 2 (VB₂) - Clean-catch midstream urine specimen.
- Expressed prostatic secretions (EPS) - Secretions expressed from prostate by digital massage after midstream urine specimen.
- Voided bladder 3 (VB₃) - First 5-10 mL of urine stream immediately after prostatic massage.

The diagnosis of bacterial prostatitis was confirmed by one of the following criteria:

- The colony count of a pathogen in VB₃ exceeded that in VB₁ or VB₂
- The colony count of a pathogen in EPS exceeded that in VB₁ or VB₂

If a patient did not have a confirmed diagnosis of bacterial prostatitis, based on the isolation of a baseline pathogen, they were discontinued from the trial by the investigator. If, however, a patient had a pathogen resistant to study drugs, they were not discontinued from the study drug unless there was failure to improve clinically. If this occurred, the patient was considered an "evaluable failure." In this case, the concomitant medication used as the alternative therapy was reported and the patient was considered evaluable for safety.

At the baseline visit (Visit 1, Day 1, V1) the patients who met all of the above criteria, were randomized to receive treatment. No other assessments were required at this visit, which was to take place as soon as the pathogen was known.

Efficacy evaluations were performed at visits 2 (V2, Day 4) and 3 (V3, Day 20). The evaluations included clinical assessment of signs and symptoms of bacterial prostatitis, as well as any new signs or symptoms since the previous visit. A routine urine culture was obtained from a clean-catch midstream urine specimen and processed by the central laboratory (SciCor). The results of this culture had no implications upon therapy unless the investigator felt that the subject's clinical condition warranted such a change. Other assessments performed at these visits included recording of vital signs, concomitant medication, study drug dosing, adverse events volunteered by the subject or observed by the investigator, and laboratory (hematology, serum chemistry, and urinalysis) evaluations.

At Visit 4 (Days 25-42; EOT for trovafloxacin, V4), an efficacy evaluation, which included clinical assessment of signs and symptoms of bacterial prostatitis, as well as any new signs or symptoms since the third visit was obtained. The investigator made a global clinical assessment, compared to the screening assessment. Quantitative bacteriological culture, as outlined above, was repeated. If expressed prostatic secretion (EPS) was not obtained at this time, bacteriological efficacy was based on urine cultures from VB₁, VB₂, and VB₃. In addition to the efficacy evaluation, other assessments included recording of vital

signs, concomitant medication, study drug dosing, adverse events volunteered by the subject or observed by the investigator, and laboratory (hematology, serum chemistry, and urinalysis) evaluations.

At Visit 5 (Days 43-59, EOT for ofloxacin, V5), an efficacy evaluation was performed in the same manner for the ofloxacin-treated patients.

The final visit or Visit 6 (Days 60-84 EOS, V6) was included for recurrent infections in those subjects cured or improved at visit 5 or visit 4. At this visit, an efficacy evaluation, which included clinical assessment of signs and symptoms of bacterial prostatitis, as well as any new signs or symptoms since the fifth visit was obtained. A global clinical assessment was made, and as in visit 5, quantitative bacteriological cultures were repeated. In addition to the efficacy evaluation, other assessments included recording of vital signs and concomitant medication. Laboratory evaluations performed at previous visits were repeated at this visit only if clinically significant results were detected at V5.

Medical Officer's Comment: *The MO underlined the word "exceeded" in the description of the fractionated urine culture methodology and points out that, although the sponsor utilized this parameter, the protocol as well as all current references and guidelines, clearly state, that the diagnosis of prostatitis is confirmed when the colony count of the organism isolated in the EPS or VB3 specimen is 10-fold that in VB1 or VB2. Therefore, the MO adhered to this parameter in the MO's analysis.*

As stated in the introduction, the MO requested modifications of the windows of evaluability and strict adherence to the lower boundaries of V4 and V5.

Compliance:

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

Protocol Amendments:

This protocol was not amended.

Concomitant Medications:

The investigator documented all concomitant medication usage at each visit. This included any therapeutic interventions. No other antimicrobials were allowed. If another antimicrobial was used, the patient was classified as a treatment failure.

