

**TABLE 8 DEMOGRAPHICS AND DISEASE SEVERITY AT ENTRY  
 PROTOCOL D87-054  
 EVALUABLE PATIENTS PER SPONSOR**

<b>Characteristic</b>	<b>Ciprofloxacin</b>	<b>Chloramphenicol</b>
<b>Total enrolled</b>	112	112
<b>Number evaluable</b>	98	100
<b>Mean age in years (SD)</b>	24.3 (8.3)	24.1 (8.1)
<b>range</b>	16-54	16-53
<b>Sex (M/F)</b>	72/26	74/26
<b>Mean weight in kg (SD)</b>	60.1 (8.2)	60.5 (8.3)
<b>range</b>	41.0-85.7	40.0-93.0
<b>Previous antimicrobials</b>	10	12
<b>Mean duration of illness in days at time of diagnosis (SD)</b>	8.9 (6.3)	9.2 (5.1)
<b>Baseline severity of illness</b>		
<b>Mild</b>	42	44
<b>Moderate</b>	56	53
<b>Severe</b>	0	3

**Comment:**

*The two treatment groups appear to be comparable at baseline. These are pooled data, as provided by the sponsor; a breakdown of the individual study sites was not done.*

The sponsor's determination of evaluability status is shown in Table 9, found on the following page:

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**TABLE 9 EVALUABILITY STATUS  
PROTOCOL D87-054  
PER SPONSOR**

<b>Characteristic</b>	<b>Ciprofloxacin</b>	<b>Chloramphenicol</b>
<b>Total enrolled</b>	112	112
<b>Total evaluable</b>	98	100
<b>Total nonevaluable</b>	14 (12.5%)	12 (10.7%)
<b>Reasons for nonevaluability:</b>		
<b>Inadequate duration of therapy</b>	3	2
<b>No pre-therapy isolate</b>	8	10
<b>Isolate resistant to study drug</b>	1	0
<b>Patient ineligible</b>	2	0

The sponsor has submitted all summary tables as pooled data from both the study sites. This reviewer will break the data down by individual investigator, then combine these results in summary tables. Before doing so, the following two tables will present the sponsor's interpretation of the clinical and bacteriologic outcomes of this study. (The definitions for the terms used in these tables are identical to those used in the previous protocol, D84-052, which are found on page 15 of this review.)

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**TABLE 10 CLINICAL OUTCOME  
PER SPONSOR  
PROTOCOL D87-054**

<b>Characteristic</b>	<b>Ciprofloxacin</b>	<b>Chloramphenicol</b>
<b>Number clinically evaluable</b>	98	100
<b>Clinical response at EOT (End of Therapy):</b>		
<b>Resolution</b>	95 (97%)	99 (99%)
<b>Marked Improvement</b>	1 (1%)	0
<b>Failure</b>	2 (2%)	1 (1%)
<b>Clinical response at F/U (Follow-up):</b>		
<b>Residual Illness</b>	0	1 (1%)
<b>Relapse</b>	0	4 (4%)
<b>Complete Recovery</b>	95 (97%)	94 (94%)
<b>Other</b>	1 (1%)	1 (1%)
<b>Missing</b>	2 (2%)	0

**Comment:**

1. This study, like study D84-052, was double-blinded. Assuming the blind was maintained, assessments of clinical response by the investigator should be relatively free of observer bias.
2. 'Missing' patients are presumably those considered lost to follow-up.

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ON ORIGINAL**

**TABLE 11 BACTERIOLOGIC OUTCOME  
PER SPONSOR  
PROTOCOL D87-054**

Characteristic	Ciprofloxacin	Chloramphenicol
<b>Number bacteriologically evaluable</b>	98	100
<b>Bacteriologic response at End of Therapy:</b>		
<b>Eradication (early, complete)</b>	95 (97%)	84 (84%)
<b>Eradication (late, complete)</b>	1 (1%)	15 (15%)
<b>Persistence</b>	1 (1%)	0
<b>Indeterminate</b>	1 (1%)	1 (1%)
<b>Bacteriologic response at Follow-up:</b>		
<b>Eradication at follow-up</b>	93 (95%)	92 (92%)
<b>Eradication with recurrence</b>	0	4 (4%)
<b>Missing</b>	5 (5%)	4 (4%)

Comment:

1. The difference in early vs. late eradication in the chloramphenicol arm, as portrayed by the sponsor, requires further explanation. The large majority of these cases (12/15 or 80%) appeared to be determined on the basis of positive stool and/or bile cultures post-initiation of therapy. Of the 13 cases with stool cultures positive post-initiation, the average was only 4 days until stools were culture negative (range 3-6 days). This is of questionable clinical significance.

Three of these 15 'late' eradications in the chloramphenicol arm appeared to have persistence of blood culture positivity; two were blood culture positive up until day 3, and one case was positive on day 4 post-initiation of therapy. However, upon further review of all blood cultures, two additional patients were found (both of which had been classified as 'early' eradications by the sponsor) in the chloramphenicol arm who had blood cultures positive up until day 3, and seven patients had blood cultures positive up until day 2 post-initiation of therapy. Of this total of 12 patients (3+2+7) treated with chloramphenicol who had any degree of persistent blood culture positivity, three (25%) were *S. paratyphi* isolates (see comment #2, below).

Comparatively, there were no patients in the ciprofloxacin arm who had ANY blood cultures positive after day one post-initiation of therapy. (The one 'late' eradication noted by the sponsor in the ciprofloxacin arm was a patient with a bile culture positive at day 8 post-initiation of therapy.)

Curiously, all of these persistent blood culture-positive patients were reported from Study Site #1.

2. This table includes both *S. typhi* and *S. paratyphi* isolates. Of the 98 evaluable ciprofloxacin patients, 14 had infection with *S. paratyphi* and 86 had *S. typhi* (two patients were considered to have double infections.) Of the 100 evaluable chloramphenicol patients, 12 had *S. paratyphi* and 88 had *S. typhi*. Efficacy analysis by causative microorganism will be presented in the Medical Officer's evaluation.

Curiously, all of the *S. paratyphi* isolates were reported from Study Site #1, Dr. Gotuzzo, in Lima, Peru.

### Medical Officer evaluation

The Medical Officer's evaluation of Study D87-054 will be broken down into the two individual study sites, by clinical and bacteriologic outcomes. This was done because, as noted above, there appeared to be clinical and microbiologic differences between the two study sites.

**TABLE 12 CLINICAL OUTCOME  
PER MEDICAL OFFICER  
STUDY SITE #1, PROTOCOL D87-054**

Characteristic	Ciprofloxacin	Chloramphenicol
Number enrolled	52	52
Not evaluable	7	6
No pre-therapy culture positive	6	5
Withdrew AMA	0	1
Isolate resistant to study drug	1	0
<b>Evaluable</b>	<b>45/52 (87%)</b>	<b>46/52 (88%)</b>
Early clinical failures	6	14
Significant worsening of signs/symptoms	1	0
Drug discontinued due to adverse event	1	0
Persistent fever or no change in clinical status after 5 days	4	13
End of Therapy culture positive	0	1
Lost to follow-up	2	0
Failed at follow-up	0	2
<b>Cured at follow-up</b>	<b>37/43 (86%)</b>	<b>30/46 (65%)</b>

Comment:

1. The difference in rates of cure at two-month follow-up was due primarily to the discrepancy in the number of chloramphenicol patients who had persistent fever for longer than five days following the initiation of therapy. This would appear to be a clinical correlate to the previously-mentioned blood culture findings (above).

