CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-676

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#:	20-676 OCT 11 1996
Name of Drug:	VAGISTAT® -1 (tioconazole 6.5%) vaginal ointment
Applicant:	Bristol-Myers Products
Indication(s):	Over-the-counter (OTC) therapy for vulvovaginal candidiasis.
Documents Reviewed:	Volumes 1, 2, and 4 through 29, stamp dated November 13, 1995.
Review Type:	Clinical.
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I. INTRODUCTION

Reviewer's Note: In this review, confidence intervals for differences in cure rates (Vagistat minus Monistat) are reported as $_{n1,n2}(l, u)_{p1,p2}$, where n1 is the number of Vagistat patients, n2 is the number of Monistat patients, l and u are the lower and upper bounds of the 95% confidence interval, respectively, p1 is the percent of Vagistat patients cured, and p2 is the percent of Monistat patients cured.

The sponsor, Bristol-Myers Products, is proposing an over-the-counter (OTC) switch of Vagistat® -1 (tioconazole 6.5%) vaginal ointment for the treatment of recurrent vaginal yeast infections. Vagistat-1 is currently approved for prescription use under NDA 19-355. This NDA contains proposed OTC labeling, a nationally projectible market research study of compliance with dosing regimens of currently approved (7 day) OTC vaginal yeast infection remedies, consumer preference information, and a review of the overall safety and efficacy profile established for Vagistat-1 based on published and unpublished study information. The sponsor states that no changes other than the proposed OTC labeling are contemplated by this application.

To support this submission, two pivotal clinical studies (protocols 145-01-93 and 145-02-93) of Vagistat-1 versus Monistat 7 were conducted by the sponsor and are reviewed in this document. In each study, patients were to complete one initial visit and two return visits (visits 2 and 3). Visit 2 was to occur between study days 12 and 16, and visit 3 was to occur between study days 30 and 35. The primary efficacy variable in both protocols was "overall therapeutic outcome" in sponsor evaluable patients, defined as a cure if the patient was both a clinical and microbiologic cure at visits 2 and 3, and otherwise as a failure. In protocol 145-01-93, the 95% confidence interval for the difference in overall therapeutic cure rates (Vagistat minus Monistat) was $_{196,192}(-15.0, 3.0)_{50.7\%,56.7\%}$ using a center adjusted model specified by the sponsor in the protocol, and $_{196,192}(-17.7, 3.1)_{50.0\%,57.3\%}$ using the normal approximation to the binomial distribution, incorporating the continuity correction, which pools all data across centers. In protocol 145-02-93, the center adjusted 95% confidence interval for the difference in overall therapeutic cure rates was $_{180,174}(-19.1, 0.8)_{50.4\%,59.6\%}$ and the unadjusted 95% confidence interval was $_{180,174}(-22.3, -0.6)_{48.9\%,60.3\%}$. In both studies the cure rates for Vagistat are low (around 50%). In the first study, the confidence intervals cover zero, but not by much. In the second study, although the two methodologies (discussed below) provide different quantitative conclusions (one confidence interval covers zero while the other does not), they do provide similar qualitative conclusions (i.e., Monistat appears to be more effective than Vagistat). In addition, the sponsor originally planned to enroll 200 evaluable patients per treatment arm (in each study). This enrollment was essentially reached in the first study, but the second study fell short by 46 patients. If the second study had enrolled as many evaluable patients as originally planned, the two methodologies for estimating the confidence interval would most likely agree both qualitatively AND quantitatively.

Reviewer's Note: The sponsor's definition of clinical cure (and hence therapeutic cure) is somewhat problematic. Clinical efficacy was based on the improvement of four signs and symptoms: itching, burning, vaginal signs (erythema and/or edema), and vulvar signs

(erythema, edema, and/or excoriations). However, the sponsor states that "signs and symptoms having a baseline score of 0 (absent) were not considered in determining clinical response at Visit 2 or Visit 3, even if the signs and symptoms worsened." The medical reviewer required both resolution of baseline symptoms AND no new symptoms for a definition of clinical, and hence therapeutic, cure. (Please see the medical officer's review for a more complete definition of the "medical officer evaluable patient group" and medical officer assigned therapeutic outcomes.) For the medical officer evaluable patient group in protocol 145-01-93, the 95% confidence interval for the difference in overall therapeutic cure rates (Vagistat minus Monistat) was $_{203,209}(-18.8, -1.6)_{58.8\%,69.0\%}$ *using the center-adjusted model and* $_{203,209}(-20.0, -0.6)_{58.6\%,68.9\%}$ *using the unadjusted model. In protocol 145-02-93, the 95% confidence interval for the difference in overall therapeutic cure rate in medical officer evaluable patients was* $_{191,195}(-26.6, -8.2)_{54.4\%,71.8\%}$ *for the center-adjusted model and* $_{191,195}(-28.9, -8.9)_{53.4\%,72.3\%}$ *for the unadjusted model. Both confidence intervals in both studies suggest that Vagistat is inferior to Monistat.*

Section II provides a more detailed description and evaluation of the two pivotal protocols 145-01-93 and 145-02-93, respectively. A supportive study conducted by the sponsor of Vagistat-1 versus Terazol-3 is also briefly mentioned. Section III provides conclusions which may be conveyed to the sponsor.

II. EVALUATION

II.A. Pivotal Study: Protocol 145-01-93

II.A.1. Methods

Protocol 145-01-93 was a multi center (25 centers), randomized, investigator-blinded, active-controlled, parallel group design, clinical trial to compare the efficacy and safety of Vagistat® -1 vaginal ointment, a current prescription product, to Monistat® 7 vaginal cream, a current over-the-counter product, in patients with proven vulvovaginal candidiasis. To maintain investigator blinding, all cartons of study medication were provided in plain white cartons and packaged to weigh approximately the same.

The study population consisted of females between the ages of 18 and 64 years with signs or symptoms indicative of vulvovaginal candidiasis that was subsequently confirmed by mycological culture. Each patients received either Vagistat-1 ointment (containing 300 mg tioconazole) administered once vaginally at bedtime on Day 1 or Monistat 7 cream (containing 100 mg miconazole nitrate) administered vaginally once daily at bedtime on Days 1 through 7. As described above, patients were to attend one initial visit, and then return for two follow-up visits, visits 2 and 3. At each follow-up visit, clinical, microbiologic, and therapeutic cure (defined as both clinical and microbiologic cure) was assessed. "Overall" clinical, microbiologic, and therapeutic outcomes were defined as "cure" if the patient was cured on the specific outcome at both visits 2 and 3, and "failure" otherwise. Overall therapeutic cure in evaluable patients was considered the primary efficacy variable by both the sponsor and FDA.

