CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-717

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA: 50-717
Generic Drug Name: fosfomycin tromethamine
Drug Trade Name: MONUROL™
Formulation: oral powder in 3 gram sachet
Drug Class: 1S
Applicant: Zambon Corporation, Division of Zambon Group, SpA

DEC 17 1996

Indications: uncomplicated urinary tract infections (acute cystitis)

Documents Reviewed: NDA Volumes 1, 8, 9, 10, 11, 12 dated May 17, 1996 submitted as original amendment for NDA 50-717.
NDA Volume 1 dated June 28, 1996 submitted as original amendment for NDA 50-717.
Electronic submission of data for study MON-US-03 dated July 25, 1996.
Statistical Review and Evaluation for NDA 50-717 dated August 18, 1995.
Medical Officer's reviews of Protocol MON-US-01 and MON-US-02.

Type of Review: Clinical/Statistical

Medical Officer: Janice Soreth, M.D., HFD-520
Statistical Reviewer: B. Sue Bell, Ph.D., HFD-725
Project Manager: B. Duvall-Miller, HFD-520

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I. Executive Summary

The applicant requests approval of a single 3 gm dose of fosfomycin tromethamine (MONUROL™) for the treatment of uncomplicated urinary tract infections (UTI) in women. To support the UTI indication, the applicant has submitted data from three domestic, randomized, parallel group, double-blind, double dummy studies which compare the safety and efficacy of a single 3 gm dose of fosfomycin tromethamine (FT) to one of the following: a 7 day course of ciprofloxacin (CP) 250 mg q. 12 h. (protocol MON-US-01), a 10 day course of trimethoprim/sulfamethoxazole (TMP/SMX) 160/800 mg q. 12 h. (protocol MON-US-02), or a 7 day course of nitrofurantoin monohydrate/macrocrystals (NF) 100 mg q. 12 h.

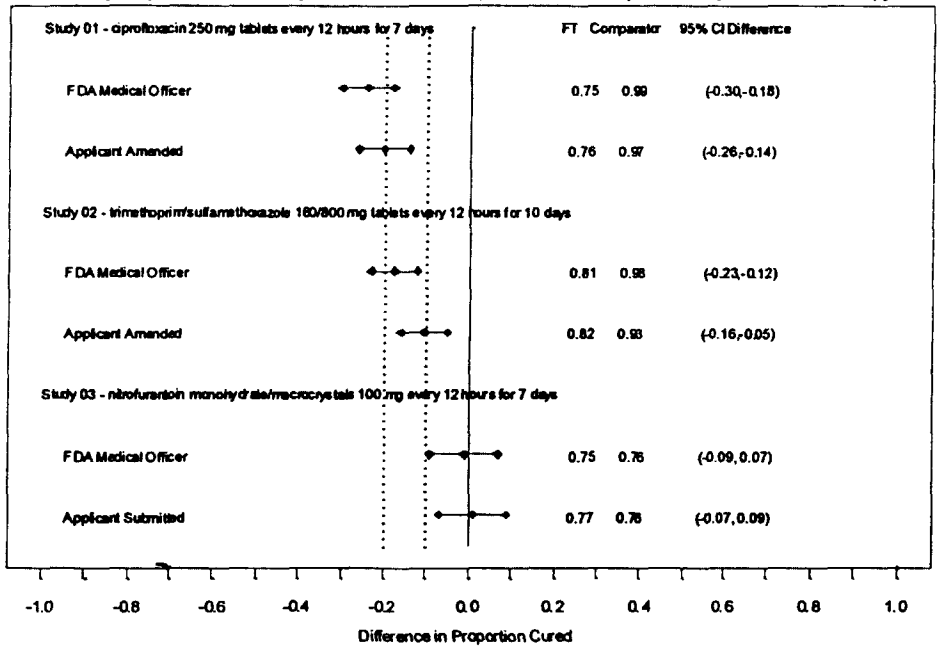
The primary efficacy variable is the rate of all bacteriologic eradication at 5-11 days after the longer course of treatment in the medical officer's evaluable patient group. Consistent with DAIDP's Points to Consider, the statistical comparison is based upon the two-sided 95% confidence interval of the difference in fosfomycin tromethamine rate minus the comparator's rate. The confidence intervals are reported as n_t, n_c (95% CI) p_t, p_c where n_t is the number in the test group, n_c is the number in the control group, p_t is the percent cured in the test group, and p_c is the percent cured in the control group.

The applicant's original request was based upon studies MON-US-01 and MON-US-02 and was not approved because these studies failed to show that FT was therapeutically equivalent in efficacy to either the CP or the TMP/SMX treatments for this indication. The 95% confidence intervals for these studies were $_{260,222}$ (-30% , -18%) $_{75\%,99\%}$ and $_{249,197}$ (-23% , -12%) $_{81\%,98\%}$ comparing FT to CP and FT to TMP/SMX, respectively. Since the efficacy percent of both comparator treatments is greater than 90%, DAIDP's Points to Consider requires that the confidence interval cross zero and that the lower bound be greater than -10%.

This amended application is based upon study MON-US-03 that shows FT is comparable to NF which is an approved drug for uncomplicated UTI. The 95% confidence interval for this study comparing FT to NF is $_{262,238}$ (-9% , 7%) $_{75\%,76\%}$. Since the efficacy percent of both treatments is in the range of 70% to 79%, DAIDP's Points to Consider requires that the confidence interval cross zero and that the lower bound be greater than -20% to establish equivalence of two treatments.

Included in the amended application was a revised analysis of the results of the first two studies performed by the applicant. In this analysis the applicant sought to follow the guidance provided in response to the original application. Figure 1 graphically compares the results of the applicant's and the medical officer's analysis of the data from each study. Even in the applicant's reanalysis, FT is still shown to be inferior to CP and TMP/SMX in the treatment of uncomplicated UTI in women.

Figure 1: 95% Confidence Intervals of Differences in Bacteriologic Eradication Rates of Single 3 gm Dose of Fosfomycin vs Multi-Dose Comparators at 5-11 Days after Longer Course of Therapy



Note: Per DAIDP's Points to Consider, in order to establish statistical equivalence the 95% CI must cross zero and remain within a lower bound of -0.10 when the effectiveness end point is greater than .90 or within -0.15 when .80-.89 effective or within -0.20 when .70-.79 effective.

Statistical evaluation of safety is based upon the Fisher's exact test comparing the rates of at least one adverse event in each of the treatment groups. A single dose of FT is not statistically different in safety from either CP (p=0.46) or NF (p=0.61). FT is statistically superior in safety to TMP/SMX (p=0.02). In all three studies, FT has a statistically significantly higher rate of diarrhea than its comparator with p-values of 0.04, <0.01, and 0.005 for CP, TMP/SMX, and NF, respectively.

II. Background

As discussed in the Executive Summary above, this application was not approved based upon the original submission. In this amendment, the applicant has provided an additional study MON-US-03, a revised analysis of the two earlier studies MON-US-01 and MON-US-02, and revised integrated summaries of efficacy and safety.

The focus of this review is study MON-US-03 and the updated integrated summaries of efficacy and safety. Refer to the Statistical Review and Evaluation dated August 18, 1995 for a detail review and analysis of studies MON-US-01 and MON-US-02.

III. Protocol MON-US-03

III.A. Study Design

The primary objective of the study was to compare the efficacy of a single dose of fosfomycin tromethamine (FT) (3 gm dose sachet) to nitrofurantoin monohydrate/macrocrystals (NF), 100 mg every 12 hours for seven days, in female patients with uncomplicated urinary tract infection. The secondary objective was to compare the safety profile of FT with that of NF. This study was designed as a prospective, parallel, active-controlled, multicenter trial with patients randomly allocated to either FT or NF. The primary efficacy endpoint was bacteriological cure. The total study period was seven weeks consisting of seven days of therapy plus 4-6 weeks follow-up. Patients assigned to the FT group received a 3 gm single dose of FT followed by placebo NF capsules every 12 hours for seven days. The patients who were assigned to the NF group were treated with the fosfomycin placebo sachet at the start of therapy, followed by NF capsules 100 mg every 12 hours for seven days.

Investigative sites through the United States were pre-qualified and then 27 appropriate centers were selected for study participation. Of these 27 centers, 26 actually enrolled patients. There was a target of 20 patients per center but 17 of the 26 centers failed to meet this goal with 8 centers enrolling less that 10 patients.

***REVIEWER COMMENT**: Investigators Costantini at study site 81 and Iravani at study site 87 were also participants in protocols MON-US-01 and MON-US-02. Further, these two investigators contributed a large proportion of the applicant's evaluable patients contributing 19%, 21% and 22% of protocols MON-US-01, MON-US-02, and MON-US-03, respectively. This raises a question as to the independence of these three studies. Investigators Harnack and Ginsburg participated in 2 of the 3 studies.*

Although the application shows that investigator Liotti at study site 88 enrolled one patient who was randomized to receive NF (volume 1, page 10-01747), no data was provided for this patient in this center in the SAS datasets provided by the applicant.

Investigator Ginsburg was a participant in both protocols MON-US-02 and MON-US-03. Refer to the medical officer's report for MON-US-02 for a discussion of reasons why this investigator's data was excluded from analysis of MON-US-02's efficacy results. In MON-US-03, the bacteriologic cure rates for Ginsburg's site was 75% (12/16) for FT and 83% (10/12) for NF. Ginsburg's center was not excluded from the analysis of MON-US-03 since the cure rates were basically consistent with those observed at other sites and, unlike in MON-US-02 where it was the largest contributor of patients, this center contributed less than 6% and was ranked sixth of the 25 centers in MON-US-03. The applicant stated that the laboratory problems experienced in the previous study were addressed during the conduct of this study by changing laboratories (volume 1, page 10-01755). However, 35 of the 51 patients enrolled at this site had already been processed using the in-house laboratory. The applicant performed an analysis excluding this site and found that it did not affect the conclusions.

Non-pregnant, non-lactating females of age 12 or older with clinical signs and/or symptoms of uncomplicated UTI were eligible for enrollment. Patients with recurrent UTI or evidence of factors predisposing to the development of UTI were excluded. Also excluded were patients with onset of symptoms for this UTI episode > 96 hours earlier, symptoms suggestive of upper UTI, and patients with known or suspected hypersensitivity to either FT or NF.

Patients who met the inclusion/exclusion criteria (see medical officer's review for further details) were randomized and began receiving treatment before baseline urine culture results were known.

***REVIEWER COMMENT**: Although the protocol permitted the inclusion of females 12-17, only three 17-year-olds and one 15-year-old were included in the evaluable group. Two additional 17-year-olds were excluded as screening failures.*

The initial baseline visit occurred on study day 0 when interested and qualified patients reviewed and signed the informed consent document, took a pre-therapy pregnancy test, had their medical history documented, and received a physical examination including vital sign measurements. Clinical laboratory evaluation, urinalysis and a quantitative urine culture and susceptibility test of the isolated uropathogens were also done as part of the baseline evaluations. After randomization, a sachet of either placebo or study medication was administered in the office and patients were sent home with the appropriate NF or placebo capsules.

At two to four days after the first dose of study medication, patients were contacted by telephone to determine their medical status. Only patients with continuing or worsening symptoms were immediately evaluated in the clinic. Three follow-up visits to the clinic were required: Visit 2 (5-9 days after first dose), Visit 3 (11-15 days after first dose), and Visit 4 (4-6 weeks after last dose). At all clinic visits, vital signs were recorded, a clinical evaluation was made, a urine sample was obtained, analyzed and cultured, and adverse events were elicited. An exit physical examination was performed at Visit 4.

III.B. Efficacy

The primary efficacy endpoint was bacteriological cure and secondary endpoints included assessments of superinfection, recurrence or new infection and clinical response. A successful overall clinical response required both a bacteriological cure and the absence of UTI symptomatology. The applicant's primary bacteriological evaluation windows were study days 5 to 11 for FT and study days 11 to 17 for NF. The medical officer used study days 11 to 17 for both FT and NF. The applicant made four assessments of bacteriological response in three temporal windows. The assessments made were: Day 5-11 (Visit 2), Day 11-17 (Visit 3), After Day 17 (with respect to original uropathogen only), After Day 17 (taking into consideration not only the original uropathogen but also the incidence of new infection and recurrence). To distinguish between the two assessments made after Day 17, the evaluation that takes into consideration new infection/recurrence is hereafter called the "Final Visit" evaluation.

***REVIEWER COMMENT**: For this review, the bacteriological cure at the final visit 4-6 weeks after the last dose is based upon the medical officer's "all sustained eradication" from the statistical review of MON-US-01 and MON-US-02 and the applicant's reporting of "Final Visit" bacteriological results in the amended application.*

Bacteriological evaluations were based upon urine specimens obtained by the midstream clean catch technique. The baseline was based upon urine collected within 96 hours prior to starting treatment. The urine cultures were performed by the local laboratory associated with the clinical site. Bacteriological cure and failure rates were calculated for the evaluable population that included all patients who had $\geq 10^5$ CFU/mL of a known uropathogen on baseline culture and who either completed the study or were discontinued due to treatment failure or failure-related reasons.

Table 1 provides an accounting of the patients included in the ITT, the modified ITT, and the evaluable populations for both the applicant's and the medical officer's analysis. There is little difference between the applicant's and medical officer's evaluable groups. The medical officer reviewed the CRFs for those patients whom the applicant had discontinued and returned two FT treated patients and one NF treated patient to the evaluable populations.