2. Of the 13 chloramphenicol patients who were considered early clinical failures on the basis of persistent fever, four (31%) had infection with *S. paratyphi*. By comparison, only 12% of the 100 (pooled) chloramphenicol patients, considered evaluable by the sponsor at the end of therapy, had *S. paratyphi* infection.

3. The only patient who had an adverse event that required discontinuation of the study drug was patient #1092, who had a rash on day #2 of ciprofloxacin. This patient, a 17 year old female, recovered without problem.

4. The only patient who had a significant worsening of signs/symptoms was also a ciprofloxacin patient. This patient, a 20 year-old male, developed increasingly severe abdominal pain and tenderness, with increasing fever and jaundice, following initiation of ciprofloxacin.

The medical officer's clinical evaluation of study site #2, Dr. Bran of Guatemala, is shown below:

**TABLE 13 CLINICAL OUTCOME  
PER MEDICAL OFFICER  
STUDY SITE #2, PROTOCOL D87-054**

Characteristic	Ciprofloxacin	Chloramphenicol
Number enrolled	60	60
Not evaluable	9	9
No pre-therapy culture positive	7	9
Withdrew AMA	1	0
Significant underlying disease	1	0
<b>Evaluable</b>	<b>51/60 (85%)</b>	<b>51/60 (85%)</b>
Early clinical failures	4	9
Significant worsening of signs/symptoms	1	1
Persistent fever or no change in clinical status after five days	3	7
End of therapy culture +	0	1
Lost to follow-up	0	0
Failed at follow-up	0	1
<b>Cured at follow-up</b>	<b>47/51 (92%)</b>	<b>41/51 (80%)</b>

**Comment:**

1. As mentioned previously, all the patients enrolled at this study site had *S. typhi* infection; there were no cases of paratyphoid fever in this group.

2. The one ciprofloxacin patient judged nonevaluable due to significant underlying disease (patient #2015) was a 19 year old female who was diagnosed with 'neoplastic anemia'. She received three days of study therapy before being withdrawn.

The following table summarizes the Medical Officer's clinical evaluation of Study 054:

**TABLE 14**  
**SUMMARY OF MEDICAL OFFICER'S CLINICAL EVALUATION**  
**PROTOCOL D87-054**

Characteristic	Ciprofloxacin	Chloramphenicol
Number enrolled	112	112
Number evaluable	96	97
Early clinical failures	10/96 (10%)	23/97 (24%)
Lost to follow-up	2	0
Failed at follow-up	0	3
Cured at follow-up	84/94 (89%)	71/97 (73%)

**Comment:**

The major contributor to the difference in clinical cure rates between the two arms of this study was the higher number of chloramphenicol patients who remained febrile longer than five days after beginning therapy. If this reason is disregarded, and only the other cited reasons for early (and late) clinical failure are considered, the rates of clinical cure are comparable: 97% (91/94) for ciprofloxacin, and 94% (91/97) for chloramphenicol.

**Bacteriologic evaluation**

The criteria for evaluability, and definitions of outcome, are the same as those used to evaluate Study 052. A blood or bone marrow-documented infection with either *S. typhi* or *S. paratyphi* must have been documented within 72 hours of initiation of therapy; cultures must have been obtained during the course of therapy to document eradication, including cultures at least 24 hours after completion of therapy; and follow-up cultures must have been obtained to document continued eradication. Also, a patient whose last blood culture was still positive at the time he became a clinical failure was again considered an early bacteriologic failure. As will be seen, Study 054 did not suffer from the problems of poor bacteriologic documentation at follow-up, as did Study 052.

The bacteriologic evaluation of study site #1 is presented in Table 15:

**TABLE 15 BACTERIOLOGIC OUTCOME  
PER MEDICAL OFFICER  
STUDY SITE #1, PROTOCOL D87-054**

Characteristic	Ciprofloxacin	Chloramphenicol
Number enrolled	52	52
Not evaluable	9 (17%)	6 (12%)
No pre-therapy culture +	6	5
Isolate resistant	1	0
Withdrew AMA	0	1
Drug d/c'ed due to clinical failure	1	0
Drug d/c'ed due to AE	1	0
Bacteriologically evaluable	43	46
Bacteriologic failures	2	4
Blood culture + when clinical failure	0	1
End of therapy culture +	2	2
Long-term f/u culture +	0	1
Lost to follow-up	2	1
Eradicated at follow-up	39/41 (95%)	41/45 (91%)

**Comment:**

1. The resistant isolate noted in the ciprofloxacin arm was actually resistant to chloramphenicol, but was appropriately excluded from analysis. The patient was given a 10 day course of study drug, and was judged a clinical and bacteriologic success by the investigator. (It is not specified whether the patient was declared ineligible, the blind broken, and simply continued on ciprofloxacin when it was ascertained that he was not in the chloramphenicol arm; otherwise, such an event leads one to question the integrity of the blinding in this study.)

For further discussion of sensitivity data, see page 39 of this review .

2. All the patients in the 'Eradicated at follow-up' groups were documented, rather than presumed, eradications. This is in sharp contrast with the previous study, in which very few (3) of the patients who were considered bacteriologically eradicated at follow-up actually had cultures documented in the material submitted by the sponsor.

3. Both of the early ciprofloxacin discontinuations (patient #1092, due to Adverse Event, and #1073, due to clinical failure) had documented negative blood cultures at the time of drug discontinuation. If otherwise, they would have been considered bacteriologic failures.

4. These data include both *S. paratyphi* as well as *S. typhi*. (An efficacy breakdown is presented below, by organism.) Of the 43 bacteriologically evaluable ciprofloxacin patients, there were 15 *S. paratyphi* and

28 *S. typhi*; the corresponding numbers for the chloramphenicol arm were 12 *S. paratyphi* and 34 *S. typhi*.

5. All of the ciprofloxacin patients received 10 days of therapy. The great majority (39/46 or 85%) of chloramphenicol patients received 15 days of therapy; six received 16 days, and one received 14 days. In contrast, study D84-052 used a higher dose of ciprofloxacin, and compared it to a shorter course (average 10 days) of chloramphenicol.

6. The average time to follow-up was similar in the two arms, 63 vs. 62 days post-completion of therapy. The range of values was considerable: 37-124 days in the ciprofloxacin arm, and 32-110 days in the chloramphenicol arm. Most follow-up encounters were within a 50-70 day window, however; there were only 8 patients in the ciprofloxacin arm, and 6 in the chloramphenicol arm, who were seen outside this timeframe. These 'out-of-the-window' patients were included in the medical officer's analysis.

The following table presents the bacteriologic evaluation of the second study site in this study, Dr. Bran of Guatemala:

**TABLE 16 BACTERIOLOGIC OUTCOME  
PER MEDICAL OFFICER  
STUDY SITE #2, PROTOCOL D87-054**

Characteristic	Ciprofloxacin	Chloramphenicol
Number enrolled	60	60
Not evaluable	8 (13%)	8 (13%)
No pre-therapy culture +	6	8
Withdrew AMA	1	0
Significant underlying disease	1	0
<b>Bacteriologically evaluable</b>	<b>52</b>	<b>52</b>
<b>Bacteriologic failures</b>	<b>1</b>	<b>3</b>
Blood culture + when clinical failure	1	2
End of Therapy culture +	0	0
Long-term f/u culture +	0	1
Lost to follow-up	0	1
<b>Eradicated at follow-up</b>	<b>51/52 (98%)</b>	<b>48/51 (94%)</b>

**Comment:**

1. All of these isolates were *S. typhi*.
2. All bacteriologic eradications are documented, as mentioned for study site #1.
3. Average time to late follow-up was similar to site #1, though with less variability; only one patient in each arm was seen outside of the 50-70 day window. Again, all patients with documented bacteriologic follow-up were considered evaluable.
4. All ciprofloxacin patients received 10 days of therapy. Unlike site #1, however, most patients in the chloramphenicol arm (40/48 or 83%) received 14 days of therapy at this study site. This is unlikely to

have been of any significance, as is demonstrated by the similar eradication rates in the chloramphenicol arms of the two sites.

