CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-992

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies[1]

Date: MAR 5 1999

NDA #: 20-992

Applicant: Duramed

Name of Drug: Cenestin™ (Synthetic Conjugated Estrogens) Tablets

Indication: Treatment of vasomotor symptoms in postmenopausal women

Documents Reviewed: Vol. 1.1, 1.5-1.11, 1.23-1.27, 4.1-4.6

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Theresa van der Vlugt, M.D. (HFD-580)

Summary of Studies

There is one clinical trial submitted with this application. Study #366 is a placebo-controlled, double-blind, multicenter, dose titration study. Subjects were menopausal women who reported at least 60 moderate to severe vasomotor symptoms per week during a 2-week baseline screening period. There were no inclusion criteria regarding age, time since last menses, FSH levels, or estrogen levels. Subjects were randomly assigned, at a 3:2 ratio, to receive either Cenestin or placebo for a 12-week treatment period. The treatment groups and sample sizes are listed in Table1.

All subjects started at a dose of 0.625 mg/day (or placebo). After 1 week on treatment, the investigator could increase the dose for a patient to 2 x 0.625 per day (1.25 mg/day total) after 1 week on treatment if she had insufficient relief of symptoms. At any time after 1 week, the investigator could decrease the dose to 0.3 mg/day if a patient showed study drug intolerance.

Table 1: Summary of Randomized, Controlled Study

Study Number (Dates Conducted)	# of Centers (Locations)	Treatment Arms; # Randomized	Indication	Duration of Treatment
#366 (9/97 – 1/98)	4 centers (3 investigators) (All U.S.)	Cenestin n=72 (variable dose regimen) Placebo n=48	Trmt. of vasomotor symptoms in postmenopausal women	12 weeks

[1] Keywords: clinical studies; one study application; baseline imbalance; treatment-by-baseline interaction

STUDY # 366

Background

Study #366 is a randomized, double blind, placebo-controlled, multicenter titration study. The objective was to compare a treatment regimen of Cenestin to a blinded placebo treatment regimen for the treatment of moderate to severe vasomotor symptoms (MSVS) in menopausal women. Subjects were menopausal women who experienced an average of at least 60 MSVS per week during a 2-week untreated baseline period. There were no entry criteria regarding age, duration since last bleeding, FSH levels, or estrogen levels. After screening, eligible subjects were randomly assigned to either the Cenestin or placebo treatment groups on a 3:2 ratio for a 12-week treatment period. A total of 120 women were randomized, 72 to Cenestin, and 48 to placebo.

The treatment regimen consisted of 3 possible dose levels: 0.3 mg/day, 0.625 mg/day, or 1.25 mg/day, with placebo tablets matching the 3 dose levels to maintain the blind for the placebo group. At the time of randomization, all subjects were assigned to receive the 0.625 mg dose level (or placebo). After 1 week of treatment, the investigator was allowed to determine dose titration as follows:

> "Women not receiving sufficient symptomatic relief after 7 days may have had their dose increased to 2 x 0.625 mg (a total of 1.25 mg) per day at the discretion of the investigator. Women who exhibited an intolerance to the treatment drug at any time had their dose decreased." (Study report, section 9.4.1)

Insufficient symptomatic relief was defined as the number of MSVS in the first week on treatment not reduced by at least 50% from the patient's baseline average (Vol. 1.11; protocol; section 11.2.3.2). An increase in dose to 1.25 mg was only an option at the Week 2 visit (after 1 week on treatment). Reduction in dose by 1 level (1.25 mg to 0.625 mg, or 0.625 mg to 0.3 mg) was allowable at any visits from Week 2 until the end of the 12-week treatment period. The actual dose regimens observed are shown in Table 2.

The applicant reported the mean change in number of MSVS per week at weeks 4, 8, and 12 as the primary endpoints. All 3 time points are included in this review, but the Medical Officer considers the 4 week and 12 week time points to be primary. Cenestin must be statistically better than placebo at both time points, so no adjustment for the 2 endpoints is necessary.

The sponsor analyzed the Kupperman Index for change in severity of vasomotor symptoms as an additional secondary variable. This is not of interest to the Medical Officer, and is therefore not included in this review.