Table 1: Applicant's and Medical Officer's accounting of patients enrolled in protocol MON-US-03.

	fosfomycin		nitrofurantoin		
	N	% of Total	N	% of Total	Total
Applicant's Analysis Groups					
Patients randomized (ITT)	375	50%	374	50%	749
Patients without 10^5 CFU/mL of a known uropathogen at baseline.	103	48%	113	52%	216
Patients with a baseline pathogen (MITT)	272	51%	261	49%	533
Patients excluded for reasons such as lost to follow-up or protocol violations.	12	33%	24	67%	36
Evaluable patient population	260	52%	237	48%	497
Medical Officer's Analysis Groups					
Patients randomized (ITT)	375	50%	374	50%	749
Patients without 10^5 CFU/mL of a known uropathogen at baseline.	103	48%	113	52%	216
Patients with a baseline pathogen (MITT)	272	51%	261	49%	533
Patients excluded for reasons such as lost to follow-up or protocol violations.	10	30%	23	70%	33
Evaluable patient population	262	52%	238	48%	500

***REVIEWER COMMENT**: In the NDA, the applicant used the term ITT to refer to the population that is normally referred to as the modified ITT population and used the term modified ITT for what is normally referred to as the evaluable or per protocol population. For consistency with the statistical reviews of the other two protocols included in this NDA and with other DAIDP reviews, the more conventional use of these terms will be used rather than the applicant's. Basically, the ITT population includes all randomized patients, the modified ITT population is a subset of the ITT population that includes those who were randomized and who have a baseline pathogen, and the evaluable population is a subset of the modified ITT population that excludes patients with protocol violations that are not related to treatment failure.*

***REVIEWER COMMENT**: Note that twice the patients were excluded from the NF arm as from the FT arm (12 for FT versus 24 for NF). This difference was due to NF losing more patients to follow-up and discontinuations due to adverse experience/intercurrent illness during the first few week of study drug administration.*

Bacteriological cure at a time point required that a urine culture be taken and that all of the uropathogens, found at baseline at levels $\geq 10^5$ CFU/mL, were reduced to levels $< 10^4$ CFU/mL. If more than one sample was taken within the window, the worst case was used.

***REVIEWER COMMENT**: Once a patient has been designated a bacteriological failure then that patient should be considered a bacteriological failure at all remaining visits. For 11 patients (6 in FT arm and 5 in NF arm) this did not appear to be the case. The CRFs for these patients were reviewed. Although the bacteriologic outcome at the applicant's primary assessment window did not require revision, most other assessments including the clinical outcomes and the final bacteriological outcome were reclassified from success to failure for these 11 patients.*

Table 2 summarizes the results from both the applicant's and the medical officer's primary outcome assessment which is bacteriological cure. As can be seen by the 95% confidence intervals of the difference in the percent cured by FT minus the percent cured by NF, FT is comparable to NF in bacteriological efficacy at all time points based upon the criteria established in DAIDP's Points to Consider. The confidence interval crosses zero and is within the lower bound of -20% required when the cure rate is between 70% and 80%.

Table 2: Applicant's and Medical Officer's bacteriological evaluation of the evaluable populations at three follow-up time points for protocol MON-US-03 where cured is the bacteriological eradication of the baseline pathogen.

	n cured / N evaluable	% cured	n cured / N evaluable	% cured	95% CI of difference in %
Applicant's Evaluation	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	200 / 260	77%	179 / 237	76%	(-7%, 9%)
by 5-11 days post therapy	215 / 260	83%	179 / 237	76%	(-0%, 15%)
at final visit 4-6 weeks after last dose	170 / 260	65%	147 / 237	62%	(-6%, 12%)
Medical Officer's Evaluation	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	196 / 262	75%	180 / 238	76%	(-9%, 7%)
by 5-11 days post therapy	215 / 262	82%	180 / 238	76%	(-1%, 14%)
at final visit 4-6 weeks after last dose	164 / 262	63%	143 / 238	60%	(-7%, 11%)

By pathogen cure rates based upon the medical officer's evaluable population are provided in Table 3. This table includes those pathogens that the applicant included in the Indications and Usage section of their proposed label.

The assessment of UTI symptomatology was evaluated using a four point scoring system for six key UTI symptoms. The six UTI symptoms evaluated were the following: flank tenderness, suprapubic tenderness, dysuria, urinary urgency, urinary burning, and urinary frequency. The following scores were used: 0 for absent or normal, 1 for very mild or slight, 2 for moderate, and 3 for severe. A patient was classified as a cure if the six UTI symptoms assessed were all scored as 0 and no concomitant antibiotic for UTI was taken in the period from baseline evaluation to the relevant assessment. Table 4 presents both the applicant's assessment and the medical officer's assessment of clinical cure based upon symptomatalogy.

***REVIEWER COMMENT**: In reviewing the applicant's data, patients were found who had moderate to severe symptoms at a visit but who were classified as symptomatic successes at that visit. For consistency with the protocol, such patients were reclassified as failures for the medical officer's evaluation.*

Note that the applicant's clinical success rates for FT improves over time from 69% to 75% for the visit 5-11 days after the 1-day FT therapy and the visit 5-11 days after end of the 7-day NF therapy, respectively. This is because some patients were failures at the visit during study days 5-11 but were free of symptoms at the visit during study days 11-17. In the medical officer's assessment, these failures should be carried forward as failures. When considered in conjunction with other misclassifications, the result is that the medical officer's clinical success rates are 68% and 63% for the visit 5-11 days after the end of the 1-day FT therapy and the visit 5-11 days after the and of the 7-day NF therapy, respectively.

The applicant also included an outcome of "overall clinical assessment" which was derived from requiring both a bacteriological success and a clinical success. However, the focus of this review is on the bacteriological outcome and the clinical symptomalogical outcome considered independently rather than in a derived combination.

Table 4: Applicant's and Medical Officer's evaluation of clinical symptoms in the evaluable populations at three follow-up time points for protocol MON-US-03 where clinical cure requires relief of UTI symptoms.

	n cured / N evaluable	% cured	n cured / N evaluable	% cured	95% CI of difference in %
Applicant's Evaluation	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	196 / 260	75%	182 / 237	77%	(-9%, 6%)
by 5-11 days post therapy	180 / 260	69%	182 / 237	77%	(-16%, 1%)
at final visit 4-6 weeks after last dose	183 / 260	70%	156 / 237	66%	(-4%, 13%)
Medical Officer's Evaluation	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	164 / 262	63%	183 / 238	77%	(-23%,-6%)
by 5-11 days post therapy	177 / 262	68%	183 / 238	77%	(-18%,-1%)
at final visit 4-6 weeks after last dose	144 / 262	55%	154 / 238	65%	(-19%, -1%)

Subgroup analysis for age, race, and weight was performed on the key bacteriological and clinical outcomes. Table 5 below presents the results for the subgroup analysis at 5-11 days post therapy in the applicant's evaluable group based upon the bacteriological cure rates. As can be noted by the p-values of the statistical tests, there were no differences between the levels in any of the subgroups. This was also the case for the clinical outcome as well as at the 4-6 week follow-up visit.

Table 5: Analysis of bacteriological efficacy by subgroup based upon rate of bacteriologic cure at 5-11 days post therapy in the applicant's evaluable group for protocol MON-US-03.

Subgroup	n cured / N evaluable	% cured	n cured / N evaluable	% cured	p-value Fisher's Exact	p-value Breslow-Day
	fosfomycin		**nitrofurantoin**			
< 45	188 / 220	85%	158 / 194	81%	0.29	0.557
45-65	18 / 25	72%	17 / 32	53%	0.18	
>65	9 / 15	60%	4 / 11	36%	0.43	
caucasian	180 / 221	81%	156 / 203	77%	0.28	0.184
black	22 / 24	92%	19 / 27	70%	0.08	
other	13 / 15	87%	4 / 7	57%	0.27	
< 110 pounds	14 / 16	88%	13 / 14	93%	1.00	0.539
110-150 pounds	139 / 168	83%	107 / 147	73%	0.04	
> 150 pounds	62 / 76	82%	59 / 76	78%	0.69	

III.C. Safety

In this clinical study, 192 of 375 (51%) FT-treated patients and 184 of 374 (49%) NF-treated patients reported at least one adverse event during the study period. A total of 417 adverse events were reported by FT-treated patients and 392 events were reported by NF-treated patients. The majority of these adverse events were considered to be mild to moderate in severity. Table 6 presents the adverse events experienced by greater than 1% of the patients by body system. Significantly more FT-treated patients reported diarrhea (14.7% versus 8%) and significantly more NF-treated patients reported pruritus (1.6% versus 0%). Seven patients in the FT group and 16 in the NF group were discontinued from the study due to an adverse event or intercurrent illness. No patient experienced a serious adverse event.

Table 6: Occurrence of Adverse Events in 1.0% or more of patients enrolled in protocol MON-US-03

Body System	Adverse Events	FT (N = 375) Number of Patients	FT (N = 375) % of Patients	NF (N = 374) Number of Patients	NF (N = 374) % of Patients	p-value Fisher's Exact
Body as a whole	headache	38	1.0	45	12.0	0.418
Body as a whole	pain	15	4.0	16	4.3	0.857
Body as a whole	back pain	13	3.5	11	2.9	0.836
Body as a whole	abdominal pain	12	3.2	5	1.3	0.139
Body as a whole	asthenia	3	0.8	6	1.6	0.340
Body as a whole	fever	2	0.5	5	1.3	0.286
Body as a whole	flu syndrome	2	0.5	4	1.1	0.451
Digestive	diarrhea	55	14.7	30	8.0	**0.005**
Digestive	nausea	25	6.7	32	8.6	0.339
Digestive	dyspepsia	8	2.1	12	3.2	0.376
Digestive	vomiting	2	0.5	8	2.1	0.063
Digestive	flatulence	2	0.5	4	1.1	0.451
Nervous	dizziness	13	3.5	10	2.7	0.673
Nervous	somnolence	4	1.1	0	0.0	0.124
Respiratory	rhinitis	16	4.3	22	5.9	0.324
Respiratory	pharyngitis	15	4.0	11	2.9	0.550
Respiratory	sinusitis	8	2.1	6	1.6	0.789
Respiratory	bronchitis	5	1.3	3	0.8	0.725
Respiratory	cough increased	5	1.3	0	0.0	0.062
Skin and skin structures	rash	2	0.5	7	1.9	0.107
Skin and skin structures	pruritus	0	0.0	6	1.6	**0.015**
Urogenital	vaginal moniliasis	18	4.8	17	4.5	1.000
Urogenital	vaginitis	14	3.7	13	3.5	1.000
Urogenital	dysmenorrhea	8	2.1	8	2.1	1.000
Urogenital	urinary frequency	6	1.6	4	1.1	0.752
Urogenital	dysuria	5	1.3	6	1.6	0.773
Urogenital	Urine abnormalitities	0	0.0	4	1.1	0.062

IV. Integrated Summaries of Efficacy and Safety

IV.A. Efficacy

Table 7 presents the medical officer's bacteriological evaluations of all three clinical trials that have been submitted in support of this NDA. The medical officer's test of cure is at the time point that is 5-11 days after the longer treatment arm. The applicant's primary assessment point was at 5-11 days after end of therapy. A long term follow-up was captured at 4-6 weeks after the end of therapy.

REVIEWER COMMENT: In the NDA, the applicant suggested making the test of cure window at 5-11 days after the start of therapy. Use of this time point implies that test for cure for the longer treatment arms be made while patients are still on therapy which is unacceptable. For the NDA submission, the applicant used as their test of cure a window 5-11 days after the end of therapy. This required an additional visit so that patients came in at what would have been 5-11 days after the end of each treatment arm. This was consistent with the choice of a primary efficacy window by the statistical reviewer of the first two studies. However, the medical officer's primary efficacy window is 5-11 days after the end of the longer therapy. The sponsor will be sensitive to the medical officer's choice of a test of cure window because it reduces their efficacy by 3%, 4%, and 7% for studies MON-US-01, MON-US-02, and MON-US-03 respectively. This reduction in apparent efficacy is most likely due to the potential for self-reinfection during the additional week of therapy required for the comparator arms. At 4-6 weeks the efficacy of FT drops by 14% in the pooled studies in contrast with a drop of 10%, 11% and 16% for ciprofloxacin, TMP/SMX, and nitrofurantoin, respectively.

Table 7: Medical Officer's bacteriological evaluation of the evaluable population for each of the three UTI studies where cured is the bacteriological eradication of the baseline pathogen.

	n cured / N evaluable	% cured	n cured / N evaluable	% cured	95% CI of difference in %
Pooled Studies	**fosfomycin**				
by 5-11 days after longer therapy	591 / 771	77%			
by 5-11 days post therapy	630 / 771	82%			
at final visit 4-6 weeks after last dose	483 / 771	63%			
Study MON-US-01	**fosfomycin**		**ciprofloxacin**		
by 5-11 days after longer therapy	194 / 260	75%	219 / 222	99%	(-30%, -18%)
by 5-11 days post therapy	203 / 260	78%	219 / 222	99%	(-26%, -15%)
at final visit 4-6 weeks after last dose	158 / 260	61%	197 / 222	89%	(-36%, -20%)
Study MON-US-02	**fosfomycin**		**TMP/SMX**		
by 5-11 days after longer therapy	201 / 249	81%	194 / 197	98%	(-23%, -12%)
by 5-11 days post therapy	212 / 249	85%	194 / 197	98%	(-19%, -8%)
at final visit 4-6 weeks after last dose	161 / 249	65%	172 / 197	87%	(-31%, -15%)
Study MON-US-03	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	196 / 262	75%	180 / 238	76%	(-9%, 7%)
by 5-11 days post therapy	215 / 262	82%	180 / 238	76%	(-1%, 14%)
at final visit 4-6 weeks after last dose	164 / 262	63%	143 / 238	60%	(-7%, 11%)

Table 8 presents the applicant's bacteriological evaluations of all three clinical trials that have been submitted in support of this NDA. The source of this information was the NDA original amendment volume 1 of 1 stamped June 28, 1996. In this amendment, the applicant reanalyzed the first two studies, MON-US-01 and MON-US-02, to be consistent with the process used in the original medical and statistical reviews of these studies. By comparing with the above table of the medical officer's results, it can be seen that there are no striking differences in the two analyses. The applicant's results are biased slightly in their favor but not sufficient to change the conclusions from those that resulted from the medical officer's original analysis.