Both of these tables (15 and 16) include all patients enrolled in this study. It is important to evaluate bacteriologic response to each of the study drugs according to infecting organism. As mentioned previously, Study Site #1 included a number of patients infected with *Salmonella paratyphi*, whereas Site #2 did not. A breakdown of the results from Site #1, according to organism and treatment arm, is presented in the following table:

TABLE 17 BACTERIOLOGIC OUTCOME  
BY TREATMENT ARM AND INFECTING ORGANISM  
PER MEDICAL OFFICER  
STUDY SITE #1, PROTOCOL D87-054

Characteristic	Ciprofloxacin		Chloramphenicol	
	<i>S. typhi</i>	<i>S. paratyphi</i>	<i>S. typhi</i>	<i>S. paratyphi</i>
Number enrolled	36	16	40	12
Bacteriologically evaluable	28	15	34	12
Bacteriologic failures	0	2	4	0
Blood culture + when clinical failure	0	0	1	0
End of therapy culture +	0	2	2	0
Long-term f/u culture +	0	0	1	0
Lost to follow-up	1	1	1	0
Eradicated at follow-up	27/27 (100%)	12/14 (86%)	29/33 (88%)	12/12 (100%)

**Comment:**

The two cases listed as *S. paratyphi* 'end-of-therapy culture positive' require elaboration. These two cases represent two of the three cases enrolled (all three being in the ciprofloxacin arm) which were listed as multiple infections. The first case, #1031, is listed as having both organisms grow from the initial cultures of both blood and bone marrow. All isolates had the same sensitivity pattern. Although five blood cultures obtained during therapy were negative, a blood culture drawn on day 1 post-therapy was positive for *S. paratyphi*; thus, the patient was called end-of-therapy culture positive.

The second case (#1036) was somewhat different; pure cultures of *S. typhi* were grown from initial blood and stool cultures. Again, five during-therapy blood cultures were negative. On day 2 post-therapy, a blood culture was positive for *S. paratyphi*. This case was also called end-of-therapy culture positive for *S. paratyphi*. It is impossible to determine whether the initial isolate was misdiagnosed as *S. typhi*, or if the day +2 isolate was misdiagnosed as *S. paratyphi*. This reviewer has decided to assume the former scenario.

The third multiple infection case (#1104) grew both organisms from blood, and *S. paratyphi* from bone marrow; all during- and post-therapy cultures were sterile. This case was considered to be an *S. paratyphi* eradication at follow-up.

All three of these cases had isolates which were uniformly sensitive to ciprofloxacin, chloramphenicol, and ampicillin.

It would appear from the above chart that the two drugs were of roughly equivalent efficacy in eradicating both types of organisms. There appears to be a trend towards lower eradication rates for paratyphi-infected patients treated with ciprofloxacin. However, the small numbers that result from such a subset analysis impede the ability to make a definitive statement. The two cases called S. paratyphi failures could possibly have been the result of errors in interpreting results of the API 20E biochemical panel or of the serologic typing studies; if so, the ciprofloxacin-treated S. paratyphi patients had an eradication rate equalling or surpassing that of the other groups.

Resistance to tested antimicrobials, as presented by the sponsor, did not appear to be a problem in this study. As mentioned previously, there was only one case of an enrolled patient requiring removal from the study because of a resistant isolate, and that was a chloramphenicol-resistant isolate from a patient in the ciprofloxacin arm. A review of sensitivity data, as presented in the sponsor's line listings, reveals the following:

**TABLE 18 SENSITIVITY PATTERNS OF CLINICAL ISOLATES  
PROTOCOL D87-054**

Antibiotic	Sensitive		Intermediate		Resistant	
	Gotuzzo	Bran	Gotuzzo	Bran	Gotuzzo	Bran
Chloramphenicol	90	103	4	0	1	0
Ciprofloxacin	95	103	0	0	0	0
Ampicillin	94	-	1	-	0	-

**Comment:**

1. In this table, each patient is considered to have one isolate, even though most patients had organisms isolated from more than one source during their pre- or during-therapy bacteriologic monitoring. If sensitivity patterns were different between isolates from different sites in a single patient, the most resistant sensitivity pattern is reported. (This was never the case.)
2. All isolates are included, regardless of evaluability status.
3. No patients were observed to develop resistance while on therapy.
4. Methods used to determine sensitivity varied. Even though the protocol specified that both broth dilution MIC's and disc susceptibilities were to be done on all isolates, Bran (site #2) reported only MIC's. (Furthermore, these were not reported in the line listings.) Gotuzzo (site #1) reports disc diameters for ciprofloxacin, with interpretation, on the line listings; for the other 2 antibiotics, however, only MIC's were performed, and only the interpretation of the MIC's were given on the line listings.
5. Bran did not test for ampicillin sensitivity in the isolates from site #2.

The above table was generated from review of the line listings for the two study sites. While compiling these data, it was noticed that the five isolates reported by Gotuzzo, which were intermediate or resistant to

chloramphenicol, were clustered in enrollment number. (The four patients with intermediate isolates were #'s 1021, 1022, 1024, and 1025; the one isolate reported as resistant to chloramphenicol, which was also the isolate reported as intermediately sensitive to ampicillin, was #1026.)

Concern over a possible methodologic problem led to review of the sensitivity data as presented in table format (Data Listing 11, pages 08-02-1039 thru 1125). A major error in data presentation was discovered in this data listing. There are multiple isolates reported which have MIC's recorded that are inconsistent with the accompanying interpretation ('S'). For instance, patient #1044 is reported to have an isolate of S. paratyphi which is sensitive to chloramphenicol and ampicillin, as well as ciprofloxacin. However, the MIC's accompanying these 'sensitive' interpretations are 32 mcg/mL for chloramphenicol, and 16 mcg/mL for ampicillin. Another isolate (#1063) was reported to be sensitive to chloramphenicol with an MIC of >32 mcg/mL. (The NCCLS breakpoints for both of these drugs are: resistant if greater than or equal to 32 mcg/mL, intermediate for 16 mcg/mL, and sensitive if less than or equal to 8 mcg/mL.) Numerous isolates were reported as 'sensitive' with no MIC value reported whatsoever. Furthermore, the isolates that WERE reported as intermediate or resistant to chloramphenicol, had MICs comparable to others in the same table that are uniformly called 'sensitive'.

A similar problem was not found with the reported ciprofloxacin data; no isolate had a reported MIC of higher than 1.0 mcg/mL. Interestingly, there were 2 isolates with ciprofloxacin MIC's of 1.0, and three with MIC's of 0.5 mcg/mL; all five of these were S. paratyphi (none of these were bacteriologic failures). Review of the MIC's for ciprofloxacin vs. the 28 S. paratyphi isolates appeared to show an overall tendency toward higher ciprofloxacin MIC's, as compared to the S. typhi group. (Given the degree of variability in the submitted MIC data, no statistical manipulations have been performed.) The breakpoints for ciprofloxacin are: resistant greater than 2 mcg/mL; intermediate 1-2 mcg/mL; and sensitive, less than or equal to 1.0 mcg/mL.

The sponsor has been contacted and the above concerns have been communicated.