Discontinuation of Therapy:

The investigator discontinued therapy if the patient showed no signs of improvement, clinical worsening or if significant laboratory abnormalities developed. If a patient was discontinued for one of these reasons, a final efficacy assessment was performed at the time of discontinuation. A final safety assessment was performed at visit 5. If the discontinuation occurred because of an adverse event, clinical and microbiological efficacy evaluations were performed at all scheduled visits through visit 6.

Study Population:

As per the original protocol, 300 patients were to be enrolled in this trial, in order to obtain 150 evaluable subjects or 75 per arm. Each study site was to attempt to enroll 5 patients.

Inclusion and Exclusion Criteria:

(Copied from pages 6 and 7 of the original protocol)

Inclusion criteria

1. Outpatient men.
2. At least 18 years of age.
3. Presumptive clinical diagnosis of bacterial prostatitis, based on the presence of one or more signs and symptoms from each of the following two groups:
 - a. Disturbances of urination, including frequency, urgency, dysuria, and/or lower urinary tract obstruction.
 - b. Pains (perineal or low back), fever, chills, and/or a tender, tense prostate on palpation.The clinical diagnosis must be supported by bacteriological confirmation (i.e., a quantitative culture of isolated pathogenic organisms).
4. Written informed consent must be obtained.

Medical Officer's Comment: *These criteria represent standard diagnostic criteria for a prostatitis diagnosis. The sponsor ensured that this study remained a clinical/microbiological study by obtaining bacteriologic confirmation prior to the institution of therapy.*

However, these criteria also allowed for the enrollment of a sub-acute or chronic population rather than an acute (see introduction).

Exclusion criteria

1. Severity of infection requiring parental antimicrobial therapy, (e.g. acute bacterial prostatitis).
2. Known hypersensitivity to any quinolone antibiotic.
3. Inpatients.
4. Non-bacterial prostatitis.
5. Presence of permanent transurethral catheter or history of cystostomy or nephrostomy.
6. History of transurethral resection of the prostate within six months of study enrollment
7. Known or suspected prostatic cancer.
8. Benign prostatic hypertrophy in the absence of findings of bacterial prostatitis.
9. Presence of any other infection at enrollment that may require treatment with an antibiotic other than the study drug.
10. Treatment with any systemic antibiotic for 24 hours or longer within seven days prior to entry into the study, unless there is documented evidence of resistance or clinical failure.
11. Treatment with another investigational drug within 30 days prior to entry into the study.
12. Evidence of significant gastrointestinal or other conditions which may affect drug absorption.
13. Evidence or history of clinically significant hematologic, renal (i.e., serum creatinine greater than 2.0 mg/dL or creatinine clearance \leq 50 mL/min), or immunologic compromise (i.e., neutropenia [total white blood cell count $<$ 2500 mm³ or absolute neutrophil count $<$ 1000 mm³]; or known AIDS).
14. History of epilepsy or seizures.
15. Prior enrollment in this protocol.
16. Subjects who for any reason, in the opinion of the investigator, may not be expected to comply with the requirements of the protocol.

Medical Officer's Comment: Although most of the exclusion criteria were standard, the sponsor specifically excluded patients with a "true" acute" prostatitis (see discussion at the beginning of the MOR).

Randomization and Blinding:

The investigator sequentially assigned study numbers to the subjects as they were determined to be eligible for treatment. The study number was entered onto the subject's case report form and the subject received study medication with the corresponding number.

Dosage Form and Administration:

(Copied from the study report)

Study medication was in the form of tablets, packaged in blister cards, and capsules, packaged in bottles, using a double-dummy technique to maintain blinding. The study drug administration schedule provided one of the following two doses of study drug, dependent upon the randomization assignment:

Trovafloxacin: 200 mg (2 tablets) daily as a single dose for 28 days
Ofloxacin: 300 mg (1 capsule) bid for 42 days

In order to maintain blinding, subjects were given the medication as outlined in the following table:

	<u>AM Administration</u>	<u>PM Administration</u>
Trovafloxacin	2- tablets x 100 mg for 28 days	1-placebo for ofloxacin for 42 days
	1-placebo for ofloxacin for 42 days	
Ofloxacin	2-placebos for trovafloxacin for 28 days	1-ofloxacin x 300 mg for 42 days
	1-ofloxacin x 300 mg for 42 days	

The blister card and bottle with the randomization number corresponding to that assigned to the subject were given to the subject on visit 1 (day 1). Subjects were instructed to begin study drug medication with the morning dose (even if it was not morning), and to complete a full day of medication on day 1. Following day 1, through day 28 of the treatment period, the subject was directed to take two tablets and one capsule in the morning and one capsule 12 hours later. From day 29 through day 42, the subject was to take one capsule in the morning and one capsule 12 hours later.