II.A.2. Results

A total of 541 patients entered the study at one of 25 different sites, 272 (50.3%) in the Vagistat-1 group and 269 (49.7%) in the Monistat 7 group. Center enrollments ranged from 5 to 60, with most centers enrolling about 20 patients. The proportion of patients completing the study, along with reasons for patients not completing the study, is summarized in Table 1. The number of patients completing the study was significantly less in the Vagistat arm ($p=0.018$), due mainly to the larger number of treatment failures in that arm ($p<0.0001$).

Table 1: Patients Completing Protocol 145-01-93

	Vagistat-1 (N=272) n (%)	Monistat 7 (N=269) n (%)
Completed Study	179 (65.8)	202 (75.1)
Discontinued	93 (34.2)	67 (24.9)
Failure to Qualify	45 (16.5)	47 (17.5)
Treatment Failure	28 (10.3)	5 (1.9)
Adverse Experience	7 (2.6)	3 (1.1)
Other Protocol Violation	4 (1.5)	5 (1.9)
Lost to Follow-Up	5 (1.8)	3 (1.1)
Patient Election	3 (1.1)	3 (1.1)
Other	1 (0.4)	1 (0.4)
Death	0 (0.0)	0 (0.0)

Of the 541 patients enrolled in the study, a total of 388 (71.7%) were considered evaluable by the sponsor for the "per-protocol" efficacy analyses: 196 (72.1%) in the Vagistat arm and 192 (71.4%) in the Monistat arm. Several more patients were included in the "intent-to-treat" (ITT) efficacy analysis by the sponsor, which is actually a modified intent-to-treat (MITT) analysis and will be referred to as such in this review since it excludes patients with a negative culture at baseline. All patients with safety data were included in the safety analysis. Table 2 summarizes reasons for patient exclusion and nonevaluability for each of the above-mentioned analyses. Reasons for exclusions were fairly consistent across treatment groups. *Note: Treatment failures were included in all efficacy analyses.*

Table 2: Evaluability status for various analyses (Sponsor), Protocol 145-01-93

Evaluability Group Reason for Exclusion	Vagistat-1 N=272 n (%)	Monistat 7 N=269 n (%)
Excluded from Safety Analysis Group	11 (4.0)	6 (2.2)
Did not use study medication	3 (1.1)	2 (0.7)
No safety data	8 (2.9)	4 (1.5)
Evaluable for Safety Analysis	261 (96.0)	263 (97.8)
Excluded from MITT Analysis Group	63 (23.2)	58 (21.6)
Admission criteria not satisfied		
Negative culture at baseline	46 (16.9)	47 (17.5)
Other admission criteria not satisfied	5 (1.8)	3 (1.1)
Did not use study medication	3 (1.1)	2 (0.7)
Patient discontinued	6 (2.2)	1 (0.4)
Prohibited medication used	3 (1.1)	4 (1.5)
Missing some post-baseline data	0 (0.0)	1 (0.4)
Evaluable for MITT Analysis	209 (76.8)	211 (78.4)
Excluded from Per-Protocol Analysis Group	76 (27.9)	77 (28.6)
Admission criteria not satisfied		
Negative culture at baseline	46 (16.9)	47 (17.5)
Other admission criteria not satisfied	5 (1.8)	3 (1.1)
Did not use study medication	3 (1.1)	2 (0.7)
Lost to follow-up	3 (1.1)	3 (1.1)
Patient discontinued	6 (2.2)	1 (0.4)
Medication used incorrectly	4 (1.5)	8 (3.0)
Prohibited medication used	4 (1.5)	5 (1.9)
Developed other vaginal infection	2 (0.7)	3 (1.1)
Departure from visit schedule	3 (1.1)	2 (0.7)
Missing some post-baseline data	0 (0.0)	3 (1.1)
Evaluable for Per-Protocol Analysis	196 (72.1)	192 (71.4)

Baseline demographic and disease status variables were similar when considering (1) all patients, and (2) patients evaluable for the per-protocol efficacy analysis. Table 3 summarizes baseline demographic and disease status variables for the per-protocol group. No statistically significant differences were noted between treatment groups in the per-protocol efficacy analysis group, although the difference in the number of vaginal infections in the year prior to the study approached significance ($p=0.06$), as did the difference in the number of patients using anti-yeast medication in the year prior to study entry ($p=0.10$). In both cases, Vagistat-1 patients tended to have had fewer infections and used less anti-

yeast medication, which could potentially bias results in favor of Vagistat. *Note: P-values given in Table 3 were calculated by the sponsor using analysis-of-variance (ANOVA) with main effects for treatment and center for continuous variables, the Cochran-Mantel-Haenszel (CMH) row mean scores test stratified by center for categorical characteristics, and the Wilcoxon rank sum test for median days since onset.*

Table 3: Demographics/Disease Status at Baseline, Per-Protocol Analysis Group (Sponsor) Protocol 145-01-93

	Vagistat-1 N = 196	Monistat 7 N = 192	p-value
Age			
Mean	30.7	29.9	0.32
Median	27.0	26.5	
Standard Deviation	10.7	9.9	
Minimum-Maximum	18-62	18-62	
Race [n (%)]			0.95
White	142 (72.4)	142 (74.0)	
Black	41 (20.9)	39 (20.3)	
Other	13 (6.6)	11 (5.7)	
Signs/Symptoms Present [n (%)]			
Itching	183 (93.4)	181 (94.3)	0.63
Burning	150 (76.5)	147 (76.6)	0.66
Vulvar Signs	176 (89.8)	171 (89.1)	0.75
Vaginal Signs	177 (90.3)	166 (86.5)	0.15
Severity of Signs/Symptoms [n (%)]			0.40
Level 1 (Least Severe)	61 (31.1)	66 (34.4)	
Level 2	76 (38.8)	76 (39.6)	
Level 3 (Most Severe)	59 (30.1)	50 (26.0)	
Discharge at Introitus [n (%)]			0.67
Yes	122 (62.2)	124 (64.4)	
No	74 (37.8)	68 (35.4)	
Number of Vaginal Infections in Past Year [n (%)]			0.06
0	76 (38.8)	66 (34.4)	
1 +	120 (61.2)	126 (65.6)	
Therapy Received in Past Year [n (%)]			0.17
Yes	112 (57.1)	121 (63.0)	
No	84 (42.9)	71 (37.0)	
Number of Usages of Anti-Yeast Medication in Past Year [n (%)]			0.10
0	97 (49.5)	80 (41.7)	
1 +	99 (50.5)	112 (58.3)	
Days Since Onset of Current Infection			
Mean	11.8	10.4	
Median	7.0	6.0	0.46
Standard Deviation	18.4	11.3	
Minimum-Maximum			

