RESULTS OF STUDY 154-120:

A total of 625 male and female patients were enrolled at 10 centers in the United States. Two additional patients were screened but never randomized. There were 311 patients (133 men, 178 women) randomized to trovafloxacin and 314 patients (137 men, 177 women) randomized to ofloxacin. Enrollment by center and the number of patients considered evaluable by the applicant is presented below:

<table>
<thead>
<tr>
<th>SITE</th>
<th>PRINCIPAL INVESTIGATOR</th>
<th>TROVAFLOXACIN</th>
<th>OFLOXACIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003</td>
<td>James McCarty, M.D.</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Fresno, CA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5012</td>
<td>Z. A. Dalu, M.D.</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>St Louis, MO</td>
<td>21 (60%)</td>
<td>26 (74%)</td>
</tr>
<tr>
<td>5068</td>
<td>Robert B. Jones, M.D.</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Indianapolis, IN</td>
<td>38 (54%)</td>
<td>46 (64%)</td>
</tr>
<tr>
<td>5069</td>
<td>David Martin, M.D.</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>New Orleans, LA</td>
<td>18 (67%)</td>
<td>17 (63%)</td>
</tr>
<tr>
<td>5162</td>
<td>Myron Cohen, M.D.</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Chapel Hill &amp; Raleigh, NC</td>
<td>21 (72%)</td>
<td>27 (93%)</td>
</tr>
<tr>
<td>5163</td>
<td>John Douglas, M.D.</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Denver, CO</td>
<td>13 (65%)</td>
<td>17 (77%)</td>
</tr>
<tr>
<td>5164</td>
<td>H. Hunter Handsfield, M.D.</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Seattle, WA</td>
<td>12 (86%)</td>
<td>11 (79%)</td>
</tr>
<tr>
<td>5165</td>
<td>Jane Schwebke, M.D.</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Birmingham, AL</td>
<td>35 (70%)</td>
<td>38 (76%)</td>
</tr>
<tr>
<td>5166</td>
<td>William McCormack, M.D.</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Brooklyn, NY</td>
<td>19 (79%)</td>
<td>17 (74%)</td>
</tr>
<tr>
<td>5167</td>
<td>Edwin Thorpe, Jr., M.D.</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Memphis, TN</td>
<td>24 (62%)</td>
<td>29 (74%)</td>
</tr>
<tr>
<td>TOTAL**</td>
<td></td>
<td>311</td>
<td>314</td>
</tr>
<tr>
<td></td>
<td></td>
<td>204 (66%)</td>
<td>231 (74%)</td>
</tr>
</tbody>
</table>

*Number in parentheses represents the percent of patients evaluable by study center and then overall.

**Of the 311 trovafloxacin patients (133 men, 178 women), 204 were evaluable (105 men, 99 women)
Of the 314 ofloxacin patients (137 men, 177 women), 231 were evaluable (111 men, 120 women).

COMMENT:
Clinical review of the patient line listings (CRTs) and spot checking of the CRFs showed that there were minimal differences in the sponsor's classification of outcome and the reviewer's classification. Specifically, there were approximately one or two
patients, both male and female, in both the trovafloxacin arm and the ofloxacin arm that could have been reclassified as evaluable, although technically their follow-up visit was at day 10 or 11. Spot checking did not disclose any serious differences, such as failures that were not recognized or reported. Within the limits of the CRT review and the random examination of the CRFs, no discrepancies were noted; thus, the applicant's data are accepted for review. The effect of accepting one or two additional patients as demonstrating eradication is to marginally raise the efficacy. Therefore, the reviewer accepts the applicant's analysis of the data.

REASONS FOR EXCLUSION OF PATIENTS FROM EVALUATION OF EFFICACY

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>TROVAFLAXACIN</th>
<th>OFLOXACIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All M F</td>
<td>ALL M F</td>
</tr>
<tr>
<td>TOTAL ENROLLED</td>
<td>311 133 178</td>
<td>314 137 177</td>
</tr>
</tbody>
</table>

- No pathogen: 73 M, 8 F (65% (37%)) vs. 54 M, 10 F (44% (25%))
- No follow-up visit: 31 M, 19 F (12) vs. 28 M, 15 F (13)
- Concom antibiotic: 2 M, 1 F (1) vs. 1 M, 1 F (0)
- Previously enrolled: 1 M, 0 F (1) vs. 0 M, 0 F (0)

EVALUABLE

- Bacteriological: 204 M, 105 F (99% (56%)) vs. 231 M, 111 F (120% (68%))

ENROLLED PATIENTS

- TROVAFLAXACIN: 133 M, 178 F
- OFLOXACIN: 137 M, 177 F

BACTERIOLOGICALLY

- TROVAFLAXACIN: 105 M, 99 (56%) vs. 111 (81%) OFLOXACIN

COMMENT:

As far as the issue of evaluable vs. nonevaluable patients, it is apparent that approximately 80% of all men (either treatment group) are evaluable. In contrast, there is a greater loss of women from the evaluable pool. The explanation for fewer evaluable women is that many more are screened because the disease can often be asymptomatic in women. The bigger question is that there is a difference between the proportion of trovafloxacin evaluable patients (56%) and the ofloxacin evaluable patients (68%) which should not have occurred by chance. Dr. Johnson at Pfizer commented that the study was conducted double-blind, and that all cultures were evaluated at a central laboratory. There is no obvious explanation for the greater percentage of negative cultures among the trovafloxacin female patients, but this has reduced the number of evaluable females on the test drug.
DEMOROGIC CHARACTERISTICS for the enrolled population and the bacteriologically evaluable population are presented in the table below.

<table>
<thead>
<tr>
<th></th>
<th>TROFAFLOXACIN</th>
<th>OFLOXACIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MALE</td>
<td>FEMALE</td>
</tr>
<tr>
<td><strong>ENROLLED PATIENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>133</td>
<td>178</td>
</tr>
<tr>
<td>Mean</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>125</td>
<td>(94%)</td>
</tr>
<tr>
<td>White</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>79</td>
<td>71</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>TROFAFLOXACIN</th>
<th>OFLOXACIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MALE</td>
<td>FEMALE</td>
</tr>
<tr>
<td><strong>BACTERIOLOGICALLY EVALUABLE PATIENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>105</td>
<td>99</td>
</tr>
<tr>
<td>Mean</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>97</td>
<td>(92%)</td>
</tr>
<tr>
<td>White</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**COMMENT:**
At entry, the patient characteristics for all patients are balanced across the different treatment groups. The balance in demographic characteristics remains also among the bacteriologically-evaluable population as well.

**CONCOMITANT MEDICATION:**
Approximately 30 women in each arm were taking OCP, some treated for vaginitis. At the end of the follow-up visit about one-half of the patients received treatment for chlamydia.
## BACTERIOLOGICAL OUTCOME IN BACTERIOLOGICALLY EVALUABLE PATIENTS

<table>
<thead>
<tr>
<th>EVALUABLE PATIENTS</th>
<th>TROVAFLOXACIN</th>
<th>OFLOXACIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MALE</td>
<td>FEMALE</td>
</tr>
<tr>
<td>SITE OF INFECTION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>URETHRA</td>
<td>104</td>
<td>2</td>
</tr>
<tr>
<td>CERVIX</td>
<td>n/a</td>
<td>94</td>
</tr>
<tr>
<td>RECTUM</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>PHARYNX</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

**COMMENT:**  
As would be expected, the major site of infection was urethra in men, cervix in women. Urethra was the site of infection in 104/105 evaluable trovafloxacin and 111/111 ofloxacin men, 1 trovafloxacin patient had gonorrhea involving only the pharynx (by culture). Cervix was the site of involvement in 94/99 evaluable trovafloxacin women; the other 5 had urethral (2), rectal (2) or pharyngeal (1) involvement. Among ofloxacin women, 116/120 had cervix as the primary site of involvement, while the remaining 4 had either rectal (2) or pharyngeal (2) involvement.