### Safety

All patients receiving study medication were considered eligible for inclusion in the safety database. Thus, the number of patients considered is equal to the number of patients enrolled, as presented in Table 6, page 27. There are a total of 112 patients in each treatment arm who are included in this database.

As mentioned in the introduction to this review, ciprofloxacin has been marketed in the United States since 1987. The maximum dosage used in the studies presently under consideration (750 mg bid ) does not exceed the maximum dosage currently allowed in the ciprofloxacin label.

### **Deaths on study**

There were no patient deaths reported in any of the studies submitted in support of this efficacy supplement. The one patient with intestinal perforation apparently recovered.

### **Withdrawals from study**

There were four patients in this study, two in each treatment arm, who were discontinued from study medication for safety reasons: in the ciprofloxacin arm, patient #1092 had an erythematous rash after the first day of ciprofloxacin, considered probably related by the investigator, which resolved one day after discontinuation of therapy; and patient #2026 suffered an intestinal perforation on day 2 of ciprofloxacin therapy, which was considered unrelated to study medication by the investigator. The two chloramphenicol safety-related withdrawals were: patient #1064, who had severe leukopenia which required discontinuation of therapy after 10 days, which was considered highly probably related to study medication; and patient #2033, who had moderately severe nausea, vomiting, and confusion, considered possibly related to therapy, and which required discontinuation on day 5. A fifth patient, #2083, had her chloramphenicol dosage reduced because of complaints of nausea, vomiting, and a metallic taste in the mouth, 'probably' associated with study drug, following 2 days of therapy. She completed her reduced dose of chloramphenicol therapy and was considered a clinical and bacteriologic cure by the sponsor (the medical officer concurs). One additional chloramphenicol patient (#2056) developed severe abdominal pain after four days of therapy, which required additional antibiotics and withdrawal from the study.

Several additional patients, in both treatment arms, were discontinued from study because of reasons other than safety-related concerns (predominantly because of the failure to isolate a pathogen from the enrollee). The entire list of withdrawn patients is presented in the following table:

**TABLE 19 ALL PATIENTS DISCONTINUED  
FROM STUDY THERAPY  
PROTOCOL D87-054**

<b>Drug</b>	<b>patient #</b>	<b># days Rx</b>	<b>Event</b>	<b>Severity</b>	<b>Association with drug</b>
<b>Ciprofloxacin</b>	1092	1	rash	moderate	probable
	2026	2	intestinal perforation	severe	none
	1073	6	abdominal tenderness	severe	--
	1005	2	no pathogen	--	--
	1049	8	no pathogen	--	--
	2023	7	no pathogen	--	--
<b>Chloramphenicol</b>	1064	11	leukopenia	severe	highly probable
	2033	5	confusion	severe	possible
	2056	4	abdominal pain	severe	--
	2015	3	other disease	--	--
	2108	1	left AMA	--	--
	2004	6	no pathogen	--	--
	2011	5	no pathogen	--	--
	2019	6	no pathogen	--	--
	2022	2	no pathogen	--	--
	2028	8	no pathogen	--	--
	2046	6	no pathogen	--	--

**Comment:**

- In general, the two arms of the study are comparable with respect to the number of times an enrolled patient required discontinuation of therapy, for whatever reason. The larger number of chloramphenicol patients is due to the larger number of 'no pathogen' discontinuations.*
- The comments regarding severity of event, and relatedness to study drug, are per the sponsor.*

The following table presents the sponsor's compilation of selected adverse events recorded in the study, regardless of relatedness to study drug administration. (These data were included in Table 25 of the sponsor's study summary tables, found on page 08-02-0700 of the submission.)

**TABLE 20 INCIDENCE RATES OF ADVERSE EVENTS  
BY BODY SYSTEM AND TREATMENT ARM  
ALL PATIENTS ENROLLED, PER SPONSOR  
PROTOCOL D87-054**

Adverse event	Ciprofloxacin	Chloramphenicol
<b>Any body system, any event</b>	30/112 (27%)	37/112 (33%)
<b>Digestive--any event</b>	7/112 (6%)	17/112 (15%)
Nausea	2/112 (2%)	2/112 (2%)
Vomiting	1/112 (1%)	4/112 (4%)
Diarrhea	2/12 (2%)	11/112 (10%)
Anorexia	2/112 (2%)	1/112 (1%)
Oral Candidiasis	0	1/112 (1%)
Increased saliva/Bad taste in mouth	0	1/112 (1%)
Intestinal perforation	1/112 (1%)	0
<b>Hematopoietic and Lymphatic--any event</b>	18/112 (16%)	22/112 (20%)
Anemia	1/112 (1%)	0
Eosinophilia	14/112 (13%)	13/112 (12%)
Reduced Leukocytes	3/112 (3%)	10/112 (9%)
<b>Neurologic--any event</b>	3/112 (3%)	1/112 (1%)
Headache	1/112 (1%)	0
Dizziness	2/112 (2%)	0
Insomnia	0	1/112 (1%)
Confusion	0	1/112 (1%)
<b>Special senses--any event</b>	2/112 (2%)	5/112 (4%)
Bad taste	2/112 (2%)	5/112 (4%)
<b>Urogenital--any event</b>	1/112 (1%)	2/112 (2%)
<b>Skin and Appendages--any event</b>	1/112 (1%)	3/112 (3%)
Rash	1/112 (1%)	0
Facial Acne	0	3/112 (3%)

**Comment:**

1. The sponsor included a calculation of the p-value for the significance of each pair of AE data included in this table. The events which were considered to be at or near statistical significance included the following:
  - Any digestive event (p = 0.031)
  - Diarrhea (p = 0.010)
  - Reduced Leukocytes (p = 0.045)
2. In general, the AE experience in this study was consistent with the labeling for each of the two study medications. The incidence of eosinophilia is considerably higher than would be expected due to a drug effect alone; this may reflect the location of the two study sites (Guatemala and Peru) and the degree of background helminth infection, as well as the stringent criteria used (any differential with 5% eos or greater) and the duration of follow-up (one of the reports of eosinophilia was given as having started 367 days AFTER completion of therapy!). In looking at the actual pre- and post-therapy values for eosinophils (which were reported only as a percentage value, relative to the total WBC count, rather than as an absolute value, which is much more meaningful), there appear to be more chloramphenicol patients with higher values. Five patients in the chloramphenicol arm had increases of more than 8% (pre-vs. post-therapy), whereas only one patient had such an increase in the ciprofloxacin arm. Such perturbations may be a reflection of the known marrow toxicity of chloramphenicol.
3. Crystalluria was not a problem during this study. There were only 2 patients in the ciprofloxacin arm, and 3 in the chloramphenicol arm, with any degree of crystalluria reported in any of the urinalyses collected during the study. No elevations in serum creatinine were seen in either treatment arm.