II.A.2.a. Efficacy

Sponsor Results: Main Analyses
Table 4 summarizes clinical, microbiologic, and therapeutic cure rates by treatment group and visit. At visit 2, therapeutic and microbiologic cure rates for Vagistat are statistically significantly different (lower) than those for Monistat. No statistically significant difference is detected in clinical cure rates, however the trend favors Monistat. At visit 3 and overall, no statistically significant differences are detected between Vagistat and Monistat in clinical, microbiologic, or therapeutic cure rates. However, again the trend in each case favors Monistat. *Note: The sponsor states that the lower therapeutic cure rate for Vagistat at Visit 2 is possibly due to the longer time since the end of treatment in the Vagistat group (typically 11-15 days) versus the Monistat group (5-9 days). However, this is irrelevant as the question of interest is how many patients are cured a specified number of days after **beginning** therapy, not after **completing** therapy.*

Reviewer's Note: The estimates of cure rates and 95% confidence intervals for the differences in such rates given in Table 4 were calculated using a center-adjusted model. This model was specified by the sponsor in their protocol and is somewhat non-standard (e.g., these estimates must be programmed by the statistician as they do not exist in any commercial software that this reviewer knows of -- FDA calculations were done using SAS and Splus), however it follows the theory developed for the Cochran-Mantel-Haenszel procedure which is standard. The more standard 95% confidence interval, which uses the normal approximation to the binomial distribution incorporating the continuity correction, for the difference in overall therapeutic cure rates (Vagistat minus Monistat) is $_{196,192}(-17.7, 3.1)_{50.0\%,57.3\%}$ *. Note that the center-adjusted cure rates are slightly different from the cure rates for the pooled data.*

(Note: When performing the Cochran-Mantel-Haenszel test to produce p-values and estimates of odds ratios, the sponsor combined small centers to avoid excluding data from such centers. This is acceptable. For some reason however, when the sponsor estimated cure rates and 95% confidence intervals, using a procedure based on the theory behind the Cochran-Mantel-Haenszel test, they did not combine small centers and thus some data was excluded. This reviewer calculated all center-adjusted 95% confidence intervals for the difference in overall therapeutic cure rates both ways, i.e., both combining small centers to use all data and not combining small centers so that some data was excluded. For both the sponsor's analysis and FDA analysis, no differences in interpretation of outcome were found. In this review, all sponsor center-adjusted 95% confidence intervals are reported without combining small centers, as this was the method the sponsor chose. To be more consistent with the testing approach, all FDA center-adjusted 95% confidence intervals are reported for the case where data from small centers has been combined.)

FDA Results: Main Analyses
For the medical officer evaluable patient group, the 95% confidence interval for the difference in overall therapeutic cure rates (Vagistat minus Monistat) using the center-adjusted model was $_{203,209}(-18.8, -1.6)_{58.8\%,69.0\%}$*. Using the unadjusted model, the 95% confidence interval for the difference in overall therapeutic cure rates was* $_{203,209}(-20.0, -0.6)_{58.6\%,68.9\%}$*. Thus, FDA analysis finds a statistically significant treatment*

difference which favors Monistat.

Table 4: Cure Rates* for Per-Protocol Analysis Group (Sponsor), Protocol 145-01-93

Visit	Outcome Variable	Vagistat-1 N=196 n (%)	Monistat 7 N=192 n (%)	95% Confidence Interval#
Visit 2	Therapeutic Cure	123 (63.9)	154 (80.1)	(-24.1, -8.2)
	Clinical Cure	177 (90.0)	184 (95.7)	(-12.0, 0.6)
	Microbiologic Cure	126 (65.4)	156 (81.2)	(-23.5, -8.0)
Visit 3	Therapeutic Cure	107 (55.4)	123 (63.4)	(-17.2, 1.2)
	Clinical Cure	123 (62.9)	137 (71.0)	(-17.0, 0.8)
	Microbiologic Cure	120 (62.4)	137 (70.8)	(-17.4, 0.5)
Overall	Therapeutic Cure	98 (50.7)	110 (56.7)	(-15.0, 3.0)
	Clinical Cure	121 (61.9)	135 (69.9)	(-16.8, 0.9)
	Microbiologic Cure	109 (56.5)	123 (63.7)	(-15.9, 1.5)

*Mantel-Haenszel estimates, stratified by center
For the estimated difference in percent (Vagistat minus Monistat)

Sponsor Results: Other Analyses
When adjusted for prior year use of anti-yeast medication, age, race, and baseline symptom severity (using the center-adjusted model), the overall therapeutic cure rates in the sponsor evaluable patient group were 50.5% for Vagistat-1 and 56.8% for Monistat 7 [95% confidence interval (-15.7%, 2.9%)].

A separate analysis was conducted by the sponsor for the subset of patients (54%) reporting the prior year's use of anti-yeast medication. The overall center-adjusted therapeutic cure rate was 44.3% for the Vagistat-1 group compared to 50.3% for the Monistat 7 group [95% confidence interval for the estimated difference (-18.0%, 5.8%)].

Patients were contacted twice by telephone (Day 2/3 and 6/7) during the first week of the study to obtain information on the incidence of the clinical signs and symptoms of burning and itching and their severity (absent, mild, moderate, severe). More improvement was apparent in both itching and burning at the second contact on Day 6/7 compared to the first contact on Day 2/3 in both treatment groups. On Day 6/7, significantly greater improvement in the symptom of burning was noted in the Vagistat group compared to Monistat ($p=0.008$). Patient diary data confirmed this finding, with significantly more Vagistat patients experiencing early relief of burning ($p=0.035$).