## BACTERIOLOGICAL OUTCOME IN **MALES:**

<table>
<thead>
<tr>
<th>ERADICATION RATES</th>
<th>TROVAFLOXACIN</th>
<th>OFLOXACIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>URETHRA</td>
<td>103/104 (99%)</td>
<td>111/111 (100%)</td>
</tr>
<tr>
<td>CERVIX</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>RECTUM</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>PHARYNX</td>
<td>5/5</td>
<td>4/4</td>
</tr>
</tbody>
</table>

## BACTERIOLOGICAL OUTCOME IN **FEMALES:**

<table>
<thead>
<tr>
<th>ERADICATION RATES</th>
<th>TROVAFLOXACIN</th>
<th>OFLOXACIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>URETHRA</td>
<td>2/2</td>
<td>0/0</td>
</tr>
<tr>
<td>CERVIX</td>
<td>93/94 (99%)</td>
<td>112/116 (97%)</td>
</tr>
<tr>
<td>RECTUM</td>
<td>27/27 (100%)</td>
<td>18/18 (100%)</td>
</tr>
<tr>
<td>PHARYNX</td>
<td>9/9</td>
<td>8/8</td>
</tr>
</tbody>
</table>

**COMMENT:**  
The bacteriological results presented above indicate that trovafloxacin is 99% effective at eradicating gonorrhea from the urethra in men and cervix in women. The size of the study meets the recommended number for men but is slightly shy of the recommended number of 100 women. As noted earlier, another two could be considered...
Evaluable although their follow-up was marginally longer. This issue will be reconsidered after the results of Study 154-107 are reviewed.

In addition, the data are adequate to support approval of treatment of rectal gonorrhea in women. However, inadequate data have been submitted to support approval of the treatment of rectal gonorrhea in males or for the treatment of pharyngeal gonorrhea in either gender.

Penicillinase-Producing Isolates:
The applicant has requested that the labeling grant approval for both penicillinase-producing and non-producing isolates. Information on how many bacteriologically-evaluable patients had isolates that were penicillinase producing was not provided in the study report but was generated by the company as an additional analysis. The information was confirmed in Appendix 5 of the study report and is summarized below (numerator represents number of patients with penicillinase producing isolates; denominator represents number of bacteriologically-evaluable patients):

<table>
<thead>
<tr>
<th></th>
<th>Trovafoxacin</th>
<th>Ofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>15/105</td>
<td>14/111</td>
</tr>
<tr>
<td>Female</td>
<td>15/99</td>
<td>13/120</td>
</tr>
</tbody>
</table>

Among men, each of them had only one isolate (urethra). Among women, there were 7 trovafoxacin and 3 ofloxacin women who had two isolates each (cervix and rectum); thus there were 22 and 16 penicillinase-producing isolates from women, respectively. All of the penicillinase-producing isolates tested were susceptible to trovafoxacin. All of the penicillinase-producing isolates from bacteriologically-evaluable patients were eradicated.

Clinical outcome was reported by the applicant and is presented below:

**CLINICAL OUTCOME IN MALES:**

<table>
<thead>
<tr>
<th></th>
<th>Trovafoxacin</th>
<th>Ofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>91/105 (87%)</td>
<td>102/111 (92%)</td>
</tr>
<tr>
<td>Improvement</td>
<td>12/105 (11%)</td>
<td>9/111 (8%)</td>
</tr>
<tr>
<td>Failure</td>
<td>2/105 (2%)</td>
<td>0/111</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**CLINICAL OUTCOME IN FEMALES:**

<table>
<thead>
<tr>
<th></th>
<th>Trovafoxacin</th>
<th>Ofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>65/99 (66%)</td>
<td>81/120 (68%)</td>
</tr>
<tr>
<td>Improvement</td>
<td>6/99 (6%)</td>
<td>16/120 (13%)</td>
</tr>
<tr>
<td>Failure</td>
<td>6/99 (6%)</td>
<td>4/120 (3%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>22 (22%)</td>
<td>19 (16%)</td>
</tr>
</tbody>
</table>
Intent-to-treat analyses of clinical outcome and bacteriological outcome were also performed by the sponsor, and patients who had missing values were counted as a persistence or eradication, respectively. Therefore, the ITT analyses showed consistently lower rates; however, they did not show a difference in outcome between the two arms which would have suggested that some bias or imbalance may exist.

USE OF CONCOMITANT ANTIBIOTICS
There appear to be only one or two patients per arm who used concomitant antibiotics during the study. One example is a patient who was prescribed SMX/TMP for sinusitis two days into the follow-up. Although trovafloxacin is being developed for the sinusitis indication also, the dosing regimen is more than the single dose given for GC. In addition, about one-half of the patients received treatment for Chlamydia after completion of the study.

STATISTICAL EVALUATION:
The applicant performed a 95% C.I. test for the study and the evaluable population actually fell within their planned + or - 10%. However, a 95% C.I. is irrelevant in this indication, where the lowest acceptable limit of the point estimate is 95%, and approximately 100 women and 100 men should be evaluated.

SAFETY RESULTS:
One female patient in the ofloxacin arm discontinued the study due to vomiting, it was not considered drug related.

There were 33 trovafloxacin patients and 27 ofloxacin patients who did not return for follow-up.

Adverse events were reported in 14% of the trovafloxacin patients and 15% of the ofloxacin patients, 8% in each arm were considered treatment-related. The table below summarizes the more common events. In addition, laboratory abnormalities were reported in approximately 15% of the patients.

<table>
<thead>
<tr>
<th>ANY ADVERSE EVENT</th>
<th>TROVAFLOXACIN</th>
<th>OFLOXACIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Related Adverse Event</td>
<td>24/311 (8%)</td>
<td>24/314 (8%)</td>
</tr>
<tr>
<td>Discontinued due to Adverse Event</td>
<td>0</td>
<td>1/314</td>
</tr>
</tbody>
</table>

APPEARS THIS WAY ON ORIGINAL
The following specific adverse events considered treatment related were reported.

<table>
<thead>
<tr>
<th>Event</th>
<th>Trovafloxacin</th>
<th>Ofloxacine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 311</td>
<td>N = 314</td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (1.6%)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Tongue paralysis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Altered bowel habit</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Moniliasis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Micturition frequency</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>total events</td>
<td>27</td>
<td>26</td>
</tr>
</tbody>
</table>

**COMMENT:**

The adverse event profile of the two regimens appears similar overall with perhaps the following suggested differences. Dizziness was noted in 5 Trovan and 3 ofloxacin patients, yet overall when headache, insomnia, somnolence etc are added there were 7 Trovan events vs. 9 ofloxacin events in the "neurologic"-type category. Vaginitis/meniliasis was reported by 5 Trovan patients vs. 10 ofloxacin patients (approximately 55% of the patients were females). Rash, pruritus or urticaria was noted in 8 Trovan patients vs. 3 ofloxacin patients. These observations need to be compared to the safety profile of Trovan overall in the review conducted by Dr. Coyne. Over 90% of the reported events were considered mild, no serious events were reported. However, for an overall conclusion regarding the safety profile of Trovan, including multiple dose use, the reader is referred to the comprehensive safety review by Dr. Coyne.

Laboratory changes, defined as clinically significant, were reported to be identified in 15% of Trovan patients and 17% of ofloxacin patients. It should be noted that approximately 80% of the enrolled patients had laboratory testing performed before and after treatment to assess for changes in laboratory values following a single dose of trovafloxacin or ofloxacin.
<table>
<thead>
<tr>
<th></th>
<th>Trovafoxacin</th>
<th>Ofloxacin</th>
<th>Definition of Clin. Significant. (relative to normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any abnormality</td>
<td>35/236 (15%)</td>
<td>42/242 (17%)</td>
<td>(&lt; 80% LLN)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0</td>
<td>0</td>
<td>(&lt; 80% LLN)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0</td>
<td>0</td>
<td>(&lt; 75% LLN)</td>
</tr>
<tr>
<td>RBC</td>
<td>0</td>
<td>0</td>
<td>(&lt;75% to &gt;125%)</td>
</tr>
<tr>
<td>Platelets</td>
<td>0</td>
<td>0</td>
<td>(&lt;75% to &gt;125%)</td>
</tr>
<tr>
<td>WBCs</td>
<td>2</td>
<td>3</td>
<td>(&gt; 1.5 x ULN)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1</td>
<td>0</td>
<td>(2 x ULN)</td>
</tr>
<tr>
<td>ALT</td>
<td>0</td>
<td>0</td>
<td>(2 x ULN)</td>
</tr>
<tr>
<td>AST</td>
<td>0</td>
<td>0</td>
<td>(&lt;0.9 or &gt;1.1)</td>
</tr>
<tr>
<td>Protein</td>
<td>0</td>
<td>0</td>
<td>(&lt;0.8 to &gt;1.2)</td>
</tr>
<tr>
<td>Albumin</td>
<td>0</td>
<td>0</td>
<td>(&gt; 1.3 x ULN)</td>
</tr>
<tr>
<td>BUN</td>
<td>0</td>
<td>0</td>
<td>(95 or &gt;1.05)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0</td>
<td>0</td>
<td>(&lt;0.9 or &gt;1.1)</td>
</tr>
<tr>
<td>Sodium</td>
<td>0</td>
<td>0</td>
<td>(&lt;0.9 or &gt;1.1)</td>
</tr>
<tr>
<td>Potassium</td>
<td>0</td>
<td>1</td>
<td>(&gt; 1.3 x ULN)</td>
</tr>
<tr>
<td>Chloride</td>
<td>0</td>
<td>0</td>
<td>(0.9 or &gt;1.1)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>0</td>
<td>0</td>
<td>(0.9 or &gt;1.1)</td>
</tr>
<tr>
<td>Urine RBC</td>
<td>14</td>
<td>16</td>
<td>(6/HPF)</td>
</tr>
<tr>
<td>Urine WBC</td>
<td>12</td>
<td>19</td>
<td>(6/HPF)</td>
</tr>
<tr>
<td>Urine SG</td>
<td>2</td>
<td>6</td>
<td>(1 or &gt;1.035)</td>
</tr>
<tr>
<td>Urine pH</td>
<td>0</td>
<td>0</td>
<td>(&lt;0.9 or &gt;1.1)</td>
</tr>
<tr>
<td>Urine Protein</td>
<td>3</td>
<td>2</td>
<td>(&gt; 2+)</td>
</tr>
<tr>
<td>Urine Glucose</td>
<td>0</td>
<td>0</td>
<td>(&gt; 2+)</td>
</tr>
<tr>
<td>Urine Ketones</td>
<td>1</td>
<td>2</td>
<td>(&gt; 1+)</td>
</tr>
</tbody>
</table>