Table 8: Applicant's bacteriological evaluation of the evaluable population for each of the three UTI studies where cured is the bacteriological eradication of the baseline pathogen.

	n cured / N evaluable	% cured	n cured / N evaluable	% cured	95% CI of difference in %
Pooled Studies	**fosfomycin**				
by 5-11 days after longer therapy	629 / 801	78%			
by 5-11 days post therapy	673 / 801	84%			
at final visit 4-6 weeks after last dose	514 / 801	64%			
Study MON-US-01	**fosfomycin**		**ciprofloxacin**		
by 5-11 days after longer therapy	205 / 268	76%	237 / 245	97%	(-26%, -14%)
by 5-11 days post therapy	222 / 268	83%	237 / 245	97%	(-19%, -8%)
at final visit 4-6 weeks after last dose	164 / 268	61%	206 / 245	84%	(-31%, -15%)
Study MON-US-02	**fosfomycin**		**TMP/SMX**		
by 5-11 days after longer therapy	224 / 273	82%	222 / 239	93%	(-16%, -5%)
by 5-11 days post therapy	236 / 273	86%	222 / 239	93%	(-12%, -1%)
at final visit 4-6 weeks after last dose	180 / 273	66%	184 / 239	77%	(-19%, -3%)
Study MON-US-03	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	200 / 260	77%	179 / 237	76%	(-7%, 9%)
by 5-11 days post therapy	215 / 260	83%	179 / 237	76%	(-0%, 15%)
at final visit 4-6 weeks after last dose	170 / 260	65%	147 / 237	62%	(-6%, 12%)

Table 9 provides cure rates for those pathogens that the applicant included in the Indications and Usage section of the proposed label. Fosfomycin data has been pooled across the three studies. The data is reported for 5-11 days after the longer course of therapy, 5-11 days post-treatment, and 4-6 weeks post-treatment.

Table 10 provides both the medical officer's and the applicant's analysis of clinical efficacy for each of the three studies at each of the three follow-up time points. Also included is an a summary of fosfomycin's clinical efficacy pooled across the studies.

Table 10: Clinical evaluation by both the medical officer and the applicant for each of the three UTI studies where clinical success requires relief of symptoms.

	n cured / N evaluable	% cured	n cured / N evaluable	% cured	95% CI of difference in %
Medical Officer's Evaluable Population					
Pooled Studies	**fosfomycin**				
by 5-11 days after longer therapy	542 / 771	70%			
by 5-11 days post therapy	575 / 771	75%			
at final visit 4-6 weeks after last dose	461 / 771	60%			
Study MON-US-01	**fosfomycin**		**ciprofloxacin**		
by 5-11 days after longer therapy	189 / 260	73%	213 / 222	96%	(-30%, -17%)
by 5-11 days post therapy	199 / 260	77%	213 / 222	96%	(-26%, -13%)
at final visit 4-6 weeks after last dose	153 / 260	59%	196 / 222	88%	(-37%, -22%)
Study MON-US-02	**fosfomycin**		**TMP/SMX**		
by 5-11 days after longer therapy	189 / 249	76%	186 / 197	94%	(-25%, -12%)
by 5-11 days post therapy	199 / 249	80%	186 / 197	94%	(-21%, -8%)
at final visit 4-6 weeks after last dose	164 / 249	66%	173 / 197	88%	(-30%, -14%)
Study MON-US-03	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	164 / 262	63%	183 / 238	77%	(-23%, -6%)
by 5-11 days post therapy	177 / 262	68%	183 / 238	77%	(-18%, -1%)
at final visit 4-6 weeks after last dose	144 / 262	55%	154 / 238	65%	(-19%,-1%)
Applicant's Evaluable Population					
Pooled Studies	**fosfomycin**				
by 5-11 days after longer therapy	623 / 801	77%			
by 5-11 days post therapy	584 / 801	73%			
at final visit 4-6 weeks after last dose	580 / 801	72%			
Study MON-US-01	**fosfomycin**		**ciprofloxacin**		
by 5-11 days after longer therapy	208 / 268	78%	220 / 245	90%	(-19%, -6%)
by 5-11 days post therapy	205 / 268	76%	220 / 245	90%	(-20%, -7%)
at final visit 4-6 weeks after last dose	189 / 268	71%	211 / 245	86%	(-23%, -8%)
Study MON-US-02	**fosfomycin**		**TMP/SMX**		
by 5-11 days after longer therapy	219 / 273	80%	204 / 239	85%	(-12%, 2%)
by 5-11 days post therapy	199 / 273	73%	204 / 239	85%	(-20%, -5%)
at final visit 4-6 weeks after last dose	208 / 273	76%	199 / 239	83%	(-14%, 0%)
Study MON-US-03	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	196 / 260	75%	182 / 237	77%	(-9%, 6%)
by 5-11 days post therapy	180 / 260	69%	182 / 237	77%	(-16%, 1%)
at final visit 4-6 weeks after last dose	183 / 260	70%	156 / 237	66%	(-4%, 13%)

IV.B. Safety

The applicant "maintains that FT shows a more favorable safety profile when compared to TMP/SMX, an equal or better profile when compared to NF, and an equal profile when compared to CIPRO." Table 11 summarizes the adverse events for the three clinical trials conducted under protocols MON-US-01, MON-US-02, and MON-US-03. Statistical evaluation of safety is based upon the Fisher's exact test comparing the rates of at least one adverse event in each of the treatment groups. A single dose of FT is not statistically different in safety from either CP (p=0.46) or NF (p=0.61). FT is statistically superior in safety to TMP/SMX (p=0.02).

Table 11: Summary of adverse events in FT and comparator treatment groups in the ITT populations of MON-US-01, MON-US-02, and MON-US-03.

	FT (N=1233)		CP (N=445)		TMP/SMX (N=428)		NF (N=374)	
Category	n	%	n	%	n	%	n	%
Patients with AEs	567	46.0%	193	43.4%	212	49.5%	184	49.2%
Patients with Probably or Definitely Related AEs	81	6.6%	28	6.3%	45	10.5%	21	5.6%
Patients with Severe AEs	53	4.3%	18	4.0%	27	6.3%	21	5.6%
Patients with Serious AEs	3	0.2%	1	0.2%	5	1.2%	0	0.0%
Patients Discontinued due to all AEs	20	1.6%	6	1.3%	18	4.2%	15	4.0%
Patients Discontinued due to AEs Related to Drug	12	1.0%	5	1.1%	18	4.2%	11	2.9%

Table 12 provides a listing of the adverse events reported by 0.5% or more of the FT-treated ITT population. The number and percent reporting the adverse event in the comparator arms is also included in the table for comparison. In each of the three studies, FT has a statistically significantly higher rate of diarrhea than its comparator with p-values based upon a Fisher's exact test of 0.04, <0.01, and 0.005 for CP, TMP/SMX, and NF, respectively.

Table 12: Number and percentage of patients experiencing an adverse reaction in descending order by percent reporting the event in the FT-treated population

		FT (N=1233)		CP (N=445)		TMP/SMX (N=428)		NF (N=374)	
Body System	**Adverse Events**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Digestive	diarrhea	128	10.4%	19	4.3%	11	2.6%	30	8.0%
Body	headache	127	10.3%	42	9.4%	46	10.7%	45	12.0%
Digestive	nausea	64	5.2%	21	4.7%	43	10.0%	32	8.6%
Respiratory	rhinitis	55	4.5%	19	4.3%	13	3.0%	22	5.9%
Urogenital	vaginitis	52	4.2%	21	4.7%	17	4.0%	13	3.5%
Urogenital	vaginal moniliasis	42	3.4%	20	4.5%	9	2.1%	17	4.5%
Body	back pain	37	3.0%	13	2.9%	5	1.2%	11	2.9%
Urogenital	dysmenorrhea	32	2.6%	7	1.6%	5	1.2%	8	2.1%
Respiratory	pharyngitis	31	2.5%	7	1.6%	9	2.1%	11	2.9%
Nervous	dizziness	28	2.3%	14	3.1%	16	3.7%	10	2.7%
Body	abdominal pain	27	2.2%	5	1.1%	2	0.5%	5	1.3%
Body	pain	27	2.2%	6	1.3%	11	2.6%	16	4.3%
Digestive	dyspepsia	22	1.8%	7	1.6%	7	1.6%	12	3.2%
Body	asthenia	21	1.7%	2	0.4%	9	2.1%	6	1.6%
Skin and skin structures	rash	17	1.4%	5	1.1%	22	5.1%	7	1.9%
Respiratory	sinusitis	15	1.2%	5	1.1%	5	1.2%	6	1.6%
Respiratory	bronchitis	13	1.1%	1	0.2%	0	0.0%	3	0.8%
Body	flu syndrome	11	0.9%	4	0.9%	5	1.2%	4	1.1%
Urogenital	urinary tract infection	11	0.9%	4	0.9%	0	0.0%	2	0.5%
Digestive	vomiting	11	0.9%	2	0.4%	12	2.8%	8	2.1%
Respiratory	cough increased	10	0.8%	6	1.3%	4	0.9%	0	0.0%
Body	infection	10	0.8%	2	0.4%	4	0.9%	0	0.0%
Digestive	abnormal stools	9	0.7%	0	0.0%	0	0.0%	0	0.0%
Body	fever	7	0.6%	1	0.2%	6	1.4%	5	1.3%
Digestive	flatulence	7	0.6%	1	0.2%	4	0.9%	4	1.1%
Urogenital	urinary frequency	8	0.6%	1	0.2%	0	0.0%	4	1.1%
Urogenital	dysuria	6	0.5%	0	0.0%	1	0.2%	6	1.6%
Cardiovascular	migraine	6	0.5%	2	0.4%	1	0.2%	2	0.5%
Musculoskeletal	myalgia	6	0.5%	2	0.4%	0	0.0%	2	0.5%
Skin and skin structures	pruritus	6	0.5%	5	1.1%	9	2.1%	6	1.6%
Nervous	somnolence	6	0.5%	0	0.0%	2	0.5%	0	0.0%

V. Summary and Conclusions

Efficacy

Statistical evaluation of efficacy is based upon the two-sided 95% confidence interval of the fosfomycin tromethamine minus comparator difference in the rate of all bacteriologic eradication rate at 5-11 days after the end of the longer treatment arm in the medical officer's evaluable patient group. The confidence intervals are reported as n_t , n_c (95% CI) p_t, p_c where n_t is the number in the test group, n_c is the number in the control group, p_t is the percent cured in the test group, and p_c is the percent cured in the control group.

In study MON-US-01, the 95% confidence interval is $_{260,222}$ (-30% , -18%) $_{75\%, 99\%}$ which demonstrates that a single dose of 3 gm fosfomycin tromethamine is therapeutically inferior in efficacy to 7 days of ciprofloxacin 250 mg q. 12h. in the treatment of uncomplicated urinary tract infections in women.

In study MON-US-02, the 95% confidence interval is $_{249, 197}$ (-23% , -12%) $_{81\%, 98\%}$ which demonstrates that a single dose of 3 gm fosfomycin tromethamine is therapeutically inferior in efficacy to 10 days of trimethoprim/sulfamethoxazole 160/800 mg q. 12h. in the treatment of uncomplicated urinary tract infections in women.

In study MON-US-03, the 95% confidence interval is $_{262, 238}$ (-9% , 7%) $_{75\%, 76\%}$ which demonstrates that a single dose of 3 gm fosfomycin tromethamine is therapeutically equivalent in efficacy to 7 days of nitrofurantoin monohydrate/macrocrystals 100 mg q. 12h. in the treatment of uncomplicated urinary tract infections in women.

Safety

Statistical evaluation of safety is based upon the Fisher's exact test comparing the rates of at least one adverse event in each of the treatment groups.

A single dose of 3 gm fosfomycin tromethamine is not statistically significantly different in safety from either 7 days of ciprofloxacin 250 mg q. 12 hr. or 7 days of nitrofurantoin monohydrate/macrocrystals 100 mg q. 12h.. In study MON-US-01, the rate of at least one adverse event is 46% (199/432) for fosfomycin tromethamine and 43% (193/445) for ciprofloxacin which produces a Fisher's exact p-value of 0.46. In study MON-US-03, the rate of at least one adverse event is 51% (192/375) for fosfomycin tromethamine and 49% (184/374) for nitrofurantoin which produces a Fisher's exact p-value of 0.61.

A single dose of 3 gm fosfomycin tromethamine is statistically superior in safety to 10 days of trimethoprim/sulfamethoxazole 160/800 mg q. 12 h. In study MON-US-02, the rate of at least one adverse event is 41% (176/426) for fosfomycin tromethamine and 50% (212/428) for trimethoprim/sulfamethoxazole which produces a Fisher's exact p-value of 0.02.

In all three studies, fosfomycin tromethamine has a statistically significantly higher rate of diarrhea than its comparators. This is the only adverse even where the direction of the effect was consistent across all three studies. In study MON-US-01, the rate of diarrhea is 8% (33/432) and 4% (19/445) for fosfomycin tromethamine and ciprofloxacin, respectively (p=0.04). In study MON-US-02, the rate of diarrhea is 9% (40/426) and 3% (11/428) for fosfomycin tromethamine and trimethoprim/sulfamethoxazole, respectively (p<0.01). In study MON-US-03, the rate of diarrhea is 14.7% (55/375) and 8% (30/374) for fosfomycin tromethamine and for nitrofurantoin, monohydrate/macrocrystals respectively (p=0.005).