Relapse rates were determined between Visits 2 and 3 for therapeutic, clinical, and

microbiologic outcome. The sponsor states that rates of clinical relapse were similar between the two groups (p=0.34), but that therapeutic and microbiologic relapse rates were significantly higher in the Monistat 7 group (p=0.005 for each comparison). *However, these relapse rates are calculated incorrectly, or at least misleadingly. The sponsor uses the total number of Vagistat and Monistat patients, respectively, in the denominator when calculating relapse rates. They should be using the number of Vagistat and Monistat patients, respectively, that were* ***cured*** *at visit 2. One cannot relapse unless one was originally cured, obviously.*

II.A.2.b. Safety

There were 156 adverse experiences reported by 98 patients (37.5%) in the Vagistat-1 group, and 160 adverse experiences reported by 105 patients (39.9%) in the Monistat 7 group. The incidence rates of adverse experiences were similar between the two treatment groups. The most frequently reported adverse experiences were vaginitis, headache, infection, and abdominal pain. In the Vagistat group, 18 patients (6.9%) reported 22 drug-related adverse experiences; in the Monistat group, 16 patients (6.1%) reported 18 drug-related adverse experiences. No differences were noted between treatment groups in either the incidence of specific adverse experiences (p=0.59) or the incidence of adverse experiences related to study drug (p=0.73). Two serious adverse experiences were reported, one in each treatment group; neither was treatment-related. Seven patients in the Vagistat group and three patients in the Monistat group were reported as having discontinued the study due to adverse experiences.

Changes in vital signs were minimal and similar between treatment groups. Comparisons of physical examination results at the end of the study with those at the beginning showed few adverse changes (changes from normal to abnormal) and no trends related to study treatment.

Table 5 summarizes adverse experiences occurring in at least 1% of patients, regardless of relationship to study drug. Table 6 summarizes drug-related adverse experiences.

Table 5: Adverse experiences occurring in ≥1% of patients , Protocol 145-01-93

	Vagistat-1 N=261 n* (%)	Monistat 7 N=263 n* (%)
Body as a whole	47 (18.0)	42 (16.0)
Headache	16 (6.1)	16 (6.1)
Infection	12 (4.6)	11 (4.2)
Abdominal Pain	10 (3.8)	8 (3.0)
Flu Syndrome	5 (1.9)	3 (1.1)
Allergic Reaction	4 (1.5)	2 (0.8)
Back Pain	1 (0.4)	4 (1.5)
Digestive system	7 (2.7)	11 (4.2)
Diarrhea	1 (0.4)	3 (1.1)
Constipation	0 (0.0)	3 (1.1)
Metabolic and Nutritional Disorders	4 (1.5)	0 (0.0)
Nervous system	5 (1.9)	4 (1.5)
Respiratory System	10 (3.8)	14 (5.3)
Rhinitis	4 (1.5)	5 (1.9)
Pharyngitis	1 (0.4)	6 (2.3)
Cough Increased	2 (0.8)	3 (1.1)
Bronchitis	3 (1.1)	1 (0.4)
Skin and Appendages	8 (3.1)	10 (3.8)
Pruritus	4 (1.5)	3 (1.1)
Rash	0 (0.0)	4 (1.5)
Special Senses	2 (0.8)	5 (1.9)
Urogenital System	45 (17.2)	47 (17.9)
Vaginitis	22 (8.4)	23 (8.7)
Dysmenorrhea	8 (3.1)	4 (1.5)
Vulvovaginal Disorder	6 (2.3)	3 (1.1)
Urinary Frequency	2 (0.8)	5 (1.9)
Leukorrhea	2 (0.8)	3 (1.1)
Dysuria	0 (0.0)	4 (1.5)
Metrorrhagia	3 (1.1)	1 (0.4)

*Number of patients, not reports.

Table 6: Adverse experiences considered related to study drug , Protocol 145-01-93

	Vagistat-1 N=261 n* (%)	Monistat 7 N=263 n* (%)
Body as a whole	4 (1.5)	2 (0.8)
Abdominal Pain	1 (0.4)	1 (0.4)
Body Odor	1 (0.4)	0 (0.0)
Bromism	1 (0.4)	0 (0.0)
Headache	1 (0.4)	0 (0.0)
Moniliasis	0 (0.0)	1 (0.4)
Digestive system	0 (0.0)	1 (0.4)
Diarrhea	0 (0.0)	1 (0.4)
Skin and Appendages	4 (1.5)	1 (0.4)
Pruritus	4 (1.5)	1 (0.4)
Special Senses	0 (0.0)	1 (0.4)
Abnormal Vision	0 (0.0)	1 (0.4)
Urogenital System	12 (4.6)	12 (4.6)
Vaginitis	8 (3.1)	8 (3.0)
Vulvovaginal Disorder	3 (1.1)	2 (0.8)
Urinary Frequency	1 (0.4)	1 (0.4)
Cervicitis	1 (0.4)	0 (0.0)
Cervix Disorder	0 (0.0)	1 (0.4)
Leukorrhea	0 (0.0)	1 (0.4)

*Number of patients, not reports.

II.B. Pivotal Study: Protocol 145-02-93

II.B.1. Methods

The design of Protocol 145-02-93 was identical to that of Protocol 145-01-93. The same comparator drug, Monistat 7, was used. The number of centers at which women, ages 17 to 64 years, were enrolled was even the same (25 -- *note: there were no investigators enrolling patients in both protocol 145-01-93 and protocol 145-02-93*).

II.B.2. Results

A total of 519 patients entered the study at 25 sites, 260 (50.1%) in the Vagistat-1 group and 259 (49.9%) in the Monistat 7 group. Center enrollments ranged from 2 to 53, with most centers enrolling about 20 patients. The proportion of patients completing the study, along with reasons for discontinuations, is summarized in Table 7. The number of patients completing the study was similar between the two treatment arms (p=0.30), but there

were significantly more discontinuations due to treatment failure in the Vagistat-1 group (p = 0.025).