The subjects were informed that compliance with taking all tablets as instructed was imperative and the investigator reviewed the following with each subject:

- Blister card and bottle labeling, clearly indicating those to be used for morning administration and evening administration
- Morning and evening dosing should be approximately 12 hours apart

- Mineral supplements, vitamins with iron or zinc, or calcium-, aluminum-, or magnesium-based antacids were not to be taken within (before or after) two hours of dosing
- Study medication was not to be taken within (before or after) two hours of meals

Indices of Compliance:

Subjects were informed that compliance with taking all tablets and capsules as instructed was imperative and were asked to bring all unused medication or empty packs to visits 2 and 3, and again to visits 4 and 5. All doses taken were to be recorded in the case report form.

Microbiologic Methods:

The central laboratory performed susceptibility testing for all bacterial isolates by disk diffusion and MICs. The criteria for determining susceptibility were copied from page 11 of the original protocol, below:

CRITERIA	Trovafoxacin		Ofloxacin	
	Zone Size (mm) 5 µg disc	MIC (µg/mL)	Zone Size (mm) 5µgdisc	MIC (µg/mL)
SUSCEPTIBLE	≥ 15	≤ 2	≥ 16	≤ 2
INTERMEDIATE	11-14	4	13-15	4
RESISTANT	≤ 10	≥ 8	≤ 12	≥ 8

Clinical Response:

Clinical response was determined by the sponsor and evaluated at Visits 4, (Days 25-42; end of treatment for trovafloxacin), and 5, (Days 43-59; end of treatment for ofloxacin), or, at the time of discontinuation from the study. This determination was primarily based upon the investigators' global assessment of the clinical presentation of the subject at the evaluation timepoint compared to the screening assessment. Subjects were assessed for signs and symptoms of bacterial prostatitis, as detailed below, and these assessments were recorded on the CRF (Copied from page 21 of the study report):

- Urinary frequency and urgency, dysuria, lower urinary tract obstruction, perineal pain, low back pain, fever >99°F (past 24 hours), chills, and prostate tenderness were to be assessed at Screening and Baseline (Visit 1) and at every clinic visit thereafter by the investigator and noted as present, absent, or not done.

The investigator classified the clinical response of the subject as cure (complete resolution of signs and symptoms of bacterial prostatitis), improved (incomplete resolution of any of the signs and symptoms of bacterial prostatitis, but no requirement for additional antibiotics), or failure (no apparent response or progression of signs and symptoms of bacterial prostatitis).

The presence or absence of recurrence was based on clinical findings at Visit 6. As stated by the sponsor:

"Only subjects cured or improved at Visit 5 were to be assessed at this visit. Their clinical response at Visit 6 was classified as success (cure or improvement at Visit 5, with no recurrence of signs or symptoms of bacterial prostatitis) or recurrence."

Medical Officer's Comment: *The MO agreed with the overall design of this trial and determined that it was consistent with those found in previously reviewed antimicrobials for the indication of prostatitis. The MO queried the sponsor as to the date of the TOC and was informed that this timepoint was at the EOT evaluation or V4 for the trovafloxacin-treated patients and V5 for the ofloxacin-treated patients. In order to maintain the blind, however, the trovafloxacin-treated patients, had an assessment at V5, concurrently with the ofloxacin-treated patients TOC (5-9 days post-therapy for the ofloxacin group and 19 – 23 days post-therapy for the trovafloxacin arm). Therefore, the trovafloxacin-treated patients had an extra evaluation at V5 and then all patients who were cured or improved, were reevaluated for recurrence at V6 (35 – 56 days post-therapy for the trovafloxacin-treated patients and 21 – 42 days post-therapy for the ofloxacin-treated patients). The MO reminds the reader that the primary endpoint in this study was clinical. The MO outlined the MO evaluable windows in the introduction.*

Bacteriological Response

Bacteriological response was determined by the sponsor and determined from the culture results at Visits 4 (Days 25-42; end of treatment for trovafloxacin), 5 (Days 43-59; end of treatment for ofloxacin), 6 (Day 60-84; end of study), or at the time of discontinuation from the study. Eradication of the baseline pathogen defined bacteriological efficacy. Bacteriological response for each subject was classified by the sponsor as eradication (complete or partial), complete persistence, or superinfection.