Subgroup analyses by age (18-44,45-65, and >65) and race (white, black, and other) did not reveal any noteworthy subgroup differences with respect to efficacy or safety.

Conclusion

A single dose of 3 gm fosfomycin tromethamine meets DAIDP's guidelines for establishing therapeutical equivalence in efficacy to 7 days of nitrofurantoin monohydrate/macrocrystals 100 mg q. 12h. in the treatment of uncomplicated urinary tract infections in women. However, the label should indicate that this treatment is therapeutically inferior to treatments of either 7 days of ciprofloxacin 250 mg q. 12h. or 10 days of trimethoprim/sulfamethoxazole 160/800 mg q. 12h. for this indication.

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This review contains 17 pages

STATISTICAL REVIEW AND EVALUATION

NDA: 50-717

AUG 18 1995

Applicant: Zambon Corporation/ Forest Laboratories, Inc.

Name of Drug: fosfomycin tromethamine (MONUROL™)

Documents Reviewed: NDA volumes 1.66-1.73, stamp dated September 29, 1994
Statistical Amendment (electronic data submission), dated January 5, 1995
Additional electronic data submitted by applicant on May 18,1995
Medical Officer's electronic data (Study 01), received June 14, 1995
Medical Officer's electronic data (Study 02), received June 29, 1995
Draft Medical Officer's Review (Study 02), received July 5, 1995
Draft Medical Officer's Review (Study 01), received July 6, 1995

Indication: uncomplicated urinary tract infections (acute cystitis)

Medical Input: Janice Soreth, M.D., HFD-520

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I. ABSTRACT

The applicant requests approval of a single 3 gm dose of fosfomycin tromethamine (MONUROL™) for the treatment of uncomplicated urinary tract infections. To support their indication, the applicant has submitted data from two domestic, randomized, parallel group, double-blind, double dummy studies which compare the safety and efficacy of a single 3 gm dose of fosfomycin tromethamine (FT) to either a 7 day course of ciprofloxacin (CP) 250 mg q. 12 h. (protocol MON-US-01) or a 10 day course of trimethoprim/sulfamethoxazole (TS) 160/800 mg q. 12 h. (protocol MON-US-02) in the treatment of women with uncomplicated urinary tract infections. The primary efficacy variable is the rate of all bacteriologic eradication at 5-11 days post treatment in the medical officer's evaluable patient group. In study 01, the eradication rate is 78% (203/260) for FT versus 99% (219/222) for CP [95% C.I.:(-26%, -15%)]. In study 02, the eradication rate is 85% (212/249) for FT versus 98% (194/197) for TS [95% C.I.:(-19%, -8%)]. The overall rate of adverse events is similar across treatments in study 01 [46% (199/432) for FT versus 43% (193/445) for CP, p=0.46], and lower for FT in study 02 [41% (176/426) FT versus 50% (212/428) for TS, p=0.02]. In both studies, FT had a higher rate of diarrhea than its comparator [study 01: 8% (33/432) versus 4% (19/445), p=0.04; study 02: 9% (40/426) versus 3% (11/428), p<0.01]. Compared to a 7 day course of ciprofloxacin 250 mg q. 12 h. or a 10 day course of trimethoprim/sulfamethoxazole 160/800 mg q. 12 h., a single 3 gm dose of fosfomycin tromethamine is inferior in efficacy, and does not have a substantial safety advantage for the treatment of uncomplicated urinary tract infections in women.

II. INTRODUCTION

The applicant requests the following indication in the **Indications and Usage** section of the proposed label:

The following treatment regimen is suggested in the **Dosage and Administration** section of the proposed label:

III. EVALUATION

III.A. STUDY DESIGN

MON-US-01 and MON-US-02 were domestic, randomized (1:1 ratio), parallel-group, active-controlled, double-blind, double-dummy, multicenter trials. Patients received either a 3 gm single oral dose of fosfomycin tromethamine packaged in a sachet, ciprofloxacin 250 mg tablets every 12 hours for seven days (study 01) or trimethoprim/sulfamethoxazole 160/800 mg tablets every 12 hours for ten days (study 02). To maintain the study blind, FT patients received 7 days (study 01) or 10 days (study 02) of placebo tablets, and CP or TS patients received a placebo sachet on the first day of therapy.

Non-pregnant, non-lactating females of age 18 or older with clinical signs and/or symptoms of uncomplicated UTI were eligible for enrollment. Patients who met the inclusion/exclusion criteria (see medical officer's review for details) were randomized to treatment before baseline urine culture results were known. According to protocol, if the baseline culture did not isolate an organism or an organism was isolated at insufficient quantities ($<10^5$ CFU) the patient was to be removed from the trial and treated according to the investigator's discretion.

By protocol convention, the baseline visit was designated as Visit 1. Four additional follow-up contacts (designated as Visits 1A, 2, 3, and 4) were required. The timing of these contacts in relation to study day is presented in Table 1. By convention, the first day of therapy was designated as study day 0, and all subsequent study days were defined in terms of the number of days after the first day of therapy. Note that due to the double-blind nature of the studies, all patients received either 7 days (study 01) or 10 days (study 02) of therapy. However, in reality, the FT patients only received one day of active therapy. Therefore, Table 1 also presents descriptions of the visit timing from both blinded and unblinded perspectives.

TABLE 1: Protocol Defined Visit Schedule

Visit	Study Day		Study Timepoint (treatment blinded)	Study Timepoint (treatment unblinded)
	MON-US-01	MON-US-02		
1	0	0	baseline assessment first day of therapy	FT: first day of therapy CP: first day of therapy TS : first day of therapy
1A	2-4	2-4	48-96 hrs after first dose of therapy	FT: 2-4 days post therapy CP: days 3-5 on therapy TS: days 3-5 on therapy
2	5-9	5-9	5-9 days after first dose of therapy	FT: 5-9 days post therapy CP: days 6-7 on therapy or 1-3 days post therapy TS: days 6-10 on therapy
3	11-15	14-18	5-9 days after last dose of therapy	FT: 11-15 days post therapy (Study 01) 14-18 days post therapy (Study 02) CP: 5-9 days post therapy TS: 5-9 days post therapy
4	34-48	37-51	4-6 weeks after last dose of therapy	FT: 5-7 weeks post therapy CP: 4-6 weeks post therapy TS: 4-6 weeks post therapy

The procedures performed at each visit are presented in Table 2. Note that Visit 1A was an optional clinic visit. However, a telephone contact was required. The noted evaluations for Visit 1A were performed only if the patient was symptomatic.

REVIEWER COMMENT: *Laboratory parameters (hematology and blood chemistry) were not measured when FT patients were on therapy. The earliest post baseline laboratory measurements for FT were taken at 5-9 days post therapy.*

TABLE 2: Protocol Defined Study Procedures

Assessment/Observation	Visit				
	1	1A[a]	2	3	4
Inclusion/Exclusion	✓				
Informed Consent	✓				
Randomization/Administration of Treatment[b]	✓				
Medical History	✓				
Physical Examination	✓				✓
Vital Signs	✓	✓	✓	✓	✓
Clinical Evaluation	✓	✓	✓	✓	✓
Pregnancy Test	✓				
Bacteriology (Urine Culture and Susceptibility)	✓	✓	✓	✓	✓
Urinalysis	✓	✓	✓	✓	✓
Hematology	✓		✓	✓	
Chemistry	✓		✓	✓	
Adverse Events	✓	✓	✓	✓	✓

[a] Visit 1A was an optional clinic visit. A telephone contact was required.

[b] The sachet and first tablet were administered under the observation of the investigator.

III.B. OUTCOME DEFINITIONS

III.B.1. BACTERIOLOGIC EFFICACY

III.B.1.a. APPLICANT

According to section 10.1 of the applicant's protocols, bacteriologic outcomes were defined as follows:

At early post therapy visit (Visit 2 for FT, Visit 3 for CP and TS) :

Cure: All initially susceptible pathogens ($\geq 10^5$ CFU) are reduced to $\leq 10^4$ CFU 5-9 days after the last dose of study medication.

Failure: Persistence of $\geq 10^5$ CFU of the initially susceptible pathogen. It will be considered a bacteriologic failure if the pathogen is present at levels $\geq 10^5$ CFU at 48-96 hours after the first dose of therapy or if the pathogen is initially eliminated at 48-96 hours after the first dose of therapy and is re-isolated at 5-9 days post therapy.

Superinfection: Growth of $\geq 10^5$ CFU of a different pathogen during therapy.

Impossible to Evaluate: A bacteriologic evaluation of cure or failure cannot be made due to, but not limited to such reasons as no bacterial pathogen isolated pretherapy, urine specimens not obtained at protocol specified time intervals, concomitant antimicrobial administration interfered with analysis, etc.

At late post therapy visit (Visit 4 for all treatments):

Recurrence: Growth of $\geq 10^5$ CFU of an initially susceptible pathogen at 4-6 weeks post therapy after demonstration of a bacteriologic cure.

New Infection: Growth of $\geq 10^5$ CFU of a different new pathogen at 4-6 weeks post therapy.

***REVIEWER COMMENTS**: These bacteriologic outcomes were assigned by the applicant's medical monitor. By design, the CRF collected information on each urine culture, but **did not** collect the investigator's interpretation of the urine culture information.*

By definition, the outcome of superinfection can occur only for CP or TS patients.

The outcomes of superinfection, recurrence, and new infection were evaluated individually in terms of yes/no responses. The applicant did not assign outcomes which account for all patients at 4-6 weeks post therapy. If a patient is a bacteriologic failure at 5-9 days post therapy, he/she should be designated as such at 4-6 weeks post therapy. If a patient is a bacteriologic cure at both time points, this should be reflected at the 4-6 week assessment. The outcome of new infection is mutually exclusive of the outcome of the initial infection; i.e., a patient may have eradication of the original infection with a new infection.

This reviewer performed an analysis of the applicant's data which accounts for all patients at the late post therapy visit using the following conventions:

Sustained Cure: bacteriologic cure at the early post therapy visit with documentation of no new infection or no recurrence at the late post therapy visit.

Sustained Cure with New Infection: bacteriologic cure at the early post therapy visit with documentation of a new infection at any time post therapy (timing of new infections was not available on the applicant's database) and with documentation of no recurrence at the late post therapy visit.

Recurrence: bacteriologic cure at the early post therapy visit with documentation of recurrence at the late post therapy visit.

Early Bacteriologic Failure: bacteriologic failure at the early post therapy visit

No Evaluation: no outcome recorded on the database for the early post therapy visit or for the late post therapy visit

Note that by protocol, visit timing was part of the definitions of the applicant's bacteriologic outcome. In section 3.8.3.1 of the study reports, the applicant extended the visit windows "In an effort to capture and analyze all available and appropriate data." The applicant's extended visit windows are presented in Table 3.

The fact that visit timing was linked to bacteriologic outcome is a major flaw in the applicant's analyses of the data. According to the applicant's definitions, a bacteriologic assessment had to be made exactly within the specified time window (see Table 3), or the medical monitor would assign patient's outcome as "Impossible

to Evaluate" or "No Evaluation". Clearly, this is an inappropriate way to handle treatment failures or recurrences, since these outcomes tend to occur at unscheduled visits. Furthermore, it is misleading to assign the outcome of "Impossible to Evaluate" or "No Evaluation" to patients who actually had assessments made, but were not within the specified time window. When the applicant assigned the outcome of "Impossible to Evaluate" or "No Evaluation" the reason for this outcome was not provided.

TABLE 3: Applicant's Window of Days for Bacteriological and Clinical Evaluations			
	TIME WINDOW (in terms of study day)		
Evaluation	FT	CP	TS
Pre-Primary (Used for superinfection)[a]	N/A	1-6	1-9
Pre-Primary (Used for new infection)	1-4	7-10	10-13
Primary (Used for primary efficacy evaluations and determination of new infection)	5-11	11-17	14-20
Post-Primary (Used for the determination of recurrence and new infection)	≥12	≥ 18	≥ 21

[a] Superinfection was not a possible outcome for patients in the FT group

III.B.1.b. MEDICAL OFFICER

The medical officer assigned bacteriologic outcomes as follows:

At early post therapy visit (Visit 2 for FT, Visit 3 for CP and TS):

Eradication: All pathogens with $\geq 10^5$ CFU at baseline are reduced to $<10^4$ CFU.

Eradication with New Infection: All pathogens with $\geq 10^5$ CFU at baseline are reduced to $<10^4$ CFU, with presence of a new pathogen at levels $\geq 10^5$ CFU during early post therapy period

Persistence: Any pathogen with $\geq 10^5$ CFU at baseline is present at $\geq 10^4$ CFU at least 48-96 hours after the first dose of therapy.

Presumed Persistence: Presence of clinical symptoms during the early post therapy period, but a urine culture was not taken at the same time as the clinical assessment.

At late post therapy visit (Visit 4 for all treatments):

Sustained eradication: All pathogens with $\geq 10^5$ CFU at baseline are reduced to $<10^4$ CFU during early post therapy and remain at $<10^4$ CFU during late post therapy.

Sustained Eradication with New Infection: All pathogens with $\geq 10^5$ CFU at baseline are reduced to $<10^4$ CFU during early post therapy and remain at $<10^4$ CFU during late post therapy, with presence of a new pathogen at levels $\geq 10^5$ CFU during late post therapy period.

Recurrence: Growth of $\geq 10^4$ CFU of an initially susceptible pathogen during late post therapy after demonstration of bacteriologic eradication during early post therapy.