Table 7: Patients Completing Protocol 145-02-93

	Vagistat-1 (N = 260) n (%)	Monistat 7 (N = 259) n (%)
Completed Study	179 (68.8)	189 (73.0)
Discontinued	81 (31.2)	70 (27.0)
Failure to Qualify	33 (12.7)	39 (15.1)
Treatment Failure	21 (8.1)	9 (3.5)
Lost to Follow-Up	8 (3.1)	10 (3.9)
Other Protocol Violation	8 (3.1)	3 (1.2)
Patient Election	6 (2.3)	3 (1.2)
Adverse Experience	4 (1.5)	2 (0.8)
Other	1 (0.4)	4 (1.5)
Death	0 (0.0)	0 (0.0)

Of the 519 patients enrolled in the study, a total of 354 (68.2%) were considered evaluable by the sponsor for the per-protocol efficacy analyses: 180 (69.2%) in the Vagistat arm and 174 (67.2%) in the Monistat arm. Several more patients were included in the modified intent-to-treat analysis. All patients with safety data were included in the safety analysis. Table 8 summarizes reasons for patient exclusion and nonevaluability for each of the three analysis groups (per-protocol, MITT, and safety). There were no statistically significant differences across treatment groups. *Note: Treatment failures were included in all efficacy analyses.*

Table 8: Evaluability status for various analyses (Sponsor), Protocol 145-02-93

Evaluability Group Reason for Exclusion	Vagistat-1 N = 260 n (%)	Monistat 7 N = 259 n (%)
Excluded from Safety Analysis Group	8 (3.1)	14 (5.4)
Did not use study medication	0 (0.0)	3 (1.2)
No safety data	8 (3.1)	11 (4.2)
Evaluable for Safety Analysis	252 (96.9)	245 (94.6)
Excluded from MITT Analysis Group	65 (25.0)	60 (23.2)
Admission criteria not satisfied		
Negative culture at baseline	41 (15.8)	43 (16.6)
Other admission criteria not satisfied	4 (1.5)	5 (1.9)
Did not use study medication	0 (0.0)	3 (1.2)
Patient discontinued	7 (2.7)	3 (1.2)
Prohibited medication used	8 (3.1)	3 (1.2)
Missing some post-baseline data	5 (1.9)	3 (1.2)
Evaluable for MITT Analysis	195 (75.0)	199 (76.8)
Excluded from Per-Protocol Analysis Group	80 (30.8)	85 (32.8)
Admission criteria not satisfied		
Negative culture at baseline	41 (15.8)	43 (16.6)
Other admission criteria not satisfied	4 (1.5)	5 (1.9)
Did not use study medication	0 (0.0)	3 (1.2)
Lost to follow-up	6 (2.3)	10 (3.9)
Patient discontinued	7 (2.7)	3 (1.2)
Medication used incorrectly	1 (0.4)	6 (2.3)
Prohibited medication used	9 (3.5)	4 (1.5)
Developed other vaginal infection	1 (0.4)	2 (0.8)
Departure from visit schedule	4 (1.5)	4 (1.5)
Missing some post-baseline data	7 (2.7)	5 (1.9)
Evaluable for Per-Protocol Analysis	180 (69.2)	174 (67.2)

Baseline demographic and disease status variables were similar when considering (1) all patients, and (2) patients evaluable for the per-protocol efficacy analysis. Table 9 summarizes baseline demographic and disease status variables for the sponsor per-protocol group. Two statistically significant differences were noted at baseline between treatment groups in the per-protocol efficacy analysis group: age (when considered categorically, i.e., <30 years, 30-45 years, and >45 years) and prior use of anti-yeast medication. Significantly fewer Vagistat patients were in the below 30 age category ($p=0.039$; 36% of Vagistat and 43% of Monistat patients were less than 30 years of age, 48% of Vagistat and 46% of Monistat were between 30 and 45 years of age, and 16% of Vagistat and 11% of Monistat patients were older than 45 years of age). A higher proportion of Vagistat patients used at least one anti-yeast medication in the year prior to study start

(p = 0.045); there was no difference between treatment groups in the number of vaginal infections in the same year (p = 0.93). The sponsor does not state whether the number of yeast infections in that year was the same across treatment groups. *Note: P-values given in Table 9 were calculated by the sponsor using analysis-of-variance (ANOVA) with main effects for treatment and center for continuous variables, the Cochran-Mantel-Haenszel (CMH) row mean scores test stratified by center for categorical characteristics, and the Wilcoxon rank sum test for median days since onset.*

Table 9: Demographics/Disease Status at Baseline, Per-Protocol Analysis Group (Sponsor) Protocol 145-02-93

	Vagistat-1 N = 180	Monistat 7 N = 174	p-value
Age			
Mean	33.7	32.4	0.14
Median	32.0	31.5	
Standard Deviation	11.1	9.4	
Minimum-Maximum	18-64	18-64	
Race [n (%)]			0.80
White	137 (76.1)	130 (74.7)	
Black	23 (12.8)	28 (16.1)	
Other	20 (11.1)	16 (9.2)	
Signs/Symptoms Present [n (%)]			
Itching	174 (96.7)	169 (97.1)	0.94
Burning	150 (83.3)	151 (86.8)	0.48
Vulvar Signs	154 (85.6)	156 (89.7)	0.28
Vaginal Signs	177 (98.3)	167 (96.0)	0.19
Severity of Signs/Symptoms [n (%)]			0.34
Level 1 (Least Severe)	52 (28.9)	40 (23.0)	
Level 2	58 (32.2)	58 (33.3)	
Level 3 (Most Severe)	70 (38.9)	76 (43.7)	
Discharge at Introitus [n (%)]			0.32
Yes	124 (68.9)	113 (64.9)	
No	56 (31.1)	61 (35.1)	
Number of Vaginal Infections in Past Year [n (%)]			0.93
0	45 (25.0)	47 (27.0)	
1 +	135 (75.0)	127 (73.0)	
Therapy Received in Past Year [n (%)]			0.23
Yes	129 (71.7)	115 (66.1)	
No	51 (28.3)	59 (33.9)	
Number of Usages of Anti-Yeast Medication in Past Year [n (%)]			0.045
0	58 (32.2)	74 (42.5)	
1 +	122 (67.8)	100 (57.5)	
Days Since Onset of Current Infection			
Mean	7.7	9.5	
Median	5.0	5.5	0.58
Standard Deviation	7.8	13.9	
Minimum-Maximum			

II.B.2.a. Efficacy

Reviewer's Note: One of the investigators in this study, Fiddes, was found to have fraudulent data. This reviewer analyzed the data both including the patients from Fiddes' center and excluding the patients from Fiddes' center. No differences were found in terms of the difference in overall therapeutic cure rates, both in the sponsor's evaluable patient group and in the medical officer's evaluable patient group. When Fiddes' patients are excluded from analysis, the 95% confidence interval for the difference in overall therapeutic cure rates (Vagistat minus Monistat) in the medical officer's evaluable patient group is $_{184,186}(-26.4, -7.4)_{53.7\%,70.6\%}$ *using the center-adjusted model and* $_{184,186}(-28.5, -8.0)_{52.7\%,71.0\%}$ *using the unadjusted model. Results presented below include the data from Fiddes' center.*