**COMMENT:**

There were relatively few laboratory abnormalities noted; the majority related to Urine WBC and RBC in both groups.

**STUDY 154-107:**

**TITLE:**

**PURPOSE:**
To assess the safety and effectiveness of three different doses of trovafoxacin in the treatment of uncomplicated gonorrhea in male and female patients.
STUDY DESIGN:
The study was a dose-ranging, randomized, single-center trial conducted in the USA, comparing a single dose of trovafloxacin 50 mg, 100 mg or 200 mg. The plan was to enroll approximately 30 male and female patients.

STUDY CONDUCT: March 31, 1994 to July 11, 1994

INCLUSION AND EXCLUSION CRITERIA:
analogous to study 154-120

DRUGS AND DOSAGE REGIMEN:

Trovafoxacin 50 mg, 100 mg or 200 mg orally, single-dose administered as a powder to be reconstituted to suspension or as a tablet

All drug was administered under direct observation. Dosing was to be done two hours before or two hours after a meal or use of antacid.

A randomization schedule was provided, with different blocks of numbers for male patients and female patients (presumably to ensure adequate enrollment of each gender).

CONCOMITANT MEDICATIONS:
analogous to study 154-120

EVALUATION OF EFFICACY:
analogous to study 154-120

SAFETY ASSESSMENT:
analogous to study 154-120

STUDY RESULTS:

A total of 39 men and women were enrolled by Dr. Edward Hook at Birmingham, Alabama. The number of patients randomized to each group, excluded from evaluation and evaluable for assessment of efficacy is summarized in the table below:
### Troyofloxacin Doses

<table>
<thead>
<tr>
<th></th>
<th>50 mg</th>
<th>100 mg</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male</td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td>Randomized</td>
<td>4</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>No pathogen</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>No follow-up</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bacteriologically Evaluable</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

### DEMOGRAPHIC DATA for all enrolled subjects:

<table>
<thead>
<tr>
<th></th>
<th>50 mg</th>
<th>100 mg</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male</td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td>Age: mean range</td>
<td>23</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Race: black other</td>
<td>4</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Weight: (kg) mean range</td>
<td>72</td>
<td>64</td>
<td>77</td>
</tr>
</tbody>
</table>

The demographic data on the bacteriologically-usable subjects were comparable.

### BACTERIOLOGICAL OUTCOME

<table>
<thead>
<tr>
<th></th>
<th>50 mg</th>
<th>100 mg</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male</td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td>Bacteriologically Evaluable</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Site of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethra</td>
<td>4</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Cervix</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Pharynx</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Rectum</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Note that all patients had eradication of *Neisseria* isolates from all sites, thus the total eradication rates supporting the efficacy of 100 mg of trovafloxacin are presented below, based on combining the results from the 50 mg and 100 mg groups. It is recognized that the study formulations included powder and tablet.

<table>
<thead>
<tr>
<th></th>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>URETHRA</td>
<td>10/10</td>
<td>0</td>
</tr>
<tr>
<td>CERVIX</td>
<td>0</td>
<td>9/9</td>
</tr>
<tr>
<td>PHARYNX</td>
<td>3/3</td>
<td>2/2</td>
</tr>
<tr>
<td>RECTUM</td>
<td>0</td>
<td>2/2</td>
</tr>
</tbody>
</table>

**SAFETY EVALUATION:**

Two patients in the 200 mg group reported somnolence (1) and asthenia (1). No other treatment related events were noted.

Trovafoxacin N = 37

<table>
<thead>
<tr>
<th>Any abnormality</th>
<th>Definition of Clinically Dsginifant (relative to normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>(&lt; 80% LLN)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>(&lt; 80% LLN)</td>
</tr>
<tr>
<td>RBC</td>
<td>(&lt; 75% LLN)</td>
</tr>
<tr>
<td>Platelets</td>
<td>(&lt; 75% to &gt; 125%)</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>(&lt; 75% to &gt; 125%)</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>(&gt; 10%)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>(&gt; 1.5 x ULN)</td>
</tr>
<tr>
<td>ALT</td>
<td>(&gt; 2 x ULN)</td>
</tr>
<tr>
<td>AST</td>
<td>(&gt; 2 x ULN)</td>
</tr>
<tr>
<td>Protein</td>
<td>(&lt; 0.9 or &gt; 1.1)</td>
</tr>
<tr>
<td>Albumin</td>
<td>(&lt; 0.8 to &gt; 1.2)</td>
</tr>
<tr>
<td>BUN</td>
<td>(&gt; 1.3 x ULN)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>(&gt; 1.3 x ULN)</td>
</tr>
<tr>
<td>Sodium</td>
<td>(&lt; 95 or &gt; 1.05)</td>
</tr>
<tr>
<td>Potassium</td>
<td>(&lt; 0.9 or &gt; 1.1)</td>
</tr>
<tr>
<td>Chloride</td>
<td>(&lt; 0.9 or &gt; 1.1)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>(&lt; 0.9 or &gt; 1.1)</td>
</tr>
<tr>
<td>Urine RBC</td>
<td>(&gt; 6/HFP)</td>
</tr>
<tr>
<td>Urine WBC</td>
<td>(&gt; 6/HFP)</td>
</tr>
<tr>
<td>Urine SG</td>
<td>(&lt; 1 or &gt; 1.035)</td>
</tr>
<tr>
<td>Urine pH</td>
<td>(&lt; 0.9 or &gt; 1.1)</td>
</tr>
<tr>
<td>Urine Protein</td>
<td>(&gt; 2+)</td>
</tr>
<tr>
<td>Urine Glucose</td>
<td>(&gt; 2+)</td>
</tr>
<tr>
<td>Urine Ketones</td>
<td>(&gt; 1+)</td>
</tr>
<tr>
<td>Urine Casts</td>
<td>(&gt; 1)</td>
</tr>
</tbody>
</table>
COMMENT:
Several patients had elevations in potassium, presence of urinary RBC and WBC. Two patients had neutrophils less than 1000/mm^3. These findings need to be taken in context of the overall safety profile of this agent from other studies.

SUMMARY AND RECOMMENDATIONS:

Two clinical studies were conducted, a dose ranging study 154-107 testing 50 mg, 100 mg or 200 mg of trovafloxacin in a total of 39 male and female patients and study 154-120 comparing 100 mg of trovafloxacin to 400 mg of ofloxacin in 625 male and female patients.

The eradication rates for *Neisseria gonorrhoeae* in bacteriologically evaluable patients from each of the studies is summarized in the table below.

**BACTERIOLOGICAL OUTCOME IN MALES** treated with trovafloxacin:

<table>
<thead>
<tr>
<th></th>
<th>154-107</th>
<th>154-120</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>URETHRA</td>
<td>10/10</td>
<td>103/104</td>
<td>113/114 (99%)</td>
</tr>
<tr>
<td>PHARYNX</td>
<td>3/3</td>
<td>5/5</td>
<td>8/8</td>
</tr>
<tr>
<td>RECTUM</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**BACTERIOLOGICAL OUTCOME IN FEMALES** treated with trovafloxacin:

<table>
<thead>
<tr>
<th></th>
<th>154-107</th>
<th>154-120</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERVIX</td>
<td>9/9</td>
<td>93/94</td>
<td>102/103 (99%)</td>
</tr>
<tr>
<td>RECTUM</td>
<td>2/2</td>
<td>27/27</td>
<td>29/29</td>
</tr>
<tr>
<td>PHARYNX</td>
<td>2/2</td>
<td>9/9</td>
<td>11/11</td>
</tr>
<tr>
<td>URETHRA</td>
<td>0</td>
<td>2/2</td>
<td>2/2</td>
</tr>
</tbody>
</table>

Thus, based on these results, it is recommended that trovafloxacin be approved for the treatment of uncomplicated gonorrhea (cervical and urethral) at a dose of 100 mg orally. In addition, the treatment of rectal gonorrhea in women may be approved. The data submitted are inadequate to approve treatment of rectal gonorrhea in males and the treatment of pharyngeal gonorrhea in any gender.