Presumed Recurrence: Presence of clinical symptoms during the late post therapy period after demonstration of bacteriologic eradication during early post therapy, but a urine culture was not taken at the same time as the clinical assessment.

Early Bacteriologic Eradication/Clinical Failure With Concomitant Antibiotic: Patients who were clinical failure/bacteriologic eradication at early post therapy who were given a concomitant antibiotic for clinical symptoms, thus precluding a late post therapy bacteriologic assessment.

Early Persistence: Persistence or presumed persistence of pathogen during early post therapy period.

Early New Infection: Presence of new infection during early post therapy period.

***REVIEWER COMMENT**: By study protocol, FT patients had 3 post therapy visits (5-9 days, 11-15 days or 14-18 days, and 5-7 weeks post treatment) where as CP or TS patients had only 2 post therapy visits (5-9 days and 4-6 weeks post treatment). To make use of this extra piece of information for the FT group, the medical officer made the distinction between "early recurrence" and "late recurrence" only for FT patients. A FT recurrence was defined as "early" if it occurred on study day 12-17 (study 01) or study day 12-20 (study 02). A FT recurrence was defined as "late" if it occurred on study day ≥18 (study 01) or study day ≥21 (study 02).*

III.B.2. CLINICAL EFFICACY

III.B.2.a. APPLICANT

According to section 10.2 of the applicant's protocols, clinical outcomes were defined as follows:

At early post therapy visit (Visit 2 for FT, Visit 3 for CP and TS):

Cure: All pre-therapy signs and symptoms have subsided in a reasonable period of time with no evidence of their resurgence at the follow up visit 5-9 days post therapy.

Improvement: Most but not all pre-therapy signs and symptoms have subsided in a reasonable period of time without complete resolution at the follow up visit 5-9 days post therapy.

Failure: No apparent response to therapy. Persistence of all pre-therapy signs and symptoms at 5-9 days post therapy.

Unassessable: A clinical judgement of cure, improvement, or failure cannot be made due to, but not limited to such reasons as improper dose or length of therapy, concomitant antimicrobial therapy, no pathogen isolated, therapy discontinued due to adverse reactions, inadequate colony count, inadequate or no follow up cultures. The investigator will be required to state the circumstances which cause the case to be rated as non-evaluable.

***REVIEWER COMMENTS**: These clinical outcomes were assigned by the study investigators.*

Although the clinical signs and symptoms at each visit (flank tenderness, suprapubic tenderness, frequency, dysuria, burning, urgency) were assessed individually on a 4 point scale (0=absent/normal, 1=mild, 2=moderate, 3=severe), the overall clinical evaluation was not directly derived from these individual symptom scores.

By protocol and CRF design, the investigator did not make an overall clinical evaluation at the late post therapy visit (Visit 4). Therefore, the applicant did not make any assessments of clinical outcome at the late post therapy visit.

There was no space on the CRF for the investigator to state the circumstances which caused the patient to have a clinical evaluation of "unassessable".

Since the clinical and bacteriologic assessments were supposed to be independent, bacteriologic circumstances should not have made a patient clinically "unassessable".

Note that by protocol, visit timing was part of the definitions of the applicant's clinical outcome. In section 3.8.3.1 of the study reports, the applicant extended the visit windows "In an effort to capture and analyze all available and appropriate data." The applicant's extended visit windows are presented in Table 3 above. See additional comments in section II.B.1.a. above.

II.B.2.b. MEDICAL OFFICER

The medical officer assigned clinical outcomes as follows:

At early post therapy visit (Visit 2 for FT, Visit 3 for CP and TS):

Cure: All or nearly all pre-therapy signs and symptoms are eliminated. One sign/symptom of a mild nature was accepted as a cure.

Failure: Persistence of pre-therapy signs and symptoms. One or more signs/symptoms of a moderate nature or two or more signs/symptoms of a mild nature were considered failures.

At late post therapy visit (Visit 4 for all treatments):

Sustained Cure: All or nearly all pre-therapy signs and symptoms eliminated during early post therapy without resurgence during late post therapy.

Relapse: All or nearly all pre-therapy signs and symptoms eliminated during early post therapy with resurgence of one or more signs/symptoms during late post therapy.

Early Clinical Cure/Bacteriologic Persistence With Concomitant Antibiotic: Patients who were bacteriologic persistence/clinical cure at early post therapy who were given a concomitant antibiotic for the persistent organism, thus precluding a late post therapy clinical assessment.

Early Failure: Presence of clinical signs/symptoms during early post therapy period.

***REVIEWER COMMENT**: By study protocol, FT patients had 3 post therapy visits (5-9 days, 11-15 days or 14-18 days, and 5-7 weeks post treatment) where as CP or TS patients had only 2 post therapy visits (5-9 days and 4-6 weeks post treatment). To make use of this extra piece of information for the FT group, the medical officer made the distinction between "early relapse" and "late relapse" only for FT patients. A FT relapse was defined as "early" if it occurred on study day 12-17 (study 01) or study day 12-20 (study 02). A FT relapse was defined as "late" if it occurred on study day ≥18 (study 01) or study day ≥21 (study 02).*

II.B.3. SAFETY

According the applicant's protocols, attribution of clinical adverse events was assigned by the investigator as follows:

Definitely related:	Relationship has been confirmed by dechallenge and rechallenge; remission and recurrence follow a reasonable temporal sequence.
Probably related:	Strong suspicion of drug association when type, time course, and relationship to dosing and/or dechallenge are considered.
Possibly related:	As suggested by type, time, course, relationship to taking of medication and external events; may follow a known response pattern to suspected drug but could have been produced by patient's clinical state and/or other therapy.
Unlikely:	Drug relationship very unlikely; no clear external cause; does not follow a known response pattern to drug.
Not related:	Clearly pre-existing or caused by a specific extraneous event; not worsened by the study treatment; not a known response pattern.

Clinical adverse events were also graded on the following scale:

Mild:	Discomfort without disruption of daily activity.
Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
Severe:	Incapacitating with inability to work or perform normal daily activity.

III.C. EXCLUSION CRITERIA FOR PATIENT ANALYSIS GROUPS

III.C.1. MODIFIED INTENT TO TREAT PATIENTS

III.C.1.a. APPLICANT

According to section 3.8.3.5 of the study reports, a patient is excluded from the applicant's modified intent to treat group if she did not have a positive urine culture ($\geq 10^5$ CFU of a least one pathogen) at baseline (study day -2 to 0).

III.C.1.b. MEDICAL OFFICER

The medical officer did not define or evaluate patients for a modified intent to treat population.

III.C.2. EVALUABLE PATIENTS

III.C.2.a. APPLICANT

According to section 3.8.3.5 of the study reports, a patient is excluded from the applicant's evaluable group if she did not have a positive urine culture ($\geq 10^5$ CFU of a least one pathogen) at baseline (study day -2 to 0), if the isolated baseline pathogen was not susceptible to both study antibiotics or susceptibility testing was not

done, if the patient was not compliant with taking the study medication (took <10 tablets in study 01 or <14 tablets in study 02) or compliance was unknown, or if the medical monitor did not deem the patient appropriate for analysis.

***REVIEWER COMMENTS**: The study reports state that the medical monitor review of patients was performed prior to breaking the study blind. However, the exclusion criteria used by the applicant's medical monitor was not documented in the study reports. Most patients who were excluded by the medical monitor were given the exclusion reason "other". The applicant provided more information on this "other" group via facsimile transmission on May 25, 1995. According to the applicant, the medical monitor excluded patients based upon a review of past medical history, past history of illness, and past surgical history, however, no specific or consistently applied criteria were given.*

The reader should note that according to the applicant's evaluability criteria, a FT patient could be excluded for not taking the appropriate number of placebo tablets.

The reader should also note that the timing of patient post-baseline visits was not a criterion for exclusion from the applicant's patient analysis groups. If an otherwise evaluable patient did not have a visit within the specified visit windows, the patient was deemed evaluable for analysis, but given the outcome "No Evaluation". See additional comments in section II.B.1.a.

III.C.2.b. MEDICAL OFFICER

A patient is excluded from the medical officer's evaluable patient group if there is no baseline pathogen with $\geq 10^5$ CFU, if there is no visit at 5-11 days post therapy (does not apply to bacteriologic persistence or clinical failure), if there is no visit at ≥21 days post therapy (does not apply to bacteriologic recurrence or clinical relapse), if the patient took <10 tablets (CP patients only) or <14 tablets (TS patients only) or tablet compliance unknown (does not apply to FT patients), if the patient had an intercurrent illness, if a concomitant antimicrobial was given for another illness, or if the patient had a protocol violation with respect to disease diagnosis.

***REVIEWER COMMENT**: Due to data inconsistencies, the medical officer also excluded all patients from investigator Ginsberg of study 02. See the medical officer's review for details.*

III.D. ANALYTICAL METHODS

III.D.1. APPLICANT METHODS

According to section 3.10 of the study reports, the applicant compared treatment groups with respect to baseline demographic variables using a t-test for quantitative variables, and a Chi-square contingency table analysis or Fisher's exact test for qualitative variables.

The applicant compared treatment groups with respect to bacteriological and clinical cure rates (on the patient level) using a Fisher's exact test. One sided 95% confidence intervals for the treatment difference in cure rate (comparator minus fosfomycin) were also computed using a normal approximation to the binomial distribution. When computing cure rates, all patients with outcomes of "no evaluation" were excluded.

The applicant did not perform center-adjusted analysis because approximately two-thirds of the centers had fewer than ten patients in one or both of the treatment groups. However, descriptive analyses by center were provided.

The applicant did not perform statistical tests of bacteriologic cure rates on the pathogen level. However, descriptive analyses by pathogen were provided.

With respect to categorical safety outcomes, the applicant compared treatments using Fisher's exact test. For quantitative safety variables such as vital sign measurements, serum chemistry and hematology results, the applicant compared treatment groups at baseline using a two sample t-test. At each post-baseline visit, the treatment groups were compared with respect to the mean change from baseline using a two sample t-test. Within each treatment group, the significance of the mean change from baseline was determined using a paired t-test.

For all tests of hypotheses, the applicant declared statistical significance if the two-sided p-value was ≤ 0.05.

***REVIEWER COMMENTS**: The applicant's primary efficacy variable was not specified in the protocol or study report.*

The applicant's method for computing confidence intervals is not appropriate for demonstrating efficacy equivalence. According to the DAIDP "Points to Consider" document, two-sided 95% confidence intervals of the FT minus comparator difference in cure rates should be used.

III.D.2. REVIEWER METHODS

Treatment group comparisons with respect to baseline demographic characteristics, baseline disease characteristics, and inclusion into the patient analysis groups were performed using the Fisher's exact test, chi-square test, two sample t-test, or Wilcoxon rank sum test where appropriate.

The treatment groups were compared for efficacy equivalence using two sided 95% confidence intervals of the FT minus comparator difference in "success" rate of each efficacy variable of interest. The confidence intervals were computed using a normal approximation to the binomial distribution and incorporated a continuity correction. The confidence intervals were interpreted using the guideline outlined on page 20 of the draft DAIDP "Points to Consider" document. Efficacy equivalence analyses were performed for the following variables:

- all bacteriologic eradication at 5-11 days post treatment (includes eradication/cure, eradication/cure with superinfection, and eradication/cure with new infection)
- bacteriologic eradication/cure at 5-11 days post treatment
- all bacteriologic eradication by the end of the longer course of therapy (day 17 for study 01 and day 20 for study 02; includes eradication and eradication with new infection; computed for MO data only)
- bacteriologic eradication by the end of the longer course of therapy (MO data only)
- all sustained eradication at 4-6 weeks post therapy (includes sustained eradication/cure and sustained eradication/cure with new infection)
- sustained bacteriologic eradication at 4-6 weeks post therapy
- bacteriologic eradication of *E. coli* isolates at 5-11 days post treatment (MO data only)
- bacteriologic eradication of *E. coli* isolates by the end of the longer course of therapy (MO data only)
- bacteriologic eradication of *E. coli* isolates at 4-6 weeks post treatment (MO data only)
- clinical cure or improvement at 5-11 days post treatment
- clinical cure at 5-11 days post treatment
- clinical cure at the end of the longer course of therapy (MO data only)
- sustained clinical cure at 4-6 weeks post therapy (MO data only)
- "overall success" at 5-11 days post treatment (overall success defined as a bacteriologic eradication or bacteriologic eradication with new infection and clinical cure; computed for MO data only)
- "complete success" at 5-11 days post treatment (complete success defined as a bacteriologic eradication or bacteriologic eradication with new infection and clinical cure and no adverse event; computed for MO data only)

This reviewer considers the rate of all bacteriologic eradication at 5-11 days post treatment in the medical officer's evaluable patient group to be the primary efficacy variable. All other efficacy variables are considered secondary.

Subset efficacy analyses by age ($\leq$65 versus >65) and race (white, black, other) were performed for the primary efficacy variable.

Treatment group comparisons of adverse event rates were performed using Fisher's exact test. Comparisons were made for the following variables:

- patients with at least one adverse event
- patients with at least one adverse event by body system
- patients with at least one adverse event by each type of event
- patients with at least one severe adverse event
- patients discontinued due to an adverse event

Subset safety analyses by age (≤65 versus >65) and race (white, black, other) were performed for the rateof at least one adverse event. All patients who took at least one dose of study medication are included in the safety analyses.

Unless otherwise stated, all tests are two sided, and the level of significance is 0.05.

All tabulated data presented in this review were obtained from the applicant's study reports, the applicant's SAS data sets, the medical officer's draft reviews dated 7/6/95 (study 01) and 7/5/95 (study 02), and the medical officer's Paradox data bases dated 6/14/95 (study 01) and 6/29/95 (study 02).