Sponsor Results: Main Analyses

Table 10 summarizes clinical, microbiologic, and therapeutic cure rates by treatment group and visit. At visit 2, therapeutic and microbiologic cure rates for Vagistat are statistically significantly different (lower) than those for Monistat. No statistically significant difference is detected in clinical cure rates, however the trend favors Monistat. At visit 3 and overall, no statistically significant differences are detected between Vagistat and Monistat in clinical or therapeutic cure rates. However, again the trend in each case favors Monistat. Microbiologic cure rates are statistically significantly different between treatment groups at visit 3 and overall; cure rates are lower for Vagistat. *Note: As in the first study, the sponsor states that the lower therapeutic cure rate for Vagistat at Visit 2 is possibly due to the longer time since the end of treatment in the Vagistat group (typically 11-15 days) versus the Monistat group (5-9 days). However, this is irrelevant as the question of interest is how many patients are cured a specified number of days after* ***beginning*** *therapy, not after* ***completing*** *therapy.*

Reviewer's Note: The estimates of cure rates and 95% confidence intervals for the differences in such rates given in Table 10 were calculated using a center-adjusted model, as described in Protocol 145-01-93. The unadjusted 95% confidence interval for the difference in overall therapeutic cure rates (Vagistat minus Monistat) is $_{180,174}(-22.3, -0.6)_{48.9\%,60.3\%}$*. Note that this interval does not cover zero, while the center-adjusted one does (although just barely). However, both confidence intervals provide the same qualitative conclusions (i.e., Monistat appears to be more effective than Vagistat). Recall that the sponsor originally planned to enroll 200 evaluable patients per treatment arm and that enrollment in this study fell short by 46 patients. If the full enrollment had been reached, the two methodologies for estimating the confidence interval would most likely agree both qualitatively AND quantitatively.*

FDA Results: Main Analyses

For the medical officer evaluable patient group, the 95% confidence interval for the difference in overall therapeutic cure rates (Vagistat minus Monistat) using the center-adjusted model was $_{191,195}(-26.6, -8.2)_{54.4\%,71.8\%}$*. Using the unadjusted model, the 95% confidence interval for the difference in overall therapeutic cure rates was* $_{191,195}(-28.9, -8.9)_{53.4\%,72.3\%}$*. Thus, FDA analysis finds a statistically significant treatment difference which favors Monistat.*

Table 10: Cure Rates* for Per-Protocol Analysis Group (Sponsor), Protocol 145-02-93

Visit	Outcome Variable	Vagistat-1 N=180 n (%)	Monistat 7 N=174 n (%)	95% Confidence Interval#
Visit 2	Therapeutic Cure	118 (66.4)	139 (79.6)	(-22.0, -4.3)
	Clinical Cure	161 (90.6)	163 (94.2)	(-10.3, 3.1)
	Microbiologic Cure	124 (69.7)	146 (83.2)	(-22.0, -5.1)
Visit 3	Therapeutic Cure	100 (56.9)	117 (66.1)	(-19.0, 0.7)
	Clinical Cure	122 (68.0)	132 (75.9)	(-17.3, 1.4)
	Microbiologic Cure	122 (69.2)	140 (78.7)	(-18.3, -0.7)
Overall	Therapeutic Cure	88 (50.4)	105 (59.6)	(-19.1, 0.8)
	Clinical Cure	120 (67.1)	128 (73.8)	(-16.1, 2.8)
	Microbiologic Cure	109 (62.1)	132 (74.3)	(-21.2, -3.1)

*Mantel-Haenszel estimates, stratified by center
For the estimated difference in percent (Vagistat minus Monistat)

Sponsor Results: Other Analyses
When adjusted for prior year use of anti-yeast medication, age, race, and baseline symptom severity (using the center-adjusted model), the overall therapeutic cure rates for sponsor evaluable patients were 51.4% for Vagistat-1 and 57.9% for Monistat 7 [95% confidence interval (-16.6%, 3.7%)].

A separate analysis was conducted by the sponsor for the subset of patients (63%) reporting the prior year's use of anti-yeast medication. The overall center-adjusted therapeutic cure rate was 44.8% for the Vagistat-1 group compared to 50.5% for the Monistat 7 group [95% confidence interval for the estimated difference (-18.8%, 7.3%)].

Patients were contacted twice by telephone (Day 2/3 and 6/7) during the first week of the study to obtain information on the incidence of the clinical signs and symptoms of burning and itching and their severity (absent, mild, moderate, severe). More improvement was apparent in both itching and burning at the second contact on Day 6/7 compared to the first contact on Day 2/3 in both treatment groups. At each telephone contact, there was greater relief of itching in the Vagistat group compared to the Monistat group ($p=0.001$ for Day 2/3 and $p=0.006$ for Day 6/7, using the CMH test stratified by center). On Day 2/3, there was also greater relief of burning in the Vagistat group ($p=0.009$; there was no difference at Day 6/7, $p=0.36$). According to patient diary data, 56.5% of patients in the Vagistat-1 group and 51.7% of patients in the Monistat 7 group (51.7%) experienced onset of complete relief of symptoms by Day 6. The distribution of the time to complete relief in the two treatment groups was marginally significant ($p=0.053$).

Relapse rates were determined between Visits 2 and 3 for therapeutic, clinical, and microbiologic outcome. All three rates of relapse (therapeutic, clinical, and microbiologic) were similar between Vagistat-1 and Monistat 7 patients. *Note: As before, relapse rates were calculated incorrectly.*

II.B.2.b. Safety

There were 94 adverse experiences reported by 59 patients (23.4%) in the Vagistat-1 group, and 107 adverse experiences reported by 75 patients (30.6%) in the Monistat 7 group. The incidence rates of adverse experiences were similar between the two treatment groups ($p=0.09$). The most frequently reported adverse experience was headache. Significantly more Monistat patients reported abdominal pain compared to Vagistat patients ($p=0.035$). No other significant differences were noted between treatment groups either in the incidence of specific adverse experiences or in the incidence of adverse experiences related to study drug. Five serious adverse experiences were reported, three in the Vagistat-1 and 2 in the Monistat 7 group; none were considered treatment-related. Four patients in the Vagistat group and two patients in the Monistat group were reported as having discontinued the study due to adverse experiences.