The applicant has provided data on at least 10 penicillinase-producing isolates of *N. gonorrhoeae* that were treated and eradicated, per gender. These isolates were susceptible to trovafloxacin. To date, the Division has not placed information on the penicillinase status of *Neisseria gonorrhoeae* in the approved labeling of any quinolone antimicrobial, because this mechanism of resistance is not linked to resistance to quinolones. Thus, the approved labeling for trovafloxacin should not mention the penicillinase status of the isolates at this time.
PROPOSED LABELING REVISION:
Carmen DeBellas, R.Ph.

Renata Albrecht, M.D.

cc: NDA 20-759
HFD-590
HFD-590/DepDir/Albrecht
HFD-520/Pharm/Ellis
HFD-520/Micro/Altaie
HFD-590/Chem/
HFD-590/CSO/Fogarty
Clinical Review GC
HFD-590/Leiss

Concurrence:
HFD-590/DD/Goldberger
HFD-590/TL/Leiss
MEDICAL REVIEW OF NDA 20-759, 20-760

Applicant:
Pfizer Inc.
Central Research Division
Eastern Point Road
Groton, CT 06340
Contact person: Ronald Trust, Ph.D., M.B.A.

Date of submission: December 27, 1996
Date received by reviewer: January 14, 1997
Date review begun: September 15, 1997
Date draft of review completed: December 2, 1997
Date review received from secondary reviewer: October 21, 1998
Date review completed: November 17, 1998

Currently approved indications: none

Material reviewed: Electronic submission

REGULATORY BACKGROUND

PROPOSED LABELLING

DRAFT LABELING

REGULATORY GUIDANCE

A. 1992 DAIDP Points to Consider
   1. Establish equivalence or superiority to an approved product in one statistically adequate and well-controlled, multicenter trial
   2. At least 50% of the clinically evaluable patients must be bacteriologically evaluable
1. Subjects b(4) are considered adults except when age-specific safety issues need to be considered.

2. Patients should be stratified at enrollment according to the type of pelvic inflammatory disease (PID)— uncomplicated or complicated

3. A diagnosis of PID must be confirmed by meeting clinical and microbiologic criteria and/or by laparoscopy and/or endometrial biopsy.

4. Patients who are seropositive for syphilis should be excluded from the study and considered to have an indeterminate outcome.

5. It is expected that the clinical cure rates for acute PID and tubo-ovarian abscess (TOA) will be b(4) respectively.

6. Treatment for acute PID due to N. gonorrhoeae and mixed anaerobes must be given parenterally for at least 4 days, and then for at least 48 hours after a favorable clinical response. Antichlamydial therapy should be given for a total of 14 days. The minimum duration of parenteral therapy for TOA should be 7 days.

7. Patients must be followed for 2-4 weeks after therapy to be eligible for evaluation of efficacy. The presence of C. trachomatis or N. gonorrhoeae, even in the absence of symptoms, is indicative of the failure of treatment.

NON-CLINICAL STUDIES
(b)(4)

Animal Pharmacology/Toxicology
See Toxicology review by A. Ellis, Ph.D.

Microbiology
See Microbiology review by S. Altaie, Ph.D.

CLINICAL STUDIES
Human Pharmacokinetics/Pharmacodynamics
See full review by P. Colangelo, Ph.D.
Trovafoxacin’s biologic half-life is approximately 9 to 11 hours. The mean bound fraction in plasma samples is approximately b(4) Steady state concentrations are achieved by the third daily dose. In adult subjects, the pharmacokinetics of trovafoxacin are not affected by age or gender. Peak blood level (Cmax) of trovafoxacin at a 200 mg oral dose is 2.5 ug/mL, and tissue/serum concentration ratios in the cervix after single and multiple doses of trovafoxacin 200 mg were 0.5 ug/mL (3-29 hr postdose) and 0.6 ug/mL (3-16 hr postdose), respectively.

Human Clinical Experience
The efficacy and safety of trovafoxacin for several indications was evaluated in 45 phase I studies and 31 phase II/III studies.
INTRODUCTION TO CLINICAL TRIALS
The applicant submitted 2 pivotal clinical trials in support of this indication: a randomized, comparative trial to assess the efficacy of trovafloxacin in ambulatory patients with PID, and the second, a randomized, double-blind, comparative trial to evaluate trovafloxacin for the treatment of hospitalized patients with complicated PID.

Study 154-122
Title: "A randomized, multi-center, investigator-blind, comparative trial of CP-116,517/CP-99,219 and cefoxitin/doxycycline for the treatment acute pelvic inflammatory disease in hospitalized subjects"

Primary objective
To compare the efficacy and safety of alatrofloxacin/trovafloxacin and cefoxitin/doxycycline in the treatment of hospitalized subjects with acute pelvic inflammatory disease.

Study Design Summary
Location
Patients
16 years and older
Study dates
5 June 1995 - 9 May 1996
Amendment dates
March 21, 1995; August 18, 1995
Study dose and duration
Alatrofloxacin IV and Trovafloxacin orally 200 mg qd for 14 days
Comparator
Cefoxitin 2gm IV q 6h PLUS
Doxycycline 100mg IV q 12h then doxycycline 100mg for total 14 days
Blinding
1:1 random assignment at each center
Method of assignment
clinical outcome at visit 4
Primary efficacy variable
clinical signs and symptoms, laboratory results
Safety variables
Therapy evaluation, days (window)
1 (within 48 hours)
Baseline
72 hours after initiation of treatment
Visit 2
14 (14-20)
End of treatment-EOT
week 4-6 after initiation of therapy
End of study-EOS
79 (alatrofloxacin/trova)/ 79 (cefoxitin/doxycycline)
Number of subjects randomized
79

STUDY POPULATION
Inclusion criteria
1. Hospitalized women. Women of childbearing potential (i.e., not surgically sterile ≤ one year post menopausal) with a negative urine or serum gonadotropin pregnancy test immediately prior to entry in the study and using adequate contraception both during and for one month after the end of treatment.
2. At least 16 years of age.
3. Presumptive diagnosis of acute PID. While subject enrollment may have been based on a diagnosis established solely on clinical grounds, the diagnosis may, at the investigator's discretion, have been confirmed by laparoscopy or by endometrial biopsy (with the histological finding of polymorphonuclear leukocytes and/or plasma cells). Clinical and/or laparoscopic staging followed Hager's criteria (see below). Clinical diagnosis must have been substantiated by all of the following (a through c):
a. Lower abdominal tenderness, with or without rebound (unilateral or bilateral)
b. Tenderness upon motion of the cervix and uterus
c. Adnexal tenderness (unilateral or bilateral)
d. In addition, at least one of the following must have been present:
   (1) Evidence suggesting cervical infection with *Neisseria gonorrhoeae*
       and/or *Chlamydia trachomatis*:
       (a) Mucopurulent endocervicitis
       (b) Positive Gram stain for Gram-negative intracellular diplococci
       (c) Endocervical Gram stain demonstrating ≥ 10 WBC/oil immersion field (x 1,000)
       (d) Positive result in a rapid diagnostic screening test for *C. trachomatis*
   (2) Purulent material obtained by culdocentesis or laparoscopy (if performed)
   (3) Inflammatory mass suspected on bimanual examination and
       confirmed by ultrasound
   (4) Fever (admission temperature ≥ 38°C [100.4°F])
   (5) Leukocytosis (WBC ≥ 10,500/mm³)
   (6) Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
   (7) Plasma cell endometritis (> 1 plasma cell/HPF on endometrial biopsy [if performed])

Medical officer’s comments:
The medical reviewer agrees with the criteria as outlined, which are standard diagnostic criteria for PID.

GRADING OF PID BY CLINICAL EXAMINATION
I. Uncomplicated: Limited to tube(s) and/or ovary(ies)
   A. Without pelvic peritonitis
   B. With pelvic peritonitis
II. Complicated: Inflammatory mass or abscess involving tube(s) and/or ovary(ies)
   A. Without pelvic peritonitis
   B. With pelvic peritonitis
III. Spread to structures beyond pelvis, i.e., ruptured tubo-ovarian abscess
NOTE: Subjects with Grade III PID were excluded from the study.