**Laboratory safety**

Laboratory safety data were analyzed by the sponsor and presented in a summary table, Table 30 of the study summary tables (page 08-02-0718). In this table, important laboratory parameters and deviations from baseline values are defined, then the number of patients with each of these deviations is given for both treatment arms:

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ON ORIGINAL**

**TABLE 22 INCIDENCE OF CHANGES IN LABORATORY TESTS  
BY TREATMENT ARM  
PER SPONSOR  
PROTOCOL D87-054**

Laboratory test	Definition of change from baseline	Ciprofloxacin	Chloramphenicol
<b>Hemoglobin</b>	Decrease of 1.5 gm% or more	13/97 (13%)	24/101 (24%)
	Decrease of 3.0 gm% or more	4/97 (4%)	3/101 (3%)
<b>Hematocrit</b>	Decrease of 5% or more	20/89 (22%)	38/91 (42%)
	Decrease of 15% or more	8/89 (9%)	10/91 (11%)
<b>Total WBC</b>	Decrease of 1.5 x 1000/cu mm	17/97 (18%)	26/102 (25%)
	Decrease of 3.0 x 1000/cu mm	6/97 (6%)	8/102 (8%)
	Decrease of 4.0 x 1000/cu mm	4/97 (4%)	7/102 (7%)
<b>Serum creatinine</b>	Increase of 0.5 mg/dl or more	2/94 (2%)	1/99 (1%)
	Increase of 1.0 mg/dl or more	0/94 (0%)	0/99 (0%)
<b>SGOT</b>	Increase of 75% of baseline or more	5/95 (5%)	6/100 (6%)
<b>SGPT</b>	Increase of 75% of baseline or more	7/96 (7%)	9/100 (9%)
<b>Alk Phosphatase</b>	Increase of 50% of baseline or more	4/69 (6%)	5/71 (7%)
<b>Total bilirubin</b>	Increase of 0.5 mg/dl or more	3/89 (3%)	2/90 (2%)

**Comment:**

1. The denominator in each cell is the number of patients who had that particular lab value drawn on at least 2 occasions, such that a comparison to a baseline value could be made.
2. The timing of the 'follow-up' lab, in relation to the 'baseline' value, is not specified in the text of the sponsor's report. Presumably, any lab value drawn during the post-initiation of therapy period which met the specified criteria, would cause that patient to be counted.
3. Many of these changes reflect the usual clinical course of acute typhoid fever. Changes in hematocrit and peripheral WBC count are to be expected, as well as mild changes in liver function studies. The only

*difference between the two treatment groups found by the sponsor to be statistically significant (at the  $p = 0.006$  level) was the decrease of 5% or more in hematocrit. Whether this represents drug toxicity of chloramphenicol, as opposed to the underlying disease process, is difficult to ascertain. The two treatment groups were relatively similar in terms of their baseline severity of infection, although there were 3 patients in the chloramphenicol group, vs. none in the ciprofloxacin group, who were considered to have severe infection at entry (see Table 7 of summary tables, page 08-02-0673). There were no reports of long-term bone marrow toxicity in the chloramphenicol group; the one withdrawal due to such an AE (patient #1064) had recovery of his WBC count.*

*In reviewing the data listings to examine the nature of these hematocrit changes more closely, it was found that only 21 patients in the chloramphenicol arm of the study had any change in hematocrit of at least 5% (see pages 08-02-1455-1458 for site #1, and pages 08-02-2204-2207 for site #2). Of these, 19 were from site #1. A total of ten patients treated with chloramphenicol had normal or high hematocrits at baseline, and low hematocrits at post-therapy follow-up. Comparatively, only 9 such patients were found in the ciprofloxacin data listings, and 4 of these had normal/high baseline values with low post-therapy hematocrits. This discrepancy (the sponsor cites 20 ciprofloxacin patients and 38 chloramphenicol patients as having such changes) is probably due to the table being generated as speculated in comment #2 above, whereas the data listings cited in this comment only present pre- and post-therapy values.*

*In conclusion, it is possible that the observed difference in number of patients experiencing a transient change of 5% or more in hematocrit was, in fact, due to chloramphenicol toxicity. However, such a degree of change is also consistent with the underlying disease process, is clinically insignificant, and was not reported to lead to any long-term sequelae (although the duration of follow-up for most patients was not sufficiently long to detect the idiosyncratic bone marrow toxicity, which may develop months after drug exposure). More profound changes in hematocrit, as noted in the above table, were equally distributed between the two treatment groups.*

## **CONCLUSIONS REGARDING STUDY D87-054**

- 1. This two-center study was well designed and executed. The flaws evident in the previously-reviewed study (D84-052) were, for the most part, avoided in this study. The enrollment goals of both study sites (100 patients per site) were met. Bacteriologic studies, particularly immediately post-therapy and at the time of long-term follow-up, were collected and documented. Long-term follow-up was at two months, rather than at two weeks.**
- 2. This study used the dose of ciprofloxacin (500 mg q12h) that the sponsor proposes to include in the labeling. The previous study used 750 mg q12h.**
- 3. Ciprofloxacin-treated patients had a more rapid clinical response. The rate of early clinical failure in the two groups was 10% (10/96) for ciprofloxacin and 24% (23/97) for chloramphenicol, with the majority of these failures (20/23 chloramphenicol patients) being due to the larger number who had persistence of fever for more than five days.**
- 4. Bacteriologic eradication rates were comparable between the two groups, with ciprofloxacin being slightly higher than chloramphenicol (for**

the two study sites combined, 90/93 or 97% for ciprofloxacin, and 89/96 or 93% for chloramphenicol). There was no evidence that one drug was superior to the other in terms of rapidity of clearance of bacteremia.

5. There was a small but potentially significant difference in eradication rates of S. typhi vs. S. paratyphi for ciprofloxacin. Although there was no direct correlation (i.e., the two S. paratyphi ciprofloxacin failures had ciprofloxacin MIC's of 0.030 and 0.003 mcg/mL, with the breakpoint for susceptibility being 1.0 mcg/mL or less), there appeared to be a tendency for higher MICs among the 28 clinical isolates of S. paratyphi.

6. In general, ciprofloxacin was better tolerated than chloramphenicol. The safety experience for both drugs was consistent with the known toxicities. Chloramphenicol patients had a higher rate of gastrointestinal side effects, particularly diarrhea, as well as a higher rate of mild decrease in hematocrit. Given the clinical course of the underlying disease, however, it is difficult to definitively ascribe these findings to chloramphenicol.

## SUPPORTIVE STUDIES

### **STUDY SN 866: A comparative study of ciprofloxacin with co-trimoxazole in the treatment of Salmonella enteric fever.**

This portion of the submission consists of a ten-page summary of a study performed by Drs. B.M. Limson and R.T. Littaua in the Philippines during 1985-86.

The study was a randomized, open-labeled, prospective evaluation of ciprofloxacin 500 mg bid x 10 days vs. co-trimoxazole (160 mg trimethoprim/800 mg sulfamethoxazole) bid x 14 days. Twenty patients were enrolled in each treatment arm. All patients were required to have positive blood cultures for either S. typhi or S. paratyphi. Enrollment consisted of 28 S. typhi patients (15 in the ciprofloxacin arm, and 13 in the co-trimoxazole arm), 9 S. paratyphi A patients (4 ciprofloxacin, 5 co-trimoxazole), and 3 S. paratyphi B patients (1 ciprofloxacin, 2 co-trimoxazole).

The results of this study are reported in tabular form on page 08-02-2279 of the submission. The ciprofloxacin arm had a reported 100% clinical efficacy rate, and a 100% bacteriologic eradication rate; the rates for co-trimoxazole were 90% and 90%. Both of the treatment failures in the co-trimoxazole arm were in patients infected with S. paratyphi A. Five of the 20 ciprofloxacin patients were reported to have experienced an adverse event: four with abdominal discomfort, and one with dizziness. None of the courses of

therapy had to be discontinued.

Comment:

*This portion of the submission is considered supportive only. The results are comforting only insofar as no substantially different results are presented. It is interesting to note that the failures in the co-trimoxazole arm were both S. paratyphi, substantiating the suggestion from Study D87-054 that this organism may be more difficult to treat than S. typhi. Unfortunately, no sensitivity data are presented. It would have been interesting to see what the MICs vs. ciprofloxacin were for the paratyphi isolates, compared to the typhi isolates, in this geographically distant site (i.e., compared to those mentioned above, which were from Peru).*

**STUDY SN 322: Clinical evaluation of ciprofloxacin in the Philippines.**

This portion of the submission consists of a paper, taken from a publication entitled "Excerpta Medica, Asia Pacific Congress Series", No. 62, 1988. This apparently was a study presented at the 'First Philippine Ciprofloxacin Symposium'. The lead author is again Dr. B. Limson; there are six additional co-authors listed.