Changes in vital signs were minimal and similar between treatment groups. Comparisons of physical examination results at the end of the study with those at the beginning showed few adverse changes (changes from normal to abnormal) and no trends related to study treatment.

Table 11 summarizes adverse experiences occurring in at least 1% of patients, regardless of relationship to study drug. Table 12 summarizes drug-related adverse experiences.

Table 11: Adverse experiences occurring in ≥1% of patients, Protocol 145-02-93

	Vagistat-1 N = 252 n* (%)	Monistat 7 N = 245 n* (%)
Body as a whole	26 (10.3)	30 (12.2)
Headache	12 (4.8)	8 (3.3)
Abdominal Pain	1 (0.4)	7 (2.9)
Flu Syndrome	3 (1.2)	5 (2.0)
Infection	4 (1.6)	3 (1.2)
Pain	3 (1.2)	1 (0.4)
Cardiovascular system	3 (1.2)	3 (1.2)
Migraine	1 (0.4)	3 (1.2)
Digestive system	3 (1.2)	10 (4.1)
Diarrhea	2 (0.8)	3 (1.2)
Nervous system	1 (0.4)	4 (1.6)
Respiratory system	14 (5.6)	20 (8.2)
Pharyngitis	7 (2.8)	8 (3.3)
Rhinitis	3 (1.2)	6 (2.4)
Sinusitis	1 (0.4)	5 (2.0)
Skin and appendages	4 (1.6)	8 (3.3)
Pruritus	0 (0.0)	3 (1.2)
Special senses	4 (1.6)	0 (0.0)
Conjunctivitis	3 (1.2)	0 (0.0)
Urogenital system	22 (8.7)	18 (7.3)
Vaginitis	6 (2.4)	9 (3.7)
Dysmenorrhea	2 (0.8)	3 (1.2)
Leukorrhea	4 (1.6)	0 (0.0)
Metrorrhagia	3 (1.2)	1 (0.4)

*Number of patients, not reports.

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Table 12: Adverse experiences considered related to study drug, Protocol 145-02-93

	Vagistat-1 N=252 n* (%)	Monistat 7 N=245 n* (%)
Body as a whole	1 (0.4)	0 (0.0)
Allergic Reaction	1 (0.4)	0 (0.0)
Digestive system	0 (0.0)	1 (0.4)
Diarrhea	0 (0.0)	1 (0.4)
Skin and Appendages	0 (0.0)	1 (0.4)
Pruritus	0 (0.0)	1 (0.4)
Urogenital System	4 (1.6)	4 (1.6)
Vaginitis	2 (0.8)	4 (1.6)
Leukorrhea	1 (0.4)	0 (0.0)
Vulvovaginal Disorder	1 (0.4)	0 (0.0)
Vulvovaginitis	1 (0.4)	0 (0.0)

*Number of patients, not reports.

II.C. Integrated Efficacy Results (Protocols 145-01-93 and 145-02-93)

Reviewer's Note: Rather than perform a formal meta-analysis of the efficacy data presented in protocols 145-01-93 and 145-02-93, the sponsor has simply pooled the data and summarized the results. Since the two protocols were identical, this is acceptable.

A total of 1060 patients entered study 145-01-93 or 145-02-93 at one of 50 total sites. Of these patients, 742 were evaluable for the sponsor per-protocol analysis (376 Vagistat-1, 366 Monistat 7). A total of 814 patients were included in the MITT analysis (404 Vagistat-1, 410 Monistat 7).

Table 13 summarizes clinical, microbiologic, and therapeutic outcome by treatment group at visits 2, 3, and overall, for the sponsor evaluable patient group. *In each comparison (i.e., each variable at each visit), there is a statistically significant difference in outcome, with Vagistat having a lower cure rate than Monistat.*

The primary efficacy criterion overall therapeutic response rate, was examined by age group, race, baseline severity of signs and symptoms, and use of anti-yeast medication during the past year. In Protocol 145-02-93, there was a statistically significant imbalance between treatment groups with respect to age group distribution and the proportion of anti-yeast medication users in the past year. A supplementary analysis of therapeutic response, adjusting for the above four baseline factors, was conducted. Adjusting for these factors, the overall therapeutic response (cure) rate for the combined studies was 51.0% in the Vagistat-1 group and 57.4% in the Monistat 7 group.

Overall therapeutic cure rate was evaluated separately in patients reporting the use of anti-yeast medication in the past year. The overall therapeutic cure rate, stratified by center, for the combined data was 44.5% for the Vagistat-1 group and 50.4% for the Monistat 7 group.

Table 13: Cure Rates* for Per-Protocol Analysis Group (Sponsor), Combined Analysis

Visit	Outcome Variable	Vagistat-1 N=376 n (%)	Monistat 7 N=366 n (%)	95% Confidence Interval#
Visit 2	Therapeutic Cure	241 (65.1)	293 (79.9)	(-20.6, -8.8)
	Clinical Cure	338 (90.3)	347 (95.0)	(-9.3, -0.1)
	Microbiologic Cure	250 (67.4)	302 (82.1)	(-20.4, -9.0)
Visit 3	Therapeutic Cure	207 (56.1)	240 (64.7)	(-15.3, -1.8)
	Clinical Cure	245 (65.3)	269 (73.3)	(-14.5, -1.6)
	Microbiologic Cure	242 (65.6)	277 (74.6)	(-15.2, -2.7)
Overall	Therapeutic Cure	186 (50.6)	215 (58.1)	(-14.2, -0.8)
	Clinical Cure	241 (64.4)	263 (71.7)	(-13.8, -0.9)
	Microbiologic Cure	218 (59.2)	255 (68.8)	(-15.8, -3.3)

*Mantel-Haenszel estimates, stratified by center
For the estimated difference in percent (Vagistat minus Monistat)

II.D. Supportive Study

One additional prospective, open label (i.e., not blinded), multi center (13 sites), comparative study was performed by Mead-Johnson Laboratories, a former division of Bristol-Myers Squibb. This study is mentioned only briefly here, and will not be reviewed in full. In this study, protocol VAG 9101, patients with clinically and mycologically confirmed vulvovaginal candidiasis were randomized to receive either one dose of Vagistat-1 6.5% ointment or three nighty doses of Terazol-3 (terconazole 0.8%) cream.