The presence or absence of recurrence was based on bacteriological findings at Visit 6. Only subjects with complete or partial eradication at Visit 5 were assessed at this visit. Bacteriological response at Visit 6 was classified as success (complete or partial eradication of pathogens at Visit 5 with no recurrence of the eradicated pathogen at Visit 6) or recurrence.

Quantitative bacterial cultures were repeated at V4 and V5; the central laboratory processed these cultures. If expressed prostatic secretions (EPS) were not obtainable at that time, bacteriological efficacy was based on urine cultures from VB₁, VB₂ and VB₃.

Medical Officer's Comment: *As noted above, the sponsor and not the investigator made the determination of bacteriologic response, the opposite of what occurred with clinical response. The sponsor also made the ultimate determination of overall response.*

Only patients who were cured or improved were seen at V6 and the sponsor stated that "all failures were carried forward from earlier timepoints".

Safety Assessments:

An adverse event was defined as a sign or symptom, illness, or clinically important test abnormality, and was monitored up to Visit 5.

All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the adverse event page of the CRF. Following resolution of the adverse event or at the end of the study, the investigator's judgment of causality of the adverse event was recorded.

Adverse events were classified as serious if they were fatal; life threatening; resulted in permanent disability; required inpatient hospitalization or prolongation of hospital stay; or involved congenital anomaly, cancer, or drug overdose. Any other adverse experience considered by the investigator to be serious was also reported to the Pfizer-appointed monitor immediately by telephone. Serious adverse events were monitored throughout the study and for 30 days after the last dose of study drug. All deaths were immediately reported, regardless of elapsed time between last dose in a clinical trial and the death, and thus extended beyond the 30-day post-study timepoint. In case of death, a summary of available autopsy findings was submitted as soon as possible to the Pfizer-appointed monitor.

Medical Officer's Comment: *The MO queried the sponsor as to the adverse event monitoring. The MO was unclear if an adverse event documented in the period after V5 was recorded on the CRF. The*

sponsor's text implied that this was not the case and that only those events that had occurred prior and up to V5 were recorded and followed-up. The sponsor confirmed this statement because "V6 was so far out that it would have been unlikely for any adverse event which could have occurred in this period to have been drug-related".

Clinical Laboratory Tests:

Hematology, serum chemistry, and urinalysis evaluations were performed at screening (Day -5); no laboratory assessments were performed at baseline (Day 1). Hematology, serum chemistry, and urinalysis evaluations were performed at Visits 2 (Day 4), 3 (Day 20), 4 (Day 25-42), and 5 (Day 43-59). Additional laboratory safety tests were only to be obtained at Visit 6 (Days 60-84) if clinically indicated, or if a clinically significant abnormality was present at Visit 5.

Study Monitoring

The study was monitored routinely through site visits by the sponsor or by CROs (Contract Research Organizations), under the supervision of the sponsor.

Data Analysis (as per the sponsor):

(Copied from the study report)

"The data analysis plan outlined in the protocol included an assessment of clinical and bacteriological response between the two groups at specific timepoints during the study (Visits 4, 5 and end of study). However, due to the differing dosing durations, it was thought that comparisons between the treatment arms at the same visit could artificially favor the comparator agent due to its longer treatment duration (i.e., Visit 4 was one week post-therapy for trovafloxacin and during therapy for ofloxacin). Therefore, additional analyses were performed to assess response in relation to dosing. These new analyses assessed clinical and bacteriological response one week post-therapy (Visit 4 for trovafloxacin subjects and Visit 5 for ofloxacin subjects) and clinical response was again assessed three to six weeks post-therapy (last nonmissing observation between Days 46 and 70 for trovafloxacin and end of study visit for ofloxacin)."

***Medical Officer's Comment:** The above statement reflected the manner in which the sponsor ultimately evaluated the data. This schema provided for a staggered analysis. These decisions were made by the sponsor prior to unblinding the data thus ensuring a fair and reasonable comparison.*

At this point, the MO again points out that although the windows of evaluation for V4, V5, and V6 were outlined above, the sponsor, prior to unblinding, widened these out "in order to capture as many patients as possible."