***REVIEWER NOTE**: When the medical officer's analysis group exclusion criteria as stated in section II.C.2.b. were applied to the medical officer's data bases, the resultant groups of evaluable patients differed from those presented in the medical officer' s draft reviews. However, the inconsistencies did not grossly impact study conclusions. In this review, the medical officer's evaluable patient groups as presented in the medical officer's draft reviews of 7/6/95 (study 01) and 7/5/95 (study 02) are used in all efficacy analyses.*

III.E. RESULTS

***REVIEWER NOTE:** Three investigators (Harnack, Costantini, and Iravani) participated in both studies. These centers enrolled 17% (147/877) and 21% (179/854) of the patients in protocols MON-US-01 and MON-US-02, respectively. The independence of these trials is questionable.*

III.E.1. PROTOCOL MON-US-01

A total of 877 patients were enrolled across 32 centers. Enrollment by center ranged from 1 to 74. By randomization, 432 and 445 patients were allocated to receive FT and CP, respectively.

The number of patients included in each analysis group is displayed in Table 4. In each analysis group, the percentage of included FT patients is numerically greater than the percentage of included CP patients. However, the treatment difference is significant only in the MO evaluable group. The treatment difference in the percentage of patients included in this analysis group is mainly due to an imbalance with regard to the number of patients without a pathogen at baseline [149 (34%) for FT versus 180 (40%) for CP]. An imbalance also exists with regard to the number of patients excluded by the MO for a missing or late 5-11 day post therapy visit [5 (1%) for FT versus 11(3%) for CP, see medical officer's review]. This phenomenon is directly linked to treatment efficacy, since a "cure" outside the 5-11 day window would be excluded from the analysis, but a "failure" outside of the window would not be excluded from the analysis.

TABLE 4: Study 01 Patients Included in Analysis Groups

analysis group	FT (N=432)		CP (N=445)		p-value[1]
	included	(%)	included	(%)	
applicant modified ITT	283	(66)	265	(60)	0.070
applicant evaluable	231	(53)	212	(48)	0.091
MO evaluable	260	(60)	222	(50)	0.002

[1] P-value from Fisher's exact test.

Within the analysis groups, the treatments did not differ significantly with respect to baseline demographic characteristics or baseline disease characteristics. In general, patients studied were young, white females.

Only 10 of the 32 centers had at least 10 patients per treatment included in any of the analysis groups. Since enrollment by center was generally small, meaningful by center analyses could not be performed.

Bacteriologic results at 5-11 days post treatment are presented in Table 5. The rate of all eradication for FT is 83%, 84%, and 78% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. For CP, the rate of all eradication is 99% in all analysis groups. The rates for eradication/cure are similar. At 5-11 days post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of all eradication, and a significantly lower rate of eradication/cure than CP.

TABLE 5: Study 01 Bacteriologic Outcomes at Early Post Therapy Visit (5 to 11 days post treatment) (study day 5-11 for FT, study day 11-17 for CP)

outcome	modified ITT				evaluable							
	applicant				applicant				MO			
	FT (N=283)		CP (N=265)		FT (N=231)		CP (N=212)		FT (N=260)		CP (N=222)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
all eradication	**225**	**(83)**	**231**	**(99)**	**189**	**(84)**	**187**	**(99)**	**203**	**(78)**	**219**	**(99)**
eradication/cure	225	(83)	231	(99)	189	(84)	187	(99)	196	(75)	218	(98)
cure with superinfection (applicant outcome only)	-		0	(0)	-		0	(0)	-		-	
eradication with new infection (MO outcome only)	-		-		-		-		7	(3)	1	(<1)
all persistence	**45**	**(17)**	**2**	**(1)**	**35**	**(16)**	**1**	**(<1)**	**57**	**(22)**	**3**	**(1)**
persistence/failure	45	(17)	2	(1)	35	(16)	1	(<1)	54	(21)	2	(1)
presumed persistence	-		-		-		-		3	(1)	1	(<1)
applicant "no evaluation"*	**13**		**32**		**7**		**24**		**-**		**-**	
denominator excluding applicant "no evaluation"	**270**		**233**		**224**		**188**		**260**		**222**	
95% C.I.[§]: all eradication	**(-21, -11)**				**(-20, -10)**				**(-26, -15)**			
eradication/cure only	**(-21, -11)**				**(-20, -10)**				**(-29, -17)**			

* This category is excluded from the applicant analyses. The reasons for "no evaluation" were not provided by the applicant.
§ Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

Bacteriologic results at the end of the longer course of therapy (study day 17) for the MO evaluable analysis group are presented in Table 6. The rate of all eradication is 75% for FT compared to 99% for CP. The rates for eradication only are similar. The confidence interval results show that at the end of the longer course of therapy, FT has a significantly lower rate of all eradication, and a significantly lower rate of eradication than CP.

TABLE 6: Study 01 Medical Officer Bacteriologic Outcomes By Study Day 17 (5-17 days post therapy for FT, 5-11 days post therapy for CP)

outcome	MO evaluable patients			
	FT (N=260)		CP (N=222)	
	n	(%)	n	(%)
all eradication	**194**	**(75)**	**219**	**(99)**
eradication	187	(72)	218	(98)
eradication with new infection	7	(3)	1	(<1)
all persistence/early recurrence	**66**	**(25)**	**3**	**(1)**
MO early recurrence (study day 12-17 for FT only)	9	(3)	-	-
persistence	54	(21)	2	(1)
presumed persistence	3	(1)	1	(<1)
95% C.I.[a]: all eradication	**(-30, -18)**			
eradication only	**(-32, -20)**			

[a] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

Bacteriologic results at 4-6 weeks post treatment are presented in Table 7. The rate of all sustained eradication for FT is 71%, 71%, and 61% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The rate of all sustained eradication for CP is 95%, 96%, and 89% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 4-6 weeks post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of all sustained eradication than CP.

The rate of sustained eradication/cure for FT is 64%, 65%, and 57% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The rate of sustained eradication/cure for CP is 91%, 92%, and 86% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 4-6 weeks post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of sustained eradication/cure than CP.

Bacteriologic results for *E. coli* isolates in the MO evaluable analysis group are presented in Table 8. The rate of *E. coli* eradication for FT is 81%, 77%, and 69% at 5-11 days post treatment, by study day 17, and at 4-6 weeks post treatment, respectively. The rate of *E. coli* eradication for CP is 98%, 98%, and 90% at 5-11 days post treatment, by study day 17, and at 4-6 weeks post treatment, respectively. As demonstrated by the 95% confidence interval results, FT has a significantly lower rate of *E. coli* eradication than CP at all time points. Due to small numbers of isolates, meaningful analyses of other urinary pathogens could not be performed.

TABLE 7 : Study 01 Bacteriologic Outcomes at Late Post Therapy Visit (approximately 4-6 weeks post treatment) (study day ≥12 for FT, study day ≥18 for CP)

outcome	modified ITT				evaluable							
	applicant (computed by reviewer)				applicant (computed by reviewer)				MO			
	FT (N=283)		CP (N=265)		FT (N=231)		CP (N=212)		FT (N=260)		CP (N=222)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
all sustained eradication	**183**	**(71)**	**210**	**(95)**	**153**	**(71)**	**173**	**(96)**	**158**	**(61)**	**197**	**(89)**
sustained eradication/cure	166	(64)	201	(91)	141	(65)	166	(92)	148	(57)	192	(86)
sustained erad./cure with new infection	17	(7)	9	(4)	12	(6)	7	(4)	10	(4)	5	(2)
all recurrence/persistence	**75**	**(29)**	**10**	**(5)**	**63**	**(29)**	**8**	**(4)**	**87**	**(33)**	**20**	**(9)**
applicant recurrence (regardless of timing)	30	(12)	8	(4)	28	(13)	7	(4)	-	-	-	-
MO early recurrence (study day 12-17 for FT only)	-	-	-	-	-	-	-	-	9	(3)	-	-
MO late recurrence (study day ≥18)	-	-	-	-	-	-	-	-	19	(7)	11	(5)
MO presumed late recurrence (study day ≥18)	-	-	-	-	-	-	-	-	2	(1)	6	(3)
early persistence/fail (documented or presumed)	45	(17)	2	(1)	35	(16)	1	(<1)	57	(22)	3	(1)
MO patients without long term bacteriologic follow up[@]	-	-	-		-	-	-	-	**15**	**(6)**	**5**	**(2)**
early bact. erad./ clinical failure with concomitant antibiotic	-	-	-		-	-	-	-	8	(3)	4	(2)
early eradication with new infection	-	-	-		-	-	-	-	7	(3)	1	(<1)
applicant "no evaluation"[*]	**25**		**45**		**15**		**31**		-		-	
applicant "no evaluation" at early visit	13		32		7		24		-		-	
applicant "no evaluation" at late visit	12		13		8		7		-		-	
denominator excluding applicant "no evaluation"	**258**		**220**		**216**		**181**		**260**		**222**	
95% C.I.[#]: all sustained eradication	**(-31, -18)**				**(-32, -17)**				**(-36, -20)**			
sustained eradication/cure	**(-34, -20)**				**(-34, -18)**				**(-37, -22)**			

[@]As a worst case analysis, these patients have been included in the medical officer analyses as bacteriologic failures. According to the medical officer, most of these patients received a concomitant antibiotic after the early post therapy visit.

[*] This category is excluded from the applicant analyses. The reasons for "no evaluation" were not provided by the applicant.

[#] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 8: Study 01 95% C.I. of the FT minus CP Difference in Bacteriologic Eradication Rate for *E. Coli* Isolates According to Medical Officer Evaluable Group

study time	eradication rate				95% C.I.[a]
	FT (N=216)		CP (N=187)		
	n	(%)	n	(%)	
early post therapy visit (5-11 days post therapy)	175	(81)	184	(98)	(-23, -11)
by study day 17 (5-17 days post therapy for FT; 5-11 days post therapy for CP)	167	(77)	184	(98)	(-27, -15)
late post therapy visit (approximately 4-6 weeks post therapy)	149	(69)	168	(90)	(-29, -13)

[a] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

Clinical results at 5-11 days post treatment are presented in Table 9. The rate of cure or improvement for FT is 96%, 83%, and 77% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The rate of cure or improvement for CP is 100%, 95%, and 96% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 5-11 days post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of cure or improvement than CP.

The cure rate for FT is 81%, 83%, and 77% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The cure rate for CP is 94%, 95%, and 96% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 5-11 days post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower cure rate than CP.

Tables 10 and 11 display clinical results at the end of the longer course of therapy (study day 17) and at 4-6 weeks post therapy, respectively, for the MO evaluable analysis group. At study day 17, the cure rate is 73% for FT compared to 96% for CP. At 4-6 weeks post therapy, the sustained cure rate is 59% for FT compared to 88% for CP. The confidence interval results show that FT has a significantly lower cure rate than CP at both time points.

At 5-11 days post treatment, the rate of "overall success" (defined as a bacteriologic eradication or bacteriologic eradication with new infection and clinical cure) in the MO evaluable analysis group is 67% (174/260) for FT and 95% (211/222) for CP. The 95% confidence interval of the FT minus CP difference in overall success rate is (-35%, -21%), which shows that FT has a significantly lower rate of overall success than CP.

At 5-11 days post treatment, the rate of "complete success" (defined as a bacteriologic eradication or bacteriologic eradication with new infection and clinical cure and no adverse event) in the MO evaluable analysis group is 37% (95/260) for FT and 50% (112/222) for CP. The 95% confidence interval of the FT minus CP difference in complete success rate is (-23%, -5%), which shows that FT has a significantly lower rate of complete success than CP.

***REVIEWER COMMENT**: In the MO evaluable analysis group, 54% (141/260) of FT patients and 55% (121/222) of CP patients did not have an adverse event. The 95% confidence interval of the FT minus CP difference in the rate of no adverse event is (-10%, 9%), which shows that the treatments are similar with respect to the rate of no adverse events.*

TABLE 9: Study 01 Clinical Outcomes at Early Post Therapy Visit (5 to 11 days post treatment)
(study day 5-11 for FT, study day 11-17 for CP)

outcome	modified ITT				evaluable							
	applicant				applicant				MO			
	FT (N=283)		CP (N=265)		FT (N=231)		CP (N=212)		FT (N=260)		CP (N=222)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
cure or improvement	**247**	**(96)**	**230**	**(100)**	**177**	**(83)**	**178**	**(95)**	**199**	**(77)**	**213**	**(96)**
cure	207	(81)	217	(94)	177	(83)	178	(95)	199	(77)	213	(96)
improvement	40	(16)	13	(6)	0	(0)	0	(0)	-	-	-	-
failure	**9**	**(4)**	**0**	**(0)**	**37**	**(17)**	**10**	**(5)**	**61**	**(23)**	**9**	**(4)**
applicant "no evaluation"*	**27**		**35**		**17**		**24**		**-**		**-**	
denominator excluding applicant "no evaluation"	**256**		**230**		**214**		**188**		**260**		**222**	
95% C.I.[#]: cure or improvement	**(-6, -1)**				**(-18, -5)**				**(-26, -13)**			
cure	**(-20, -7)**				**(-18, -5)**				**(-26, -13)**			

* This category is excluded from the applicant analyses. The reasons for "no evaluation" were not provided by the applicant.
# Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 10: Study 01 Medical Officer Clinical Outcomes By Study Day 17 (5-17 days post therapy for FT, 5-11 days post therapy for CP)				
outcome	MO evaluable patients			
	FT (N=260)		CP (N=222)	
	n	(%)	n	(%)
cure	**189**	**(73)**	**213**	**(96)**
all failure	**71**	**(27)**	**9**	**(4)**
MO early relapse (study day 12-17 for FT only)	10	(4)	-	-
early failure	61	(23)	9	(4)
95% C.I.[a]: cure	**(-30, -17)**			

[a] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 11: Study 01 Medical Officer Clinical Outcomes At the Late Post Therapy Visit (approximately 4-6 weeks post treatment) (study day ≥12 for FT, study day ≥18 for CP)				
outcome	MO evaluable patients			
	FT (N=260)		CP (N=222)	
	n	(%)	n	(%)
sustained cure	**153**	**(59)**	**196**	**(88)**
all failure	**87**	**(33)**	**24**	**(11)**
MO early relapse (study day 12-17 for FT only)	10	(4)	-	-
MO late relapse (study day ≥18)	16	(6)	15	(7)
early failure	61	(23)	9	(4)
patients without long term clinical follow up[b]	**20**	**(8)**	**2**	**(1)**
early bacteriologic failure/clinical cure with concomitant antibiotic	20	(8)	2	(1)
95% C.I.[a]: sustained cure	**(-37, -22)**			

[a] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.
[b] As a worst case analysis, these patients have been included clinical "failures", since they received a concomitant antibiotic.