No statistically significant differences were seen between the two treatment groups in either efficacy or safety. Table 14 summarizes the proportion of patients in each treatment group evaluable for safety, intent-to-treat efficacy, and per-protocol efficacy analysis. Table 15 summarizes therapeutic response (i.e., patients considered both a clinical and a mycological cure) for the per-protocol efficacy analysis group.

Table 14: Patients Evaluable for Various Analyses (Sponsor), Supportive Study

	Vagistat-1 N = 138 n (%)	Terazol-3 N = 138 n (%)
Evaluable for Safety Analysis	135 (97.8)	133 (96.4)
Evaluable for ITT Analysis	122 (88.4)	123 (89.1)
Evaluable for Per-Protocol Analysis	119 (86.2)	115 (83.3)

Table 15: Therapeutic Response for Per-Protocol Efficacy Analysis Group (Sponsor), Supportive Study

	Vagistat-1 N = 119 n (%)	Terazol-3 N = 115 n (%)	95% Confidence Interval*
Visit 2#	104 (85.2)	103 (86.6)	(-10.1, 7.5)
Visit 3##	85 (71.4)	91 (79.1)	(-18.7, 3.3)
Overall	79 (66.4)	85 (73.9)	(-19.2, 4.2)

*For the difference in proportions (Vagistat minus Terazol).
#Eight to ten days from the last day of therapy.
##Twenty-eight to thirty-five days from the last day of therapy.

III. CONCLUSIONS (Which May be Conveyed to the Sponsor)

The sponsor, Bristol-Myers Products, is proposing an over-the-counter (OTC) switch of Vagistat® -1 (tioconazole 6.5%) vaginal ointment for the treatment of recurrent vaginal yeast infections. Vagistat-1 is currently approved for prescription use under NDA 19-355. Two pivotal clinical studies (protocols 145-01-93 and 145-02-93) of Vagistat-1 versus Monistat 7 were conducted by the sponsor to support the switch to OTC.

1. The first study, protocol 145-01-93, fails to show equivalence of Vagistat-1 to Monistat 7. For patients considered evaluable by the reviewing medical officer, the 95% confidence interval for the difference in overall therapeutic cure rates (Vagistat minus Monistat) was $_{203,209}(-18.8, -1.6)_{58.8\%,69.0\%}$ *using a center-adjusted model and* $_{203,209}(-20.0, -0.6)_{58.6\%,68.9\%}$ *using an unadjusted model.*

2. The second study, protocol 145-02-93, also fails to show equivalence of Vagistat-1 to Monistat 7. The 95% confidence interval for the difference in overall therapeutic cure rates (Vagistat minus Monistat) in medical officer evaluable patients was $_{191,195}(-26.6, -8.2)_{54.4\%,71.8\%}$ *for the center-adjusted model and* $_{191,195}(-28.9, -8.9)_{53.4\%,72.3\%}$ *for the unadjusted model.*

RECOMMENDED REGULATORY ACTION:

The data provided by the sponsor in this submission fails to show that Vagistat-1 is an equivalent product to Monistat 7. In both studies, when the two drugs are compared in the medical officer's evaluable patient group in terms of the primary efficacy variable, overall therapeutic cure rate, a statistically significant difference is found and Vagistat-1 has the lower cure rate. Thus, the statistical reviewer recommends that this application not be approved.

10/4/96

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Concur: Daphne Lin, Ph.D.
Acting Team Leader, Anti-Infective Group, DB IV

10/11/96

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cc:
Orig. NDA #20-676
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HFD-725/Dr. Lin
HFD-725/Dr. Silliman
HFD-344/Dr. Thomas
Chron.
This review contains 24 pages and 15 tables.

Addendum to Statistical Review and Evaluation

JAN 10 1997

NDA#:	20-676
Name of Drug:	VAGISTAT® -1 (tioconazole 6.5%) vaginal ointment
Applicant:	Bristol-Myers Products
Indication(s):	Over-the-counter (OTC) therapy for vulvovaginal candidiasis.
Statistical Reviewer:	Nancy Paul Silliman, Ph.D., HFD-725
Medical Officer:	Joseph Winfield, M.D., HFD-520
Project Manager:	Steve Trostle, HFD-520

Note: Confidence intervals given below are for the difference in overall therapeutic cure rate (Vagistat minus Monistat) and are reported as $_{n1,n2}(l, u)_{p1,p2}$, *where n1 is the number of Vagistat patients, n2 is the number of Monistat patients, p1 is the percent of Vagistat patients cured, p2 is the percent of Monistat patients cured, and l and u are the lower and upper bounds of the 95% confidence interval, respectively. Confidence intervals are constructed as described in the original review.*

After the statistical review of Vagistat was completed, a major amendment was submitted to NDA 20-676 by the sponsor and the medical officer reevaluated his evaluable patient group. This addendum describes the statistical analysis of the updated medical officer evaluable patient group. Note that the conclusions from this new analysis are the same as before. In each study, there is a statistically significant difference in overall therapeutic cure rates for Vagistat and Monistat, with fewer Vagistat patients being cured.

In protocol 145-01-93, the 95% confidence interval for the difference in overall therapeutic cure rates (medical officer evaluable patient group) is $_{203,200}(-19.9, -2.4)_{57.2\%,68.4\%}$ using the center adjusted method, and $_{203,200}(-21.2, -1.5)_{57.1\%,68.5\%}$ using the unadjusted method (i.e., the normal approximation to the binomial distribution method, incorporating the continuity correction). In protocol 145-02-93, the center adjusted 95% confidence interval for the difference in overall therapeutic cure rates (medical officer evaluable patient group) is $_{192,192}(-23.3, -4.6)_{55.9\%,69.8\%}$ and the unadjusted 95% confidence interval is $_{192,192}(-25.7, -5.5)_{54.7\%,70.3\%}$.

Recall that one investigator in protocol 145-02-93, Fiddes, was found to have committed fraud. The 95% confidence intervals corresponding to those given above, but excluding the data from Fiddes' center, are $_{185,183}(-22.3, -3.1)_{55.8\%,68.5\%}$ for the center-adjusted method and $_{185,183}(-24.6, -3.9)_{54.6\%,68.9\%}$ for the unadjusted method. Note that conclusions are the same whether Fiddes' data is included or excluded.

1/7/97

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This addendum contains 2 pages.