This study was an open, non-comparative evaluation of ciprofloxacin in the setting of a variety of in-patient infections, at a total of six separate medical centers in the Manila area. Among the 78 patients considered evaluable in this study, there were 20 cases of typhoid fever.

Entry criteria used to make the diagnosis of typhoid criteria are not given. The dosage used was 500 mg tid for anywhere from 7 to 14 days; other patients received ciprofloxacin "...100-200 mg iv every 12 hours, depending on the severity of the infection, the pathogen isolated, the condition of the patient (i.e., state of the immune system), and renal function." The report claims that 19/20 patients with typhoid fever due to S. typhi had bacteriologic eradication. One patient had persistent infection, but the nature of this (persistent bacteremia despite ciprofloxacin therapy, or stool cultures positive only) is not specified. Adverse experiences reported included two episodes of diarrhea.

Comment:

*This paper is considered to be of testimonial value only. The results are not inconsistent with those reported in the previously-reviewed studies.*

**STUDY SN 9970: Ciprofloxacin in Salmonella infection and abdominal typhoid.**

This final portion of the submission consists of a paper (with English translation) taken from the journal Dtsche Med Wschr 111 (42): 1599-1602,

1986. This paper is a series of ten case reports of patients with various *Salmonella* infections, treated with various oral doses of ciprofloxacin for various lengths of time. Three of these cases were blood culture-confirmed typhoid fever, all of which were acquired during travel to Nepal. The first case described (Case #4) was declared a clinical failure after three days of ciprofloxacin 500 mg bid; the second (Case #5) received 500 mg bid for five days, became afebrile after three days, and had complete bacteriologic eradication; and the third (Case #10) received 500 mg bid for 14 days, with resolution of fever on day 7, and end-of-therapy stool cultures negative.

Comment:

*Two of these three cases would have been called clinical failures by this reviewer, given the data presented in this paper. Again, this paper is considered to be of testimonial value only.*

**OVERALL MEDICAL OFFICER CONCLUSIONS  
EFFICACY SUPPLEMENT 19-537/S-015**

1. The submitted clinical data support the efficacy of ciprofloxacin in the treatment of typhoid fever due to *Salmonella typhi*. Although Study D84-052 was relatively small and poorly executed, the second study (D87-054), given the two geographically distinct study sites, the numbers enrolled, and the efficient execution of the protocol, provides adequate data for review. In essence, this study can be considered to be two separate studies. The clinical efficacy was superior to the comparator, chloramphenicol, mainly based on fewer patients with prolonged fever in the ciprofloxacin arm(s). Bacteriologic eradication rates were roughly the same, with ciprofloxacin showing a slight advantage.
2. No unexpected ciprofloxacin-related safety issues were raised. Toxicities reported in the ciprofloxacin-treated patients consisted primarily of mild gastrointestinal events and eosinophilia. The high rate of eosinophilia (13%) in the ciprofloxacin-treated patients was of uncertain significance; a similar rate was seen in the chloramphenicol patients. The observed laboratory perturbations were similar, with the exception of higher rates of hematopoietic disturbances in the chloramphenicol-treated patients. These changes may have been a reflection of the underlying disease process; however, given the known myelotoxicity of chloramphenicol, these perturbations must be carefully noted.

T

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**INDICATIONS AND USAGE** section: add the following: "Typhoid Fever (enteric fever) caused by *Salmonella typhi*. NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been adequately studied."

**CONTRAINDICATIONS** section: no changes.

**WARNINGS** section: no changes.

**PRECAUTIONS** section: no changes.

**ADVERSE REACTIONS** section: no changes.

**OVERDOSAGE** section: no changes.

**DOSAGE AND ADMINISTRATION** section:

1. The term, "and for typhoid fever is 500 mg every 12 hours" should be added to the sentence, "The recommended adult dosage for Infectious Diarrhea is 500 mg every 12 hours."
2. An entry for Typhoid Fever should be added to the **DOSAGE GUIDELINES** chart found in this section, such that the line, "Typhoid Fever...Mild/Moderate...500 mg...q12h...1000 mg" is added to the columns headed, respectively, "Location of Infection...Type or Severity...Unit Dose...Frequency...Daily Dose."
3. The sentence "Typhoid fever should be treated for 10 days" should be added to the paragraph which begins, "The duration of treatment depends upon..."

**HOW SUPPLIED** section: no changes.

**ANIMAL PHARMACOLOGY** section: no changes.

**APPEARS THIS WAY  
ON ORIGINAL**

^ ^  
/S/

Philip E. Coyne, Jr., MD  
Medical Officer  
DAIDP, HFD-520

cc: NDA 19-537

HFD-340

HFD-520

HFD-520/MO/Coyne

HFD-520/Pharm/Buiko

HFD-520/Micro/Dionne

HFD-520/Chem/Shetty

HFD-520/CSO/Fogarty

HFD-520/SMO/RAlbuerne (info only) *msa 4/14/93*

HFD-520/SMO/SAlpert (info only)

Concurrence Only:

HFD-520/DivDir/MLumpkin

HFD-520/DepDir/LGavrilovich

HFD-520/SMO/RAlbrecht

*MAN  
4/3/93*

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ON ORIGINAL

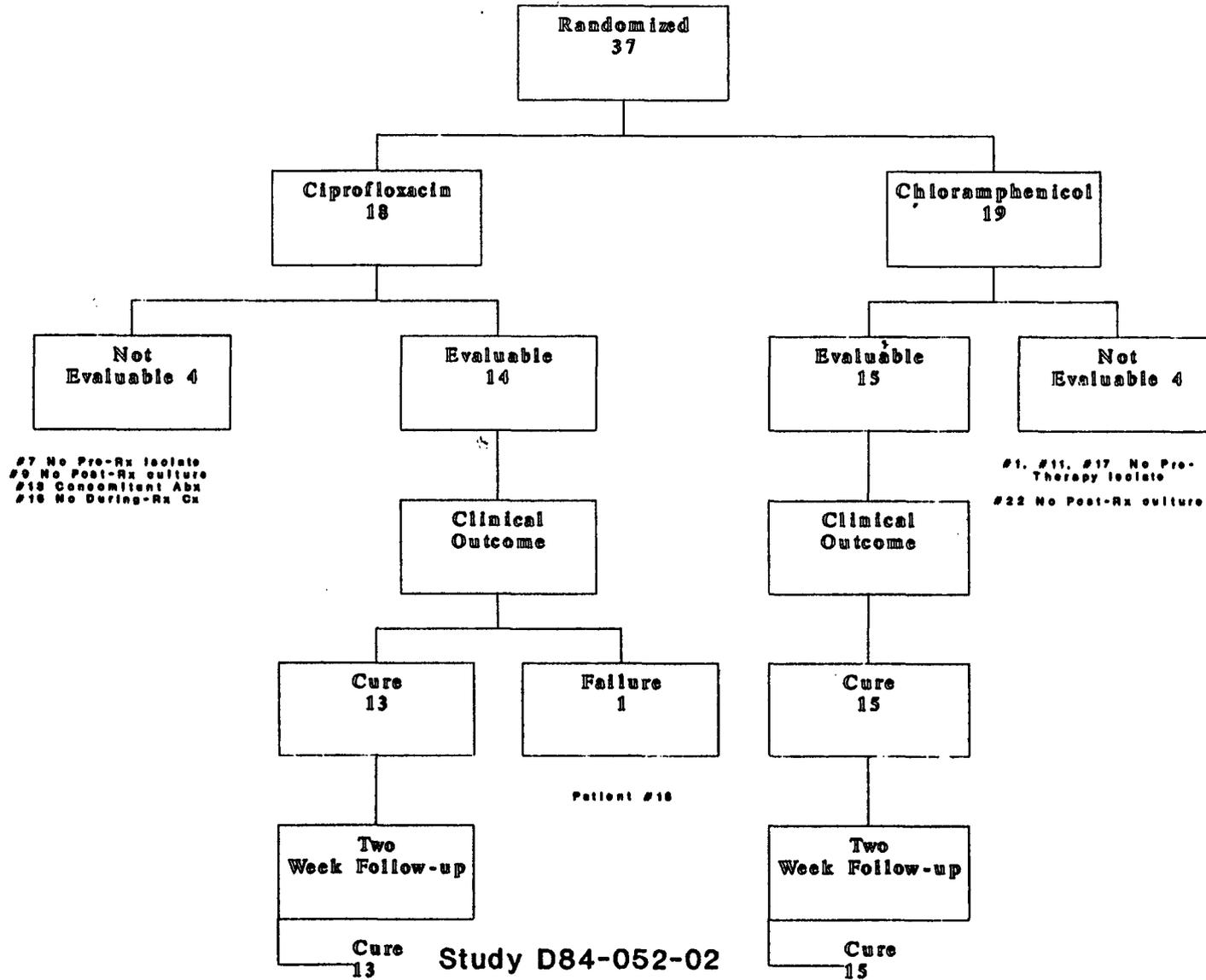
ATTACHMENT 1

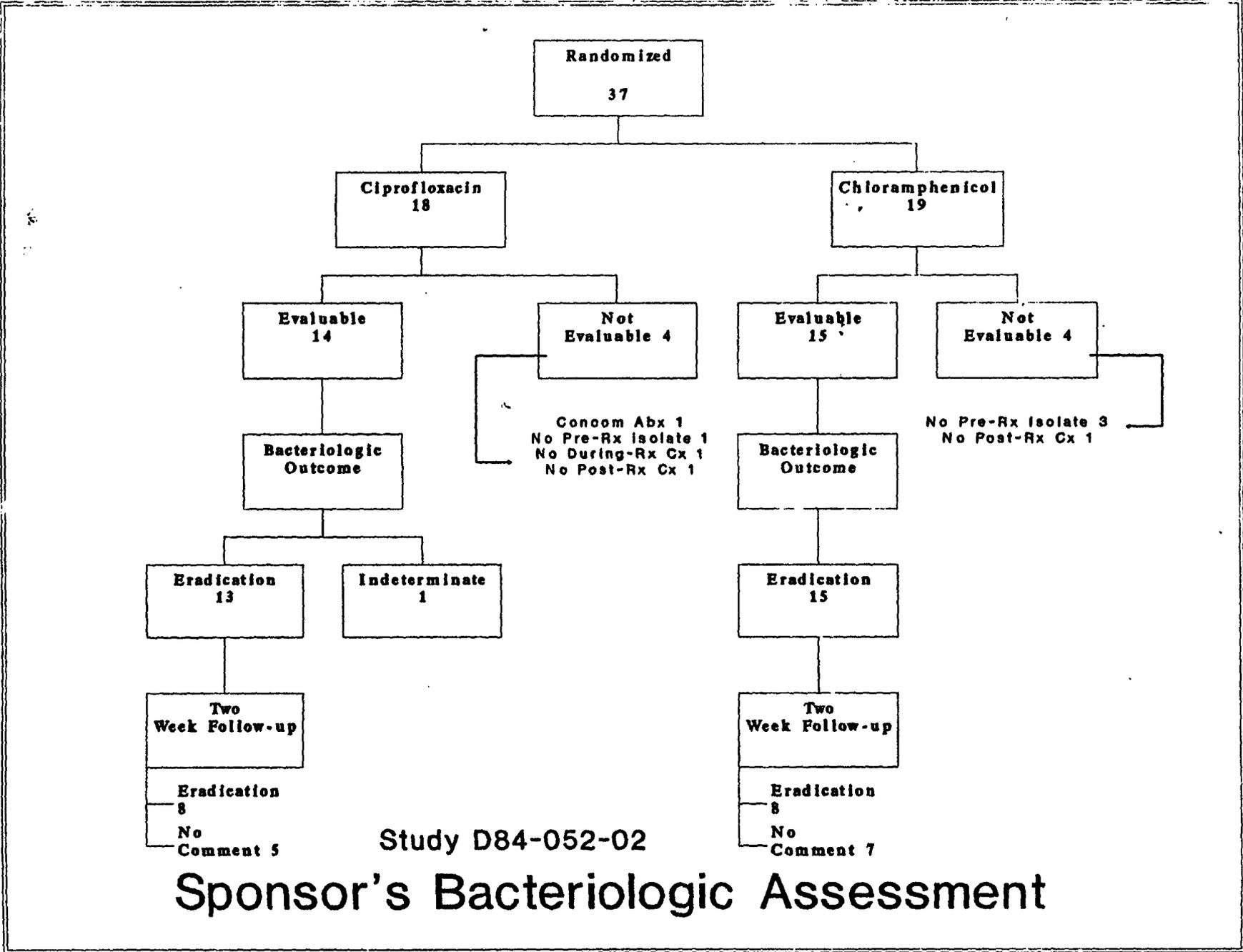
10. CIPROFLOXACIN TYPHOID STUDY FLOW CHART

PROCEDURE	PRE <sup>1</sup> RX	DURING RX WEEKS			POST RX	
		1	2	3	1 Day	2 Week
History	X				X	X
Evaluation of Patient for Eligibility	X					
Physical Examination	X	X	X	X	X	X
Obtain Signed Informed Consent	X					
Monitor Clinical Signs and Symptoms <sup>2</sup>	X	X	X	X	X	X
Bacteriological Studies of Blood, Urine & Stool	X	X <sup>3</sup>	X	X	X	X
Complete Blood Count	X	X	X	X	X <sup>4</sup>	
Urinalysis with Micro Exam of Sediment	X	X	X	X	X <sup>4</sup>	
Blood Chemistries	X	X	X	X	X <sup>4</sup>	
Blood for Drug Assay <sup>5</sup>	X	X	X	X	X	
Monitor Bacteriological Response Drug		X	X	X	X	X
Monitor for Adverse Effects					X	