SEVERITY OF DISEASE BY LAPAROSCOPIC EXAMINATION
Mild: Erythema, edema, no spontaneous purulent exudate;* tubes freely moveable
Moderate: Grossly purulent material evident; erythema and edema more marked.
Tubes may not be freely moveable, and fimbria stoma may not be patent.
Severe:
   1. Pyosalpinx or inflammatory complex
   2. Abscess*  
* The tubes may have required manipulation to produce purulent exudate.
* The size of any pelvic abscess should be measured.
Exclusion criteria

1. Pregnant women, nursing mothers, or women of childbearing potential not practicing adequate means of contraception
2. Known or suspected hypersensitivity or intolerance to any quinolone antibiotic, clindamycin, or lincomycin.
3. Outpatients.
4. Suspected ruptured tubo-ovarian abscess (TOA) on admission.
5. Intrauterine device in place which the subject refuses to have removed within 24 hours of entry into the study.
6. History of pelvic or abdominal surgery within the 30 days prior to admission.
7. Presence of any other infection at enrollment that may have required treatment with an antibiotic other than the study drugs. A single dose regimen for treatment of trichomoniasis after clinical response had been demonstrated was acceptable.
8. Treatment with any systemic antibiotic for 24 hours or longer within two weeks prior to entry into the study, unless there was documented evidence of clinical failure.
9. Treatment with another investigational drug within 30 days prior to entry into the study.
10. Evidence of significant gastrointestinal or other conditions which may have affected drug absorption.
11. Evidence or history of clinically significant hematologic, renal (i.e., serum creatinine greater than 2.0 mg/dL or creatinine clearance or immunologic compromise (i.e., neutropenia [total white blood cell count 1000/mm³] or known AIDS).
12. History of epilepsy or seizures.

Medical officer’s agrees with criteria as outlined. Patients with trichomoniasis during the study could receive a single dose of therapy with an appropriate agent after the assessment of clinical and microbiologic outcome; these patients were not excluded and were eligible for evaluability.

SUBJECT EVALUATION VISITS

Visit 1 at day 1 (Baseline)
Within 24 hours prior to the start of therapy, baseline visit assessments included a history and a targeted physical examination, a serum or urine gonadotropin pregnancy test for women of childbearing potential, a standard panel of blood and urine safety tests, and a serologic test for syphilis (FTA or RPR).

In an attempt to standardize and semiquantitate clinical severity of PID and to assess the clinical response to therapy, a Clinical Tenderness Score (CTS) was used (see below). Upon entry into the study, the CTS (maximum CTS = 42), extent of fever, and white blood cell count were determined for each subject. The subject's body temperature and CTS were also assessed at the follow-up visits, two and four to six weeks following initiation of therapy.

CLINICAL TENDERNESS SCORE FOR PID (MAXIMUM = 42)

A. The following areas were assessed:
   1. Abdominal tenderness (direct); score each quadrant
   2. Abdominal tenderness (rebound); score each quadrant
   3. Cervical motion tenderness
   4. Uterine tenderness
   5. Adnexal tenderness, left
6. Adnexal tenderness, right
7. Adnexal mass, left
8. Adnexal mass, right

B. Scoring
1. Tenderness
   0 = tenderness absent
   1 = tenderness described by subject but not manifested by changes in facial expression or abdominal muscle tone
   2 = tenderness resulting in altered facial expression or abdominal muscle tone
   3 = tenderness causing observable marked distress

2. Adnexal masses, scored by size
   0 = no mass
   1 = mass < 2 cm
   2 = mass 2-5 cm
   3 = mass > 5 cm

While they may have been obtained by use of culdocentesis, the following specimens were required from each subject (a and b):

a. Culture by swab of the endocervix and rectum for *N. gonorrhoeae*, and *C. trachomatis* from the endocervix by culture (strongly recommended), antigen detection, or other acceptable rapid nonculture test.

b. endometrial material for anaerobic and facultative culture and for isolation of *N. gonorrhoeae*, and *C. trachomatis* by culture (strongly recommended), antigen detection, or other acceptable rapid nonculture test. All isolates of *C. trachomatis* were to be frozen at -70°C for possible susceptibility testing later.

c. For those subjects undergoing laparoscopy (at the investigator’s discretion), a directed culture from the fallopian tube was to be obtained for aerobic and anaerobic cultures and for isolation of *N. gonorrhoeae*. *C. trachomatis* was to be sought by culture, antigen detection, or other acceptable rapid nonculture test. Peritoneal fluid was to be cultured for the same microorganisms.

Visit 2 at 72 hours
Failure to demonstrate response at 72 hours after initiation of therapy (i.e., reduction in the CTS, and/or reduction in fever, and/or reduction in white blood cell count) constituted clinical failure, and the investigator was to remove the subject from study treatment and institute alternative treatment. The battery of blood and urine tests performed at baseline was repeated.

Switching from intravenous to oral therapy
The subject’s need for continued intravenous therapy was checked daily between days 3 and 7 of therapy. It was appropriate to switch to oral therapy if:

a. Resolution of fever (based on daily maximum temperature) and reduction in white blood cell count, ESR, and CRP were documented
b. Improving CTS noted

Visit 3 at 2-4 days following completion of therapy
Endocervical and rectal specimen cultures for *N. gonorrhoeae*, and endocervix culture (strongly recommended), antigen detection, or other acceptable rapid non-culture test for *C. trachomatis* were repeated. At the investigator’s discretion, endometrial biopsy could be repeated for
anaerobic and facultative culture and for isolation of *N. gonorrhoeae*. Bacteriological response of *N. gonorrhoeae* and *C. trachomatis* was based on the assessments at visits 3 and 4.

The battery of blood and urine tests performed at baseline was repeated and an interval sexual history was obtained.

On the assumption that some investigators would perform a repeat endometrial biopsy at this visit, the primary assessment of bacteriological response of anaerobic and aerobic bacteria was made at this visit.

Visit 4 at 2-4 weeks following completion of therapy
Visit 4 was the primary efficacy endpoint for clinical response and final bacteriological response of *N. gonorrhoeae* and *C. trachomatis*.

Endocervical and rectal specimens were assessed for *N. gonorrhoeae* and *C. trachomatis* (endocervix only). Endometrial biopsy was not required at this visit. Other procedures performed at visit 4 included recording of interval sexual history, vital signs, adverse events and repeat of the battery of blood and urine tests performed at baseline and at visits 2 and 3.

Medical officer’s comments:
The reviewer agrees with the overall design and notes that the timing of visits, including the TOC visit, was consistent with the IDSA/FDA guidelines. The guidelines note that interim analyses could be performed to assess clinical response 72 hours after the start of therapy and 2-4 days after the completion of therapy. Patients with *N. gonorrhoeae* or *C. trachomatis* isolated at the final evaluation, even in the absence of symptoms, were considered treatment failures.

**Susceptibility testing**
Susceptibility to CP-99,219, ofloxacin, and clindamycin was determined by disk diffusion and minimum inhibitory concentrations (MICs) for all pathogenic isolates (except *C. trachomatis*), whether at baseline or at follow-up. Criteria for determining susceptibility to the study drugs ("susceptibility breakpoints") are summarized below.

<table>
<thead>
<tr>
<th>Trovafloxacin</th>
<th>Ofloxacin</th>
<th>Clindamycin</th>
</tr>
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<tbody>
<tr>
<td><strong>Criteria</strong></td>
<td><strong>MIC (µg/mL)</strong></td>
<td><strong>Zone Diameter (mm)</strong></td>
</tr>
<tr>
<td>Susceptible (For <em>N. gonorrhoeae</em>)</td>
<td>≤ 2</td>
<td>≥ 15</td>
</tr>
<tr>
<td>Intermediate (For <em>N. gonorrhoeae</em>)</td>
<td>4</td>
<td>11-14</td>
</tr>
<tr>
<td>Resistant (For <em>N. gonorrhoeae</em>)</td>
<td>≥ 8 (-)</td>
<td>≤ 10 (-)</td>
</tr>
</tbody>
</table>

Note: Results using the 10 µg disks were not available during the study report period.