Specifically, V4, as per the protocol was to be performed at study days 33 – 35 but was performed at study days 25 – 42. This implies that although this visit was initially scheduled at 5 – 9 days post-therapy for the trovafloxacin-treated patients, that it could have been done within 3-4 days post-therapy and extending up to 2 weeks post-therapy.

For those patients evaluated at V5, this window was extended to study days 43 – 59 or from 5 – 9 (days 47 – 51) days post-therapy to 1 – 17 days post-therapy.

These changes were not made during the study or prior to breaking the blind.

The MO requested clarification and was informed that "in order to be evaluable for a cure"; the minimum amount of treatment necessary was 21 days.

As determined by the MO and based upon the pharmacokinetic profile of trovafloxacin, the MO's lower boundary for V4 and V5 was maintained at 5 – 9 days post-therapy for both treatment groups and the MO proposed different evaluability windows (see above) for each timepoint.

Subject Subsets:

The sponsor presented results for the following subsets (copied from page 24 of the study report):

All Randomized Subjects

The all randomized subjects subset included all subjects who were randomized to a treatment group, regardless of whether or not a particular subject received any study medication.

All Treated Subjects

The all treated subjects subset included all subjects who received one or more doses of active double-blind study medication. This subset was used for all safety tables.

Clinical Intent-to-Treat Subjects

The clinical intent-to-treat subjects subset included those subjects in the all randomized subjects subset who had a confirmed diagnosis of bacterial prostatitis. Some subjects in this subset may have never received study medication.

Clinically Evaluable Subjects

The clinically evaluable subjects subset included all subjects in the clinical intent-to-treat subjects subset who received study medication, unless any one or more of the criteria for non-evaluability applied.

Bacteriological Intent-to-Treat Subjects

The bacteriological intent-to-treat subjects subset included those subjects in the clinical intent-to-treat subjects subset with at least one baseline pathogen. Some subjects in this subset may never have received any study medication.

Bacteriologically Evaluable Subjects

The bacteriologically evaluable subjects subset included all subjects in the clinically evaluable subjects subset with at least one baseline pathogen, unless one or more of the criteria for non-evaluability applied.

Medical Officer's Comment: *As in previously reviewed trials, the sponsor provided extensive analyses of the data for multiple subgroups. The MO presented only the efficacy analyses for the clinically and bacteriologically evaluable populations. As noted previously, these populations are by protocol the same, although, in the study, the sponsor presents a clinically-evaluable population and a subpopulation of bacteriologically-evaluable patients..*

Both the sponsor and the MO presented safety analyses for ALL treated subjects.

Clinical Evaluability Criteria:

As per the sponsor, if any of the following were present, the subject was considered non-evaluable for clinical efficacy (copied from page 25 of the study report):

1. **Insufficient Therapy:** A subject who discontinued study medication, for any reason other than insufficient therapeutic effect, before completing 21 days of active double-blind therapy was not evaluable.

Medical Officer's Comment: *The MO agreed with this criterion with the prerequisite, that ALL failures diagnosed as such at V2 (days 3-5 on therapy), were carried forward. Therefore an evaluable failure could have received as little as 3 to 5 days of therapy, whereas, an evaluable cure must have received a minimum of 21 days of therapy.*

2. **Prior Antibiotic Usage:** A subject was not evaluable if the subject had been treated with any systemic antibiotic for 24 hours or longer within 7 days prior to enrollment and without documented evidence of resistance or clinical failure.

Medical Officer's Comment: *The MO agreed with this criterion. The practical application was to ensure the enrollment of patients with true pathogens.*

3. **Concomitant Antibiotics Given for Intercurrent Illness:** A subject who was prescribed a concomitant antibiotic (at any time before the one week post-therapy assessment in the new analyses; at any time before the Visit 5 assessment per the protocol) that was potentially effective against the condition under study was not evaluable if the concomitant antibiotic was given for an adverse event or intercurrent illness. The use of concomitant antibiotic therapy due to insufficient therapeutic effect of the study medication was not a reason for exclusion from the clinically evaluable subjects subset. For the purpose of subject evaluability, prior antibiotic use that ended on Day 1 was not considered to be concomitant.