Footnotes

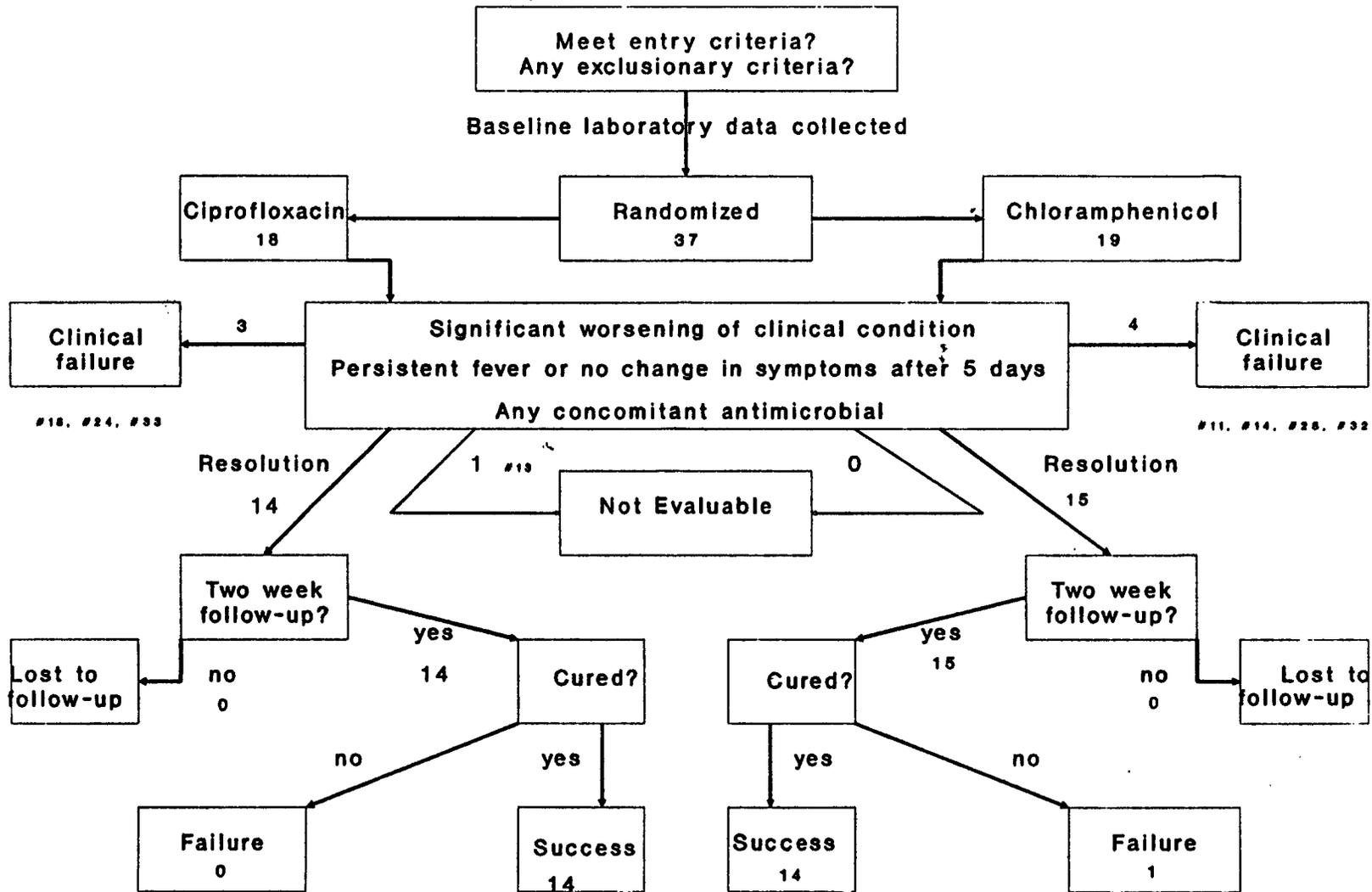
1. Within 24 hours prior to onset of drug therapy.
2. Daily throughout therapy
3. Additional during-treatment-cultures should be obtained as indicated (blood cultures daily during the 1st week of therapy).
4. Tests which yield abnormal results considered potentially related to the study drug, should be repeated at appropriate intervals to assess reversibility of the abnormalities.
5. Blood samples for assay of ciprofloxacin will be collected at 1 - 2 hours after the 1st daily administration for selected study patients.





ATTACHMENT 3

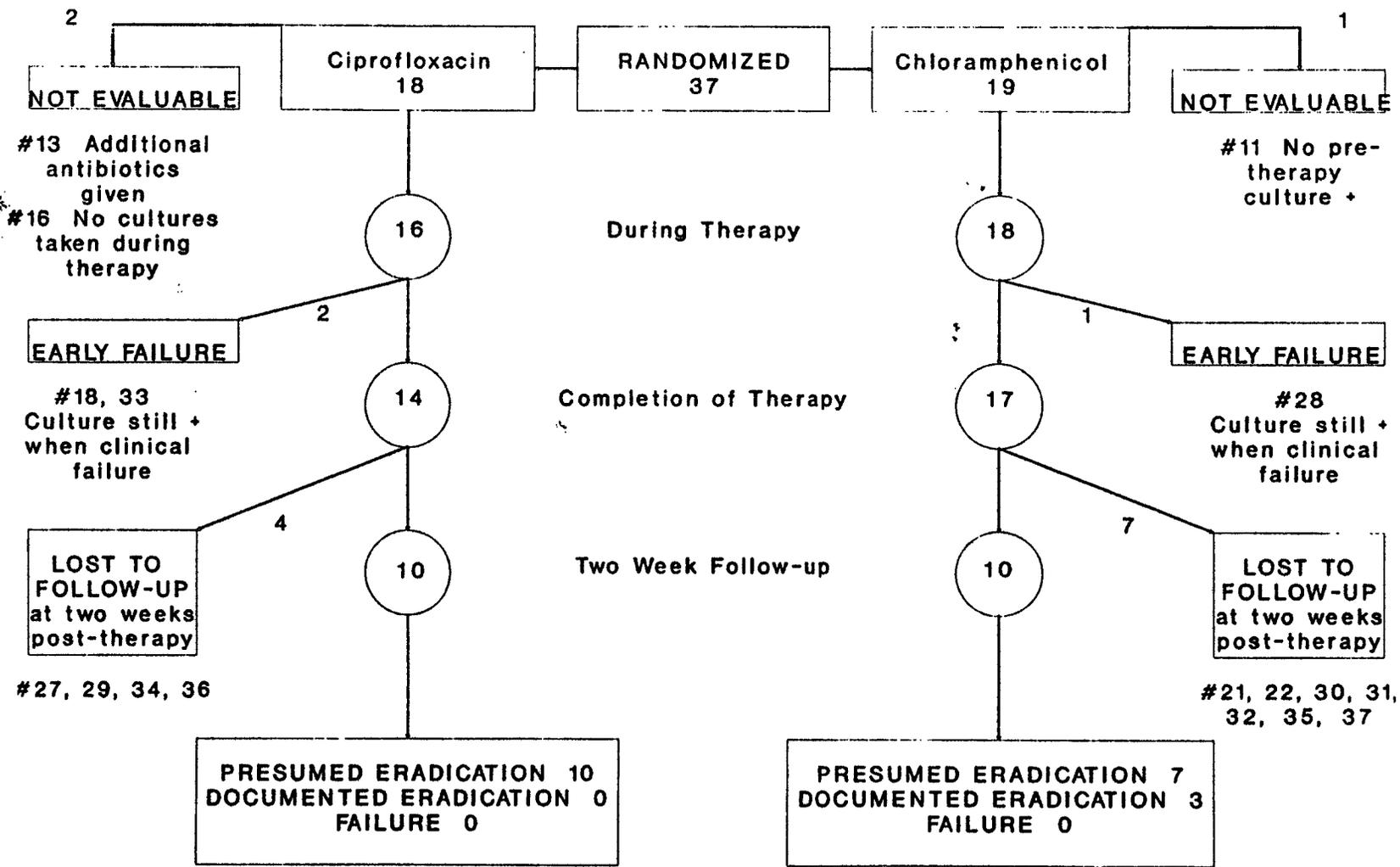
Study D84-052-02  
**Sponsor's Bacteriologic Assessment**



ATTACHMENT 4

# Medical Officer's Clinical Assessment

Study D84-052-02



ATTACHMENT 5

## Medical Officer's Bacteriologic Assessment Study D84-052-02