(-) No intermediate or resistant strains of *N. gonorrhoeae* currently identified.
Clinical Evaluations

On the basis of the investigator’s assessments of the CTS, extent of fever, and white blood cell count, clinical efficacy was classified by the sponsor at two interim timepoints (72 hours after the initiation of therapy and 2-4 days following completion of therapy), with a final classification at 2-4 weeks following completion of therapy. The following guidelines were used:

Interim assessments

a. **Presumptive clinical cure**
   1) Reduction of the CTS by ≥70% AND
   2) Resolution of fever and leukocytosis

b. **Presumptive clinical improvement**
   1) Reduction of the CTS by 30-70% AND
   2) Resolution of fever and leukocytosis

c. **Unsatisfactory response**
   1) Reduction of the CTS by <30% within 2-4 days following completion of therapy AND
   2) Persistence of fever and/or leukocytosis

d. **Un evaluable response**
   1) Subject’s withdrawal from the study for other than clinical failure
   2) Institution of an additional antibiotic for the treatment of an infection unrelated to PID
   3) Erroneous diagnosis
   4) Surgical intervention during the first 48-72 hours of therapy

   **(NOTE:** Subjects requiring such surgery after 72 hours were considered clinical failures).

In addition, failure to demonstrate response at 72 hours after initiation of therapy constituted clinical failure.

Final assessment

The overall clinical response was based on the global assessment of the subject by the investigator at visit 4 (2-4 weeks following completion of therapy). The potential outcomes were:

a. **Clinical cure**
   1) Reduction of the CTS and mass score by ≥70% AND
   2) Resolution of fever and leukocytosis AND
   3) No known clinical recurrence within 2-4 weeks following completion of therapy

b. **Clinical failure**
   1) Reduction of the CTS and mass score of <70% OR
   2) Persistence of fever and/or leukocytosis OR
   3) Recurrence of signs and symptoms of PID within 2-4 weeks following completion of therapy OR
   4) Therapy required for longer than 14 days
Bacteriological Evaluations
The bacteriological response was determined 2-4 days following completion of therapy and 2-4 weeks following completion of therapy. Definitions of bacteriological response were as follows:

a. Satisfactory response
   1) Eradication of N. gonorrhoeae and C. trachomatis, and actual or presumptive eradication of anaerobic and aerobic bacteria from the endometrium at the 2-4 day post-therapy assessment (determined by performance of repeat endometrial biopsy). If cultures were obtained at repeat endometrial biopsy, bacterial eradication could be determined. Without repeat endometrial biopsy, presumptive bacteriological eradication was based on the assessment of the subject’s clinical response, AND

   2) Eradication of N. gonorrhoeae and/or C. trachomatis from the endocervix (and rectum, if applicable, for N. gonorrhoeae) at the 2-4 week post-therapy assessment

b. Unsatisfactory response-Persistence of N. gonorrhoeae or C. trachomatis at either of the above assessments or actual or presumptive persistence of anaerobic or aerobic bacteria at the 2-4 day post-therapy assessment (determined by performance of repeat endometrial biopsy). If cultures were obtained at repeat endometrial biopsy, bacterial eradication could be determined. Without repeat endometrial biopsy, presumptive bacteriological eradication was based on the assessment of the subject’s clinical response.

Indeterminate (for evaluable subgroup):
   a. no baseline causative pathogen isolated
   b. relevant post-baseline cultures not obtained, unless the lack of such cultures results from concomitant antibiotic use due to bacteriological persistence
   c. concomitant antibiotic use for treatment of an intercurrent illness

Medical officer's comments:
The reviewer agrees with the definitions as outlined by the applicant.

Applicant's Criteria for Clinical evaluability (from study report)
Subject evaluability was based on data collected at Visit 4. If any of the following was present, the subject was considered non-evaluable for clinical efficacy:

1. Study medication discontinued, for any reason other than insufficient therapeutic effect, before the protocol specific minimum requirement (7 days)

2. Treatment with any systemic antibiotic for 24 hours or longer within 2 weeks prior to enrollment unless clinical failure.

3. Concomitant antibiotic prescribed at any time before the Visit 4 assessment that was potentially effective against the condition under study. 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.

4. Intercurrent Illness whose clinical course confounded the clinical evaluation of the disease or condition under investigation. In order to be evaluable, a subject must have had an assessment in the Visit 4 analysis window, unless:
   - the subject was given an antibiotic for insufficient response at any time during study, up to and including the last day of the Visit 4 analysis window, or
   - the subject was discontinued due to lack of efficacy,
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline Day 1</th>
<th>Visit 2 /72 h</th>
<th>Visit 3, Days 16-18</th>
<th>Visit 4, Days 28-42</th>
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<tr>
<td>Compliance Checks</td>
<td>X</td>
<td>X</td>
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<td>Informed Consent</td>
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<td>Demographic Information</td>
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<td>Targeted Physical Examination</td>
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<td>Concomitant Medication</td>
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</tr>
<tr>
<td>Vital Signs</td>
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<td>Clinical ()</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Gynecologic/Endometrial Biopsy, and/or Laparoscopy ()</td>
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<td>2. Serum Chemistry</td>
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<td>3. Urinalysis</td>
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<td>X</td>
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<tr>
<td>4. Microbiology ()</td>
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<td>a. (N. gonorrhoeae) Cultures ()</td>
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<td>b. (C. trachomatis) Cultures or Assays ()</td>
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<td>X</td>
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<td>c. Anaerobic/aerobic Cultures ()</td>
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<td>5. FTA or RPR ()</td>
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<td>6. Pregnancy Test</td>
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</tr>
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</table>

**Adverse Events**

\(\) Assessments to be done daily during hospitalization
\(\) Dependent upon which procedure(s) is(are) performed; endometrial biopsy required at baseline for microbiology (with histology optional)
\(\) At investigator's discretion
• the subject had surgical intervention on Day 4 or later, or the investigator's clinical assessment was failure before Visit 4.

Applicant's Criteria for Bacteriological Evaluable (from study report)
If any of the following was present, the subject was considered non-evaluable for bacteriological efficacy:

1. No baseline causative pathogen (N. gonorrhoeae, C. trachomatis and/or pathogenic anaerobic or aerobic bacteria) was isolated and the subject did not have a positive non-culture chlamydial test at baseline.

2. The baseline culture (and non-culture chlamydial test) was done more than 2 calendar days before the first dose of study medication.

3. No culture (or non-culture chlamydial test) obtained at Visit 4 unless:
   • The subject was given an antibiotic for insufficient response, at any time up to and including the last day of the evaluable End of Study analysis window, or
   • The subject had a baseline pathogenic anaerobic or aerobic bacteria and the investigator's clinical response was recorded in the appropriate window.
   • The subject had a baseline pathogenic anaerobic or aerobic bacteria and the investigator's clinical response was failure prior to the End of Study window.

Medical officer's (MO) evaluability criteria
A. The primary efficacy variable is clinical response at the 4-6 week visit.
   Patients were clinically non-evaluable if:
   • insufficient therapy ---MO accepted patients who received at least 10 days of the study drug unless they were clinical failures early in the course of treatment
   • unprotected sexual contact during study
   • no clinical assessment 2-4 weeks after completion of study therapy
   • positive serologic test for syphilis (indeterminate status)
   • patients who received antibiotics within 2 weeks prior to study initiation
   • IUD in place >24 hours after initiation of study therapy
   • missing data and data outside study windows
   • no baseline clinical assessment
   • incorrect baseline diagnosis
   • concomitant antimicrobial therapy during study unrelated to PID

B. Clinical failures will be those patients who:
   • require surgery after 72 hours of study therapy
   • clinically cured but bacteriologic failure
   • insufficient therapy with study drug due to poor clinical response
   • required concomitant systemic antimicrobial therapy due to poor clinical response or persistent pathogen
   • subjects who were given alternate treatment due to poor response to the study drug or persistent pathogen were considered evaluable

C. Bacteriologically non-evaluable:
The reviewer agrees with the applicant's criteria.
Statistical considerations
Assuming the clinical cure rate for the reference drug was 90%, the number of subjects required for each treatment group to ensure with 80% probability that the 95% confidence limits for the true difference in efficacy does not exceed 10% was 142 subjects per treatment group. The planned enrollment of 300 subjects was statistically adequate (under the assumption of a 90% cure rate for the comparative group). All statistical tests of significance were performed as two-sided tests (unless otherwise specified). No adjustments were made to significant levels for multiple endpoints on the same data. Baseline comparability of the treatment groups was assessed for age, race, and weight.

The primary efficacy endpoints were clinical and bacteriological responses at visit 4, four to six weeks following initiation of therapy. Modified "intent to treat" and "evaluable" clinical analyses were performed, comparing clinical and bacteriologic outcomes four to six weeks following initiation of therapy. The Cochran-Mantel-Haenzel test controlling for center were used to compare the treatments for clinical and bacteriological response. Also, 95% confidence intervals were produced for the difference between treatment effects for cure and eradication rates.

Criteria for Safety evaluation
Adverse events including serious adverse events were monitored up to visit 4, four to six weeks following initiation of therapy. Serious adverse events were monitored throughout the study and for 30 days after the last dose of study drug.