Subset efficacy analyses by age (≤65, >65) and race (white, black, other) for the rate of all bacteriologic eradication at 5-11 days post treatment in the medical officer's evaluable group are presented in Table 12. Confidence interval results were performed only for those subsets with ≥10 patients per treatment group. Efficacy results were consistent across the subgroups.

TABLE 12: Study 01 Subgroup Efficacy Analysis of Rate of All Bacteriologic Eradication At 5-11 Days Post Treatment According to Medical Officer Evaluable Group					
subgroup	eradication rate				95% C.I.[#]
	FT		CP		
	n/N	(%)	n/N	(%)	
age ≤65	188/240	(78)	210/213	(99)	(-26, -14)
age >65	15/20	(75)	9/9	(100)	-
race white	179/229	(78)	200/202	(99)	(-27, -15)
race black	13/18	(72)	12/13	(92)	(-52, 12)
race other	11/13	(85)	7/7	(100)	-

[#] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction. Confidence intervals are presented only for those subgroups with at least 10 patients per treatment group.

A summary of safety outcomes as reported in the applicant's study report is presented in Table 13. FT and CP are similar with respect to the rates of at least one adverse event, at least one treatment related adverse event, at least one severe adverse event, and discontinuation due to an adverse event. FT has significantly higher rates of at least one metabolic and nutritional system adverse event, at least one diarrhea adverse event, and at least one rash adverse event.

***REVIEWER COMMENT**: Using the applicant's SAS data sets, this reviewer could not exactly reproduce some of the applicant's tabulations of adverse events presented in the study report. However, the discrepancies are minor and do not impact study conclusions.*

TABLE 13: Study 01 Summary of Safety Outcomes[1]						
outcome	FT (N=432)		CP (N=445)		p-value[2]	95% C.I.[3]
	n	(%)	n	(%)		
at least one adverse event (AE)	199	(46)	193	(43)	0.46	(-4, 10)
at least one treatment related (definitely or probably) AE	36	(8)	28	(6)	0.30	(-2, 6)
at least one severe AE	14	(3)	18	(4)	0.59	(-4, 2)
discontinued due to an AE	6	(1)	6	(1)	>0.99	(-2, 2)
at least one metabolic and nutritional system AE	9	(2)	2	(<1)	0.04	(0, 3)
at least one diarrhea AE	33	(8)	19	(4)	0.04	(0, 7)
at least one rash AE	10	(2)	3	(1)	0.05	(0, 3)

[1] Numbers were obtained from the applicant's study report tables. Outcomes are presented only for those body system and individual events with a statistically significant treatment difference (0.05 level).
[2] Two sided p-value from Fisher's exact test.
[3] Two sided 95% confidence intervals of the FT minus CP difference in event rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

Subset safety analyses by age (≤65, >65) and race (white, black, other) for the rate of at least one adverse event are presented in Table 14. No noteworthy subgroup differences were observed.

TABLE 14: Study 01 Subgroup Safety Analysis of Rate of at Least One Adverse Event [1]

subgroup	adverse event rate				p-value[2]	95% C.I.[3]
	FT		CP			
	n/N	(%)	n/N	(%)		
all patients	193/432	(45)	198/445	(45)	>0.99	(-7, 7)
age ≤65	178/397	(45)	194/425	(46)	0.83	(-8, 6)
age >65	15/35	(43)	4/20	(20)	0.14	(-5, 51)
race white	172/374	(46)	177/398	(44)	0.71	(-6, 9)
race black	14/41	(34)	14/28	(50)	0.22	(-42, 11)
race other	7/17	(41)	7/19	(37)	>0.99	(-33, 42)

[1] Numbers were obtained from reviewer analyses of the applicant's SAS data sets.
[2] Two sided p-value from Fisher's exact test.
[3] Two sided 95% confidence intervals of the FT minus CP difference in event rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

III.E.2. PROTOCOL MON-US-02

A total of 854 patients were enrolled across 30 centers. Enrollment by center ranged from 3 to 78. By randomization, 426 and 428 patients were allocated to receive FT and TS, respectively.

The number of patients included in each analysis group is displayed in Table 15. In each analysis group, the percentage of included FT patients is numerically greater than the percentage of included CP patients. However, the treatment difference is significant only in the MO evaluable group. The treatment difference in the percentage of patients included in this analysis group is mainly due to an imbalance with regard to the number of patients without a pathogen at baseline [115 (27%) for FT versus 146 (34%) for TS]. An imbalance also exists with regard to the number of patients excluded by the MO for a missing or late 5-11 day post therapy visit [1 (<1%) for FT versus 11(3%) for TS, see medical officer's review]. This phenonmenon is directly linked to treatment efficacy, since a "cure" outside the 5-11 day window would be excluded from the analysis, but a "failure" outside of the window would not be excluded from the analysis.

TABLE 15: Study 02 patients included in Analysis Groups

analysis group	FT (N=426)		TS (N=428)		p-value[1]
	included	(%)	included	(%)	
applicant modified ITT	291	(68)	266	(62)	0.081
applicant evaluable	213	(50)	193	(45)	0.171
MO evaluable	249	(58)	197	(46)	<0.001

[1] P-value from Fisher's exact test.

Within the analysis groups, the treatments did not differ significantly with respect to baseline demographic characteristics or baseline disease characteristics. In general, patients studied were young, white females.

Only 7 of the 30 centers had at least 10 patients per treatment included in any of the analysis groups. Since enrollment by center was generally small, meaningful by center analyses could not be performed.

Bacteriologic results at 5-11 days post treatment are presented in Table 16. The rate of all eradication for FT is 89%, 90%, and 85% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. For TS, the rate of all eradication is 98% in all analysis groups. The rates for eradication/cure are similar. At 5-11 days post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of all eradication, and a significantly lower rate of eradication/cure than TS.

Bacteriologic results at the end of the longer course of therapy (study day 20) for the MO evaluable analysis group are presented in Table 17. The rate of all eradication is 81% for FT compared to 98% for TS. The rates for eradication only are similar. The confidence interval results show that at the end of the longer course of therapy, FT has a significantly lower rate of all eradication, and a significantly lower rate of eradication than TS.

TABLE 16: Study 02 Bacteriologic Outcomes at Early Post Therapy Visit (5 to 11 days post treatment) (study day 5-11 for FT, study day 14-20 for TS)

outcome	modified ITT				evaluable							
	applicant				applicant				MO			
	FT (N=291)		TS (N=266)		FT (N=213)		TS (N=193)		FT (N=249)		TS (N=197)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
all eradication	**246**	**(89)**	**207**	**(98)**	**187**	**(90)**	**166**	**(98)**	**212**	**(85)**	**194**	**(98)**
eradication/cure	246	(89)	206	(98)	187	(90)	165	(98)	204	(82)	190	(96)
cure with superinfection (applicant outcome only)	-		1	(<1)	-		1	(<1)	-		-	
eradication with new infection (MO outcome only)	-		-		-		-		8	(3)	4	(2)
all persistence	**30**	**(11)**	**4**	**(2)**	**21**	**(10)**	**3**	**(2)**	**37**	**(15)**	**3**	**(2)**
persistence/failure	30	(11)	4	(2)	21	(10)	3	(2)	37	(15)	37	(2)
presumed persistence	-		-		-		-		-		-	
applicant "no evaluation"*	**15**		**55**		**5**		**24**		**-**	**-**	**-**	**-**
denominator excluding applicant "no evaluation"	**276**		**211**		**208**		**169**		**249**		**197**	
95% C.I.[#]: all eradication	**(-13, -4)**				**(-13, -3)**				**(-19, -8)**			
eradication/cure	**(-13, -4)**				**(-13, -3)**				**(-20, -9)**			

* This category is excluded from the applicant analyses. The reasons for "no evaluation" were not provided by the applicant.
# Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 17: Study 02 Medical Officer Bacteriologic Outcomes By Study Day 20 (5-20 days post therapy for FT, 5-11 days post therapy for TS)

outcome	MO evaluable patients			
	FT (N=249)		TS (N=197)	
	n	(%)	n	(%)
all eradication	**201**	**(81)**	**194**	**(98)**
eradication	190	(76)	190	(96)
eradication with new infection	11	(4)	4	(2)
all persistence/early recurrence	**48**	**(19)**	**3**	**(2)**
MO early recurrence (study day 12-20 for FT only)	11	(4)	-	-
persistence	37	(15)	3	(2)
presumed persistence	-		-	-
95% C.I.[a]: **all eradication**			(-23, -12)	
eradication/cure			(-26, -14)	

[a] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

Bacteriologic results at 4-6 weeks post treatment are presented in Table 18. The rate of all sustained eradication for FT is 79%, 81%, and 65% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The rate of all sustained eradication for TS is 92%, 92%, and 87% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 4-6 weeks post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of all sustained eradication than TS.

The rate of sustained eradication/cure for FT is 74%, 75%, and 64% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The rate of sustained eradication/cure for TS is 88%, 87%, and 84% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 4-6 weeks post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of sustained eradication/cure than TS.

Bacteriologic results for *E. coli* isolates in the MO evaluable analysis group are presented in Table 19. The rate of *E. coli* eradication for FT is 86% and 70% at 5-11 days post treatment and at 4-6 weeks post treatment, respectively. The rate of *E. coli* eradication for TS is 98% and 90% at 5-11 days post treatment and at 4-6 weeks post treatment, respectively. As demonstrated by the 95% confidence interval results, FT has a significantly lower rate of *E. coli* eradication than TS at both time points. *E. coli* eradication rates by study day 20 were not provided in the medical officer's review. Due to small numbers of isolates, meaningful analyses of other urinary pathogens could not be performed.

Clinical results at 5-11 days post treatment are presented in Table 20. The rate of cure or improvement for FT is 99%, 76%, and 80% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The rate of cure or improvement for TS is 100%, 93%, and 94% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 5-11 days post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of cure or improvement than TS.

The cure rate for FT is 77%, 76%, and 80% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The cure rate for TS is 93%, 93%, and 94% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 5-11 days post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower cure rate than TS.

TABLE 18 : Study 02 Bacteriologic Outcomes at Late Post Therapy Visit (approximately 4-6 weeks post treatment) (study day ≥12 for FT, study day ≥21 for TS)

outcome	modified ITT				evaluable							
	applicant (computed by reviewer)				applicant (computed by reviewer)				MO			
	FT (N=291)		TS (N=266)		FT (N=213)		TS (N=193)		FT (N=249)		TS (N=197)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
all sustained eradication	**209**	**(79)**	**190**	**(92)**	**164**	**(81)**	**155**	**(92)**	**161**	**(65)**	**172**	**(87)**
sustained eradication/cure	196	(74)	181	(88)	152	(75)	147	(87)	159	(64)	165	(84)
sustained erad./cure with new infection	13	(5)	9	(4)	12	(6)	8	(5)	2	(1)	7	(4)
all recurrence/persistence	**55**	**(21)**	**16**	**(8)**	**39**	**(19)**	**13**	**(8)**	**75**	**(30)**	**17**	**(9)**
applicant recurrence (regardless of timing)	25	(9)	12	(6)	18	(9)	10	(6)	-	-	-	-
MO early recurrence (study day 12-20 for FT only)	-	-	-	-	-		-	-	11	(4)	-	-
MO late recurrence (study day ≥21)	-	-	-	-	-		-	-	27	(11)	14	(7)
MO presumed late recurrence (study day ≥21)	-	-	-	-	-		-	-	-	-	-	-
early persistence/fail (documented or presumed)	30	(11)	4	(2)	21	(10)	3	(2)	37	(15)	3	(2)
MO patients without long term bacteriologic follow up[e]	-	-	-	-	-	-	-	-	**13**	**(5)**	**8**	**(4)**
early bact. erad./ clinical failure with concomitant antibiotic	-	-	-	-	-	-	-	-	2	(1)	4	(2)
early eradication with new infection	-	-	-	-	-	-	-	-	11	(4)	4	(2)
applicant "no evaluation"[*]	**27**		**60**		**10**		**25**		-		-	
applicant "no evaluation" at early visit	12		5		5		24		-		-	
applicant "no evaluation" at late visit	15		55		5		1		-		-	
denominator excluding applicant "no evaluation"	**264**		**206**		**203**		**168**		**249**		**197**	
95% C.I.[$]: all sustained eradication	**(-20, -7)**				**(-19, -4)**				**(-31, -15)**			
sustained eradication/cure	**(-21, -6)**				**(-21, -4)**				**(-28, -12)**			

[e] As a worst case analysis, these patients have been included in the medical officer analyses as bacteriologic failures. According to the medical officer, most of these patients received a concomitant antibiotic after the early post therapy visit.