Medical Officer's Comment: *This statement allowed for the exclusion of patients who failed therapy and who were given another antimicrobial prior to their follow-up visit. This would primarily have affected the trovafloxacin-treated patients. The MO queried the sponsor as to how often this occurred. The sponsor replied that ALL evaluable failures were carried forward and that it was extremely unlikely that this situation occurred. The MO determined that since the potential existed, ALL patients who received concomitant antimicrobials and who were excluded, would require a detailed review.*

4. **Intercurrent Illness:** A subject who developed an intercurrent illness whose clinical course confounded the evaluation of the subject's clinical response was not evaluable. The Pfizer Clinical Group determined intercurrent illnesses that caused a subject to be not evaluable for this reason.

Medical Officer's Comment: *The MO queried the sponsor as to the meaning of this statement. The sponsor replied that this situation was not applicable in this indication. The MO determined that ALL patients excluded from the analyses for this reason would require detailed review.*

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 any time during the study, up to and including the last day of the analysis window in the new analyses; end-of-study analysis window per the protocol.

Medical Officer's Comment: *The MO agreed with this criterion.*

6. **No Post-Baseline Assessment in the Evaluable Analysis Window:** In order to be evaluable a subject must have had an assessment in evaluable timepoint windows one week post-therapy for the new analyses; Visit 5 per the protocol, unless
 - the investigator's clinical response was a failure at the previous visit for ofloxacin subjects in the new analyses; failure at the previous visit per the protocol, or
 - the subject was given an antibiotic for insufficient response before or during the one week post-therapy window in the new analyses; Visit 5 window per the protocol.

Medical Officer's Comment: *The sponsor refers only to V5 in this statement but verified to the reviewer that V4 was considered the TOC for the trovafloxacin-treated patients and V5 for the ofloxacin-treated patients. The MO agreed with this criterion with the addition of the lower boundary as previously stated and, for the MO's analysis the change in the analysis windows (see above). Please note that the sponsor did not update the study report to reflect the staggered TOC analysis in all of the following paragraphs but that the MO confirmed that this was what was implied.*

Per protocol, a subject was included in the analysis at the end of study assessment if the subject was:

- clinically evaluable at the Visit 5 assessment, and
- was not given any antibiotics for intercurrent illness before the assessment at the end of study visit, and
- had a clinical assessment in the appropriate window or was given an antibiotic for insufficient response at any time during the study, up to and including the last day of the end of study analysis window, or the subject was a clinical failure at Visit 4 or 5.

A subject was included in the new analyses three to six weeks post-therapy based on the protocol-defined evaluability for Visit 5 and at the end of study assessment:

Criteria for Bacteriological Evaluability:

As per the sponsor, if any of the following were present, the subject was considered non-evaluable for bacteriological efficacy (copied from pages 26 – 27 of the study report):

1. No Baseline Pathogen: No baseline causative pathogen was isolated.
2. Baseline Culture Outside Baseline Visit Window: The baseline culture was done more than 5 calendar days before the first dose of double-blind study medication.
3. No Post-Baseline Cultures: Post-baseline cultures were not obtained, unless:
 - subject was given an antibiotic for insufficient response, at any time up to and including the last day of the one week post-therapy analysis window in the new analyses; Visit 5 analysis window per the protocol, or
 - the investigator's clinical response was recorded in the appropriate window (presumed eradication and presumed persistence are defined by clinical response when post-baseline cultures are missing), or
 - there was a prior clinical failure.

Per protocol, bacteriologically evaluable subjects were excluded from the analysis at the end of study visit if:

- they were excluded from the clinical analysis at the end of study visit, or
- they did not have a culture result or clinical response in the appropriate window, unless given an antibiotic for inadequate response or the subject was a clinical failure at Visit 4 or 5.

In the new analyses, bacteriological response was not performed three to six weeks post-therapy.

Medical Officer's Comment: *The MO agreed with sponsor's criteria of bacteriologic evaluability and points out that all failures were carried forward. However, from these statements, it became apparent that although this was a clinical/microbiological study in that a patient had to have a "pathogen" in order to be considered evaluable, the ultimate outcome for that pathogen was determined by clinical response if follow-up cultures were not obtained.*

The sponsor's final statement confirms that the bacteriologic TOC was performed at V4 and V5 per arm and that V6 was performed merely in order to assess for recurrences.