The clinical laboratory tests outlined below were performed at baseline and on visits 2 and 3.
- Hemoglobin, hematocrit, red blood cells, white blood cells, differential count, platelets, and ESR.
- AST, ALT, total bilirubin, LDH, alkaline phosphatase, urea, creatinine, total protein, albumin, sodium, potassium, bicarbonate, chloride, and random blood glucose, and C-reactive protein.
- Microscopy and urine chemistry (protein, glucose, ketones, bilirubin, pH, urobilinogen, blood and nitrate).

INVESTIGATORS AND STUDY SITES

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>CENTER</th>
<th>PRINCIPAL INVESTIGATOR</th>
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<tr>
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<td>5248</td>
<td>Carol Terregino, MD</td>
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<td>James McGregor, MD</td>
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<td></td>
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<td>Stanley Gall, MD</td>
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<td>James West, MD</td>
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<td>Harvey Friedenson, MD</td>
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<td>David Baker, MD</td>
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<td>Gregory Fossum, MD</td>
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<td>David Hensell, MD</td>
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<td>Abner Korn, MD</td>
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<td>Maurizio Maccato, MD</td>
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<td>Rebecca Ryder, MD</td>
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<td>Richard Derman, MD</td>
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<td></td>
<td>5905</td>
<td>Harold Wittcoff, MD</td>
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<td></td>
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<td>Dean Coonrod, MD</td>
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<td></td>
<td>5907</td>
<td>Joseph Mortola, MD</td>
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<td>Elizabeth Trupin Campbell, MD</td>
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<tr>
<td></td>
<td>5919</td>
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<td></td>
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<td>Harinhar Pershad Singh, MD</td>
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<td></td>
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<td>John Larsen, MD</td>
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<tr>
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<td>Mark Martens, MD</td>
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<tr>
<td></td>
<td>6327</td>
<td>Janice Bacon, MD</td>
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<td>Cheryl Walker, MD</td>
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<td>Howard Offenberg, MD</td>
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<tr>
<td>South Africa</td>
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<td>Peter De Jong, MD</td>
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<td>Hendrik Cronje, MD</td>
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<td>6508</td>
<td>Cornelius Prins, MD</td>
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<td>6509</td>
<td>Barelind Lindeque, MD</td>
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<td></td>
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<td>Johan De Souza, MD</td>
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RESULTS

PATIENT ENROLLMENT AND DISPOSITION

<table>
<thead>
<tr>
<th>Table 122.1 Patients evaluable (per applicant) by center</th>
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</thead>
<tbody>
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<td>center ID</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>total randomized</td>
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<tr>
<td>Total</td>
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</table>
Medical officer's comments:
Only 4 of 36 US sites (3752, 5754, 5866, 6109) randomized more than 5 patients into the trial and only 1 US (6109) site randomized more than 10 patients into the trial. The 5 South Africa sites (6506-6510) that participated in the trial accounted for 40/79 (50.6%) and 43/79 (54.4%) patients enrolled in the trovafloxacin and cefoxitin/doxycycline arms, respectively; 32/53 (60%) and 35/55 (64%) of the evaluable patients in the alatro/trova and cefoxitin/doxycycline arms, respectively, were from these same South African sites.

Table 12.2.3 Summary of Subject Disposition

<table>
<thead>
<tr>
<th></th>
<th>Alatrofloxacin</th>
<th>Cefoxitin/Doxycycline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number and Percentage (%) of Subjects</td>
<td></td>
</tr>
<tr>
<td>Randomized Subjects</td>
<td>79 (100%)</td>
<td>79 (100%)</td>
</tr>
<tr>
<td>All Treated Subjects</td>
<td>79 (100%)</td>
<td>79 (100%)</td>
</tr>
<tr>
<td>Withdrawn from Treatment</td>
<td>23 (29%)</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>Completed Treatment</td>
<td>56 (71%)</td>
<td>69 (87%)</td>
</tr>
<tr>
<td>Withdrawn from Study</td>
<td>19 (24%)</td>
<td>17 (22%)</td>
</tr>
<tr>
<td>Withdrawn during Study</td>
<td>12 (15%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Withdrawn during Follow-Up</td>
<td>7 (9%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Completed Study</td>
<td>60 (76%)</td>
<td>62 (78%)</td>
</tr>
<tr>
<td>Completed Treatment and Study</td>
<td>49 (62%)</td>
<td>60 (76%)</td>
</tr>
</tbody>
</table>

Medical officer's comments:
Fewer patients in the alatro/trova arm completed the study and treatment when compared with the cefoxitin/doxycycline arm.

Based on the applicant's calculations (outlined in the Statistical considerations section on page 12) 142 evaluable patients were needed per arm; however, only 79 patients were randomized to each of the treatment arms. Of the 79 subjects each in the alatro/trova and cefoxitin/doxycycline arms, 67% and 70% were clinically evaluable respectively, and 39% and 42% bacteriologically evaluable, respectively.
Table 122.3  Summary of Premature Discontinuations From Treatment (All Treated Subjects)

<table>
<thead>
<tr>
<th></th>
<th>Alatrofloxacina</th>
<th>Cefoxitin/dexycycline</th>
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<tbody>
<tr>
<td></td>
<td>Trovafoxacin</td>
<td>Doxycline</td>
</tr>
<tr>
<td></td>
<td>(N=79)</td>
<td>(N=79)</td>
</tr>
<tr>
<td>Total Discontinued</td>
<td>23 (29%)</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>Discontinuations Related to Study Drug:</td>
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<td></td>
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<tr>
<td>Adverse Event</td>
<td>12 (15%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Insufficient Response</td>
<td>4 (5%)</td>
<td>1 (1%)</td>
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<tr>
<td>Discontinuations Related to Study Drug:</td>
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<td></td>
</tr>
<tr>
<td>Adverse Event</td>
<td>8 (10%)</td>
<td>2 (3%)</td>
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<tr>
<td>Did not meet Randomization Criteria</td>
<td>11 (14%)</td>
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<tr>
<td>Lost to Follow-up</td>
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<tr>
<td>Other</td>
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<tr>
<td>Protocol Violation</td>
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<td>1 (1%)</td>
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<tr>
<td>Withdrawn Consent</td>
<td>1 (1%)</td>
<td>0</td>
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</table>

Medical officer’s comments:
More than twice as many patients in the trovafoxacin arm were discontinued from the study overall; discontinuations due to adverse events and insufficient response were more common in the alatro/trova arm.

Table 122.4 Summary of patients disqualified from efficacy analysis

<table>
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<th>Cefoxitin/Doxycline</th>
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<td>Clinically Not Evaluable</td>
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<td>No post- baseline clinical assessments</td>
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<td>Concomitant Antibiotic Therapy</td>
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<td>Intercurrent Illness</td>
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<td>Surgical Intervention</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Bacteriologically Not Evaluable</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>No baseline pathogen</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>No post- baseline cultures</td>
<td>20</td>
<td>19</td>
</tr>
</tbody>
</table>

Medical officer’s comments:
More patients in the alatro/trova arm were discontinued due to the use of concomitant antimicrobial therapy. Some of the reasons that concomitant antimicrobial agents were used included for an allergic reaction to study drug, and as therapy for trichomoniasis/bacterial vaginosis (metronidazole), respiratory tract infections, syphilis (procaine Penicillin G), and appendicitis.

After review of case report forms, patients disqualified from the analysis and patients who received concomitant antimicrobial therapy during the study, the reviewer accepted the applicant’s evaluable population.
**DEMOGRAPHICS**

Table 122.5 Demographic Characteristics of Treated Subjects

<table>
<thead>
<tr>
<th></th>
<th>79</th>
<th>79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-44</td>
<td>78(99%)</td>
<td>78(99%)</td>
</tr>
<tr>
<td>45-84</td>
<td>1(1%)</td>
<td>1(1%)</td>
</tr>
<tr>
<td>Mean</td>
<td>67.4</td>
<td>26.8</td>
</tr>
<tr>
<td>Minimum</td>
<td>(b)(4)</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASIAN</td>
<td>1(1%)</td>
<td>0</td>
</tr>
<tr>
<td>BLACK</td>
<td>50(63%)</td>
<td>62(78%)</td>
</tr>
<tr>
<td>COLOURED</td>
<td>0</td>
<td>1(1%)</td>
</tr>
<tr>
<td>HISPANIC</td>
<td>8(10%)</td>
<td>5(6%)</td>
</tr>
<tr>
<td>MIXED</td>
<td>8(10%)</td>
<td>4(5%)</td>
</tr>
<tr>
<td>WHITE</td>
<td>12(15%)</td>
<td>7(9%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>62.3</td>
<td>64.1</td>
</tr>
<tr>
<td>Minimum</td>
<td>(b)(4)</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Medical officer’s comments:
There were no significant differences between the two groups with regard to race, weight, and age distribution.