[*] This category is excluded from the applicant analyses. The reasons for "no evaluation" were not provided by the applicant.

[$] Two sided 95% confidence intervals of the FT minus TS difference in "success"' rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 19: Study 02 95% C.I. of the FT minus TS Difference in Bacteriologic Eradication Rate for *E. Coli* Isolates According to Medical Officer Evaluable Group

study time	eradication rate				95% C.I.
	FT (N=207)		TS (N=174)		
	n	(%)	n	(%)	
early post therapy visit (5-11 days post therapy)	179	(86)	171	(98)	(-17, -6)
by study day 20 (5-20 days post therapy for FT, 5-11 days post therapy for TS)	not given		not given		-
late post therapy visit (approximately 4-6 weeks post therapy)	145	(70)	157	(90)	(-28, -12)

[#] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 20: Study 02 Clinical Outcomes at Early Post Therapy Visit (5 to 11 days post treatment) (study day 5-11 for FT, study day 14-20 for TS)

outcome	modified ITT				evaluable					
	applicant				applicant				MO	
	FT (N=291)		TS (N=266)		FT (N=213)		TS (N=193)		FT (N=249)	TS (N=197)
	n	(%)	n	(%)	n	(%)	n	(%)	n (%)	n (%)
cure or improvement	**262**	**(99)**	**209**	**(100)**	**156**	**(76)**	**158**	**(83)**	**199 (80)**	**186 (94)**
cure	205	(77)	195	(93)	156	(76)	158	(83)	199 (80)	186 (94)
improvement	57	(22)	14	(7)	-		-		-	-
failure	**3**	**(1)**	**0**	**(0)**	**48**	**(24)**	**11**	**(7)**	**50 (20)**	**11 (6)**
applicant "no evaluation"*	**26**		**57**		**9**		**24**		-	-
denominator excluding applicant "no evaluation"	**265**		**209**		**204**		**169**		**249**	**197**
95% C.I.[#]: cure or improvement	**(-3, -1)**				**(-24, -10)**				**(-21, -8)**	
cure	**(-22, -9)**				**(-24, -10)**				**(-21, -8)**	

* This category is excluded from the applicant analyses. The reasons for "no evaluation" were not provided by the applicant.
[#] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

Tables 21 and 22 display clinical results at the end of the longer course of therapy (study day 20) and at 4-6 weeks post therapy, respectively, for the MO evaluable analysis group. At study day 20, the cure rate is 76% for FT compared to 94% for TS. At 4-6 weeks post therapy, the sustained cure rate is 66% for FT compared to 88% for TS. The confidence interval results show that FT has a significantly lower cure rate than TS at both time points.

TABLE 21: Study 02 Medical Officer Clinical Outcomes By Study Day 20
(5-20 days post therapy for FT, 5-11 days post therapy for TS)

outcome	MO evaluable patients			
	FT (N=249)		TS (N=197)	
	n	(%)	n	(%)
cure	**189**	**(76)**	**186**	**(94)**
all failure	**60**	**(24)**	**11**	**(6)**
MO early relapse (study day 12-20 for FT only)	10	(4)	-	-
early failure	50	(20)	11	(6)
95% C.I.[a]: cure	**(-25, -12)**			

[a] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 22: Study 02 Medical Officer Clinical Outcomes At the Late Post Therapy Visit
(approximately 4-6 weeks post treatment)
(study day ≥12 for FT, study day ≥21 for TS)

outcome	MO evaluable patients			
	FT (N=249)		TS (N=197)	
	n	(%)	n	(%)
sustained cure	**164**	**(66)**	**173**	**(88)**
all failure	**76**	**(30)**	**22**	**(11)**
MO early relapse (study day 12-20 for FT only)	10	(4)	-	-
MO late relapse (study day ≥21)	16	(6)	11	(6)
early failure	50	(20)	11	(6)
patients without long term clinical follow up[b]	**9**	**(4)**	**2**	**(1)**
early bacteriologic failure/clinical cure with concomitant antibiotic	9	(4)	2	(1)
95% C.I.[a]: sustained cure	**(-30, -14)**			

[a] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.
[b] As a worst case analysis, these patients have been included clinical "failures", since they received a concomitant antibiotic.

At 5-11 days post treatment, the rate of "overall success" (defined as a bacteriologic eradication or bacteriologic eradication with new infection and clinical cure) in the MO evaluable analysis group is 76% (188/249) for FT and 94% (185/197) for TS. The 95% confidence interval of the FT minus TS difference in overall success rate is (-25%, -12%), which shows that FT has a significantly lower rate of overall success than TS.

At 5-11 days post treatment, the rate of "complete success" (defined as a bacteriologic eradication or bacteriologic eradication with new infection and clinical cure and no adverse event) in the MO evaluable analysis group is 41% (103/249) for FT and 43% (85/197) for TS. The 95% confidence interval of the FT minus TS difference in complete success rate is (-11%, 8%), which shows that FT and TS are comparable with respect to the rate of complete success.

***REVIEWER COMMENT**: In the MO evaluable analysis group, 54% (134/249) of FT patients and 46% (90/197) of TS patients did not have an adverse event. The 95% confidence interval of the FT minus TS difference in the rate of no adverse event is (-2%, 18%). Although the confidence interval includes zero, the direction of the interval highlights FT's lower rate of adverse events compared to TS.*

Subset efficacy analyses by age (≤65, >65) and race (white, black, other) for the rate of all bacteriologic eradication at 5-11 days post treatment in the medical officer's evaluable group are presented in Table 23. Confidence interval results were performed only for those subsets with ≥10 patients per treatment group. Efficacy results were consistent across the subgroups.

TABLE 23: Study 02 Subgroup Efficacy Analysis of Rate of All Bacteriologic Eradication At 5-11 Days Post Treatment According to Medical Officer Evaluable Group

subgroup	eradication rate				95% C.I.[a]
	FT		TS		
	n/N	(%)	n/N	(%)	
age ≤65	195/228	(86)	177/180	(98)	(-18, -7)
age >65	17/21	(81)	17/17	(100)	(-41, 3)
race white	175/209	(84)	169/172	(98)	(-20, -9)
race black	27/29	(93)	14/14	(100)	(-21, 8)
race other	10/11	(91)	11/11	(100)	(-35, 17)

[a] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction. Confidence intervals are presented only for those subgroups with at least 10 patients per treatment group.

A summary of safety outcomes as reported in the applicant's study report is presented in Table 24. FT and TS are similar with respect to the rate of at least one severe adverse event. Compared to TS, FT has a significantly lower rate of at least one adverse event, at least one treatment related adverse event and discontinuation due to an adverse event. FT also has significantly lower rates of at least one nervous system adverse event, at least one skin and skin structure system adverse event, at least one nausea adverse event, at least one constipation adverse event, at least one dizziness adverse event, and at least one rash adverse event than TS. However, FT has significantly higher rates of at least one diarrhea adverse event and at least one abnormal stool adverse event.

***REVIEWER COMMENT**: Using the applicant's SAS data sets, this reviewer could not exactly reproduce some of the applicant's tabulations of adverse events presented in the study report. However, the discrepancies are minor and do not impact study conclusions.*

Subset safety analyses by age (≤65, >65) and race (white, black, other) for the rate of at least one adverse event are presented in Table 25. No noteworthy subgroup differences were observed.

TABLE 24: Study 02 Summary of Safety Outcomes[1]						
outcome	FT (N=426)		TS (N=428)		p-value[2]	95% C.I.[3]
	n	(%)	n	(%)		
at least one adverse event (AE)	176	(41)	212	(50)	0.02	(-15, -1)
at least one treatment related (definitely or probably) AE	25	(6)	45	(11)	0.02	(-9, -1)
at least one severe AE	20	(5)	27	(6)	0.37	(-5, 2)
discontinued due to an AE	7	(2)	18	(4)	0.04	(-5, 0)
at least one nervous system AE	12	(3)	30	(7)	<0.01	(-7, -1)
at least one skin and skin structure system AE	12	(3)	41	(10)	<0.01	(-10, -3)
at least one nausea AE	21	(5)	43	(10)	<0.01	(-9, -1)
at least one diarrhea AE	40	(9)	11	(3)	<0.01	(3, 10)
at least one constipation AE	0	(0)	8	(2)	<0.01	(-3, 0)
at least one abnormal stool AE	5	(1)	0	(0)	0.03	(0, 2)
at least one dizziness AE	5	(1)	15	(4)	0.04	(-5, 0)
at least one rash AE	3	(1)	22	(5)	<0.01	(-7, -2)

[1] Numbers were obtained from the applicant's study report tables. Outcomes are presented only for those body system and individual events with a statistically significant treatment difference (0.05 level).
[2] Two sided p-value from Fisher's exact test.
[3] Two sided 95% confidence intervals of the FT minus TS difference in event rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 25: Study 02 Subgroup Safety Analysis of Rate of at Least One Adverse Event [1]						
subgroup	adverse event rate				p-value[2]	95% C.I.[3]
	FT		TS			
	n/N	(%)	n/N	(%)		
all patients	176/426	(41)	208/428	(49)	0.03	(-14, 0)
age ≤65	163/397	(41)	194/394	(49)	0.02	(-15, -1)
age >65	13/29	(45)	14/34	(41)	0.80	(-24, 31)
race white	152/361	(42)	180/369	(49)	0.08	(-14, 1)
race black	16/46	(35)	17/36	(47)	0.27	(-36, 11)
race other	8/19	(42)	11/23	(49)	0.76	(-41, 29)

[1] Numbers were obtained from the applicant's SAS data sets.
[2] Two sided p-value from Fisher's exact test.
[3] Two sided 95% confidence intervals of the FT minus TS difference in event rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

IV. SUMMARY AND CONCLUSIONS
(Which May be Conveyed to the Sponsor)

Statistical evaluation of efficacy is based upon the two-sided 95% confidence interval of the fosfomycin tromethamine minus comparator difference in the rate of all bacteriologic eradication rate at 5-11 days post treatment in the medical officer's evaluable patient group.

Statistical evaluation of safety is primarily based upon the two-sided Fisher's exact test treatment comparison of the rate of at least one adverse event in the safety analysis group. Treatment comparisons of rates of individual adverse events are also considered.

1. In study MON-US-01, the 95% confidence interval is $_{260,\ 222}$ (-26%, -15%) $_{78\%,\ 99\%}$, which demonstrates that a single dose of 3 gm fosfomycin tromethamine is inferior in efficacy to 7 days of ciprofloxacin 250 mg q. 12h. in the treatment of uncomplicated urinary tract infections in women.

2. In study MON-US-02, the 95% confidence interval is $_{249,\ 197}$ (-19%, -8%) $_{85\%,\ 98\%}$, which demonstrates that a single dose of 3 gm fosfomycin tromethamine is inferior in efficacy to 10 days of trimethoprim/sulfamethoxazole 160/800 mg q. 12 h. in the treatment of uncomplicated urinary tract infections in women.

3. In study MON-US-01, the rate of at least one adverse event is 46% (199/432) for fosfomycin tromethamine and 43% (193/445) for ciprofloxacin. The Fisher's exact test p-value is 0.46, which indicates that a single dose of 3 gm fosfomycin tromethamine is not significantly different in safety from 7 days of ciprofloxacin 250 mg q. 12h. in the treatment of uncomplicated urinary tract infections in women.

4. In study MON-US-02, the rate of at least one adverse event is 41% (176/426) for fosfomycin tromethamine and 50% (212/428) for trimethoprim/sulfamethoxazole. The Fisher's exact test p-value is 0.02, which indicates that a single dose of 3 gm fosfomycin tromethamine superior in safety to 10 days of trimethoprim/sulfamethoxazole 160/800 mg q. 12 h. in the treatment of uncomplicated urinary tract infections in women.

5. In both studies, fosfomycin tromethamine has a significantly higher rate of diarrhea than its comparator. This is the only adverse event where the direction of the effect was consistent across the two studies. In study MON-US-01, the rate of diarrhea is 8% (33/432) and 4% (19/445) for fosfomycin tromethamine and ciprofloxacin, respectively (p=0.04). In study MON-US-02, the rate of diarrhea is 9% (40/426) and 3% (11/428) for fosfomycin tromethamine and trimethoprim/sulfamethoxazole, respectively (p<0.01).

6. Subgroup analyses by age (≤65 and >65) and race (white, black, and other) did not reveal any noteworthy subgroup differences with respect to efficacy or safety.

REVIEWER CONCLUSIONS: ***From a statistical standpoint, the applicant has failed to provide two independent, adequate and well controlled trials which demonstrate that a single dose of 3 gm fosfomycin tromethamine is therapeutically equivalent in efficacy to an approved comparator for the treatment of uncomplicated urinary tract infections in women.***

While a single dose of 3 gm fosfomycin tromethamine may have a slight safety advantage over 10 days of trimethoprim/sulfamethoxazole 160/800 mg q. 12 h., the observed differences are not substantial enough to compensate for the lack of efficacy.

RECOMMENDED REGULATORY ACTION: ***This reviewer does not recommend approval of a single dose of 3 gm fosfomycin tromethamine for the treatment of uncomplicated urinary tract infections in women.***

Elizabeth A. Turney 8/16/95

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Ralph Harkins Ph D

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Supervisory Statistician, Group 7

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for Satya D. Dubey, Ph.D.
Branch Chief, SERB

cc:
Orig. NDA 50-717
HFD-520
HFD-520/Dillon-Parker
HFD-520/Fanning
HFD-520/Albrecht
HFD-520/Soreth
HFD-713/Dubey [File: DRU 1.3.2]
HFD-713/Harkins
HFD-713/Turney
HFD-344/Lisook
Chron.
This review contains 30 pages and 25 tables.
WordPerfect 6.0/NDA50717.wpd/8-15-95