**APPLICANT’S EFFICACY ANALYSIS**

Table 122.6 Summary of Sponsor-Defined Clinical Response Rates at the End of Study Visit (Clinically Evaluable Subjects)

<table>
<thead>
<tr>
<th></th>
<th>Alatrofloxacin (N=53)</th>
<th>Cefotaxin/doxycycline (N=55)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of Study:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Subjects Assessed</td>
<td>53 (100%)</td>
<td>55 (100%)</td>
<td>(-22.8, 3.2)</td>
</tr>
<tr>
<td>Failure</td>
<td>10 (19%)</td>
<td>5 (9%)</td>
<td></td>
</tr>
</tbody>
</table>

Medical officer’s comments:
Equivalence was not demonstrated for treatment difference in clinical cure rates; at the end of study, the cefotaxin/doxycycline group had higher clinical cure rates in comparison to the alatrofloxacin/trovafloxacin group— 91 vs. 81% respectively (95% CI with continuity correction: -24.6,5.1). An insufficient number of subjects were enrolled in this study.

To see if the difference in baseline severity as manifested by the presence of an adnexal mass had an effect on the treatment response, a subset analysis was performed. The results are summarized in the table that follows.
Table 122.7  Clinical Response Rates at the End of Study for Clinically Evaluable Subjects based on the presence/absence of adnexal mass (table provided by FDA statistician)

<table>
<thead>
<tr>
<th>Subset</th>
<th>Alatro/Trova (N=53)</th>
<th>Control (N=55)</th>
<th>95% C.I.</th>
<th>P-value Breslow-Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Mass</td>
<td>13/20 (65.0%)</td>
<td>17/20 (65.0%)</td>
<td>(-51.1%, 11.1%)</td>
<td>0.616</td>
</tr>
<tr>
<td>Without Mass</td>
<td>30/33 (90.9%)</td>
<td>33/35 (94.3%)</td>
<td>(-18.8%, 12.0%)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>43/53 (81.1%)</td>
<td>50/55 (90.9%)</td>
<td>(-24.6%, 5.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Statistician's comments:
The Breslow-Day’s test demonstrates that treatment effects were homogeneous (p-value=0.616) between the subjects with mass and the subjects without mass. Please note no conclusions could be drawn from the confidence intervals for the two subgroups due to the small numbers.

Medical officer’s comments: Comparison of the subsets shows a greater treatment difference in the group with a mass than those without a mass, suggesting that the severity of illness may have been a factor in the clinical response in this study. Since there were only 3 patients in the alatro/trova and there was 1 patient in cefoxitin/doxy groups with tubo-ovarian abscesses, no subset analysis was performed for patients with tubo-ovarian abscesses.

Table 122.8  Summary of Clinical Response Rates at the End of Study For the Most Frequently Isolated Baseline Pathogensa

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Alatroloxacin ↓ Trofaxloxcin (N=53)</th>
<th>Cefoxitin/doxycycline ↓ Doxycycline (N=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. gonorrhoeae</td>
<td>11/18 (61%)</td>
<td>16/17 (94%)</td>
</tr>
<tr>
<td>Peptostreptococcus sp.</td>
<td>8/11</td>
<td>11/13</td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>4/6</td>
<td>10/10</td>
</tr>
<tr>
<td>E. coli</td>
<td>5/5</td>
<td>4/5</td>
</tr>
</tbody>
</table>

a Includes ≥5 isolates of a given pathogen in any treatment group; percentages displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline.

Medical officer’s comments:
Only 11/18 clinically evaluable patients in the alatro/trova group with *N. gonorrhoeae* and 4/6 with *C. trachomatis* isolated at baseline were considered cured at follow-up, while the cure rates in the cefoxitin/doxycycline arm were 16/17 and 10/10 patients with *N. gonorrhoeae* and *C. trachomatis*, respectively.
### Table 122.9 Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at Visit 3 and the End of Study (Clinically Evaluable Subjects)

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Investigator Assessment</th>
<th>Sponsor Assessment</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>5602-0070</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 5)</td>
</tr>
<tr>
<td>6109-0136</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 4)</td>
</tr>
<tr>
<td>6507-0200</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 18)</td>
</tr>
<tr>
<td>6507-0301</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 20)</td>
</tr>
<tr>
<td>6507-0311</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 15)</td>
</tr>
<tr>
<td>6507-0313</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 13)</td>
</tr>
<tr>
<td>6510-0272</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 7)</td>
</tr>
<tr>
<td>5768-0013</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Failure (Day 15) carried forward</td>
</tr>
<tr>
<td>6109-0132</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 4)</td>
</tr>
<tr>
<td>6109-0136</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 4)</td>
</tr>
<tr>
<td>6507-0301</td>
<td>Cure</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 20)</td>
</tr>
<tr>
<td>6510-0272</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 7)</td>
</tr>
<tr>
<td>Cefixime/doxycycline → Doxycycline:</td>
<td>Visit 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5607-0302</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 18)</td>
</tr>
<tr>
<td>6509-0232</td>
<td>Not Assessable</td>
<td>Failure</td>
<td>Concomitant antibiotics for inadequate response (Day 19)</td>
</tr>
</tbody>
</table>

### Medical officer’s comments:

Following review of the case report forms for these subjects, the reviewer is in agreement with the applicant’s assessment of outcome for these patients.

APPEARS THIS WAY ON ORIGINAL
SAFETY

Table 122.10 Summary of the Most Commonly Reported Adverse Events by Body System - All Causality (All Treated Subjects)

<table>
<thead>
<tr>
<th></th>
<th>Alatrofloxacin (N=79)</th>
<th>Cefoxitin/Doxycycline (N=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BODY SYSTEM WHO Term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APPL./INJ./INCISION/INSERTION SITE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appl./Inj./Incision/Insertion Site Infection/Inflam.</td>
<td>15 (19%)</td>
<td>19 (24%)</td>
</tr>
<tr>
<td>Appl./Inj./Incision/Insertion Site Pain</td>
<td>10 (13%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td></td>
<td>2 (3%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>CARDIOVASCULAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>10 (13%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td></td>
<td>5 (6%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>CENTRAL AND PERIPHERAL NERVOUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>11 (14%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td></td>
<td>10 (13%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>GASTROINTESTINAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>26 (33%)</td>
<td>17 (22%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (9%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (10%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (18%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td></td>
<td>9 (11%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>REPRODUCTIVE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginitis</td>
<td>8 (10%)</td>
<td>12 (15%)</td>
</tr>
<tr>
<td></td>
<td>3 (4%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>SKIN/APPENDAGES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>11 (14%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td></td>
<td>6 (8%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Number of Subjects With at Least One Adverse Event</td>
<td>57 (72%)</td>
<td>53 (67%)</td>
</tr>
</tbody>
</table>

Table 122.11 Supplemental table of most common adverse events (provided by the FDA statistician)

<table>
<thead>
<tr>
<th>Safety</th>
<th>Trovafloxacin (N=79)</th>
<th>Ofloxacin/Clindamycin (N=79)</th>
<th>Fisher’s p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central and Peripheral nervous system</td>
<td>11 (13.9%)</td>
<td>8 (10.1%)</td>
<td>0.626</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (3.8%)</td>
<td>2 (2.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (12.7%)</td>
<td>6 (7.6%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Discontinuations due to an AE</td>
<td>10/79 (12.7%)</td>
<td>4/79 (5.1%)</td>
<td>0.160</td>
</tr>
<tr>
<td>Clinically significant lab abnormalities</td>
<td>42/75 (58.3%)</td>
<td>44/77 (57.1%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Medical officer’s comments:
The differences in the adverse events for each group were not statistically significant. The rates of dizziness and headache were comparable between the two groups.
Laboratory result abnormalities
No subject in either treatment group was discontinued from treatment due to abnormal laboratory results. When corrected for baseline abnormalities, clinically significant post-baseline laboratory abnormalities were comparable between groups: 56% (42/75) in the alatrofloxacin/trovafoxacin group and 57% (44/77) in the cefoxitin/doxycycline group.

One subject (1%) in the cefoxitin/doxycycline group had clinically significant serum creatinine values; one subject (1%) in the alatrofloxacin/trovafoxacin group had clinically significant total bilirubin values; and three subjects (4%) in the alatrofloxacin/trovafoxacin group and two subjects (3%) in the cefoxitin/doxycycline group had clinically significant hemoglobin values.

Conclusions
An insufficient number of patients was enrolled in this study; equivalence was not demonstrated between alatrofloxacin/trovafoxacin and cefoxitin/doxycycline in the treatment of PID in hospitalized patients.