Table 2: Observed Dosing Regimens (ITT): Study #366

	Cenestin (n=70)		Placebo (n=47)	
	n	%	n	%
Remained on 0.625 mg dose	7	10%	9	20%
Increased to 1.25 mg dose at week 1 (no further changes)	54	77%	34	74%
Increased to 1.25 mg dose at week 1; Returned to 0.625 mg dose after week 1 (no further changes)	5	7%	2	4%
Increased to 1.25 mg dose at week 1; Returned to 0.625 mg dose at week 2 or later; Decreased to 0.3 mg dose at week 4 or later; (no further changes)	2	3%	0	0%
Decreased to 0.3 mg dose at week 1 or later (no further changes)	2	3%	0	0%
Decreased to 0.3 mg dose at week 1 or later; Returned to 0.625 mg dose at week 2 or later (no further changes)	0	0%	1	2%
Missed titration visit (stayed at 0.625)	0	0%	1	2%

Source: Vol. 4.2 and 1.13; Table 11.4.1.3-1 and Apdx. 16.2.5.3.1

This study included 4 centers, with 3 investigators. One of the investigators oversaw 2 of the centers (Site # 1 and 2). The enrollment of subjects was not evenly distributed across the centers, with one center (Site #4) having 57% of the subjects (See Table 3).

Table 3: Enrollment by Center (All Randomized): Study #366

	Cenestin (n=72)		Placebo (n=48)		Total (n=120)	
Site #; (Location); [Investigator]	n	%	n	%	n	%
1 (Lincoln, NE) [1]	11	15%	7	15%	18	15%
2 (Omaha, NE) [1]	13	18%	6	13%	19	16%
3 (Phoenix, AZ) [2]	8	11%	7	15%	15	13%
4 (Cincinnati, OH) [3]	40	56%	28	58%	68	57%

Source: Vol. 4.2, Section 10.1; and data listings

A total of 120 patients were randomized to the 2 treatment groups. The 2 groups were similar with regard to demographic characteristics at baseline, as shown in Table 4.

Table 4: Demographic characteristics (Study #366)

	Cenestin (n=72)	Placebo (n=48)
	Mean (SD)	Mean (SD)
Age (years)	49 (6)	48 (4)
Duration since last menses (months)	87 (109)	85 (92)
Weight (lbs.)	163 (34)	168 (32)
Baseline mean number of MSVS per week	97 (43)	94 (34)
	N (%)	N (%)
Race		
Caucasian	48 (67)	34 (71)
Black	21 (29)	12 (25)
Other	3 (4)	2 (4)
Smoker	21 (29)	15 (31)

Source: Vol. 4.2, Table 11.2-1

Due to the uneven distribution of the number of subjects per center across the 4 centers, this reviewer checked the demographic characteristics by center. All 4 centers had similar results for these demographic variables, except for the baseline mean number of MSVS. This will be discussed further as part of the efficacy analyses.

The disposition of the subjects in the 2 treatment groups was similar in terms of both the number of dropouts at any stage and the reason for dropouts (see Tables 5 & 6). The applicant had anticipated a dropout rate of 17% by Week 4. The actual discontinuation rate was lower than planned: only 5% at Week 4, and 9% at the end of the study at Week 12.

Of the 120 subjects randomized, 117 were included in the Intent-to-treat (ITT) population for the analyses. Two subjects dropped shortly after randomization and did not complete the diary used for the efficacy evaluation. A third subject (#048) was dropped from the efficacy analysis for being non-compliant and was judged a poor historian. This decision was agreed to by the FDA (Vol. 4.2; Section 11.4.2.2).

Table 5: Disposition of subjects by group (Study #366)

	Cenestin		Placebo	
	n	rand. %	n	rand. %
Randomized	72	100.0	48	100.0
Intent-to-treat	70	97.2	47	97.9
Completed Week 4	69	95.8	45	93.8
Completed Week 8	68	94.4	44	91.7
Completed Week 12	67	93.1	42	87.5

Source: Vol. 4.2, Table 10.1-1

Table 6: Reasons for Discontinuation (Study #366)

	Cenestin		Placebo	
	n	rand. %	n	rand. %
Dropped After Rand. (not ITT)				
Poor Compliance	1	1.4 %	0	0.0 %
Adverse event	1	1.4 %	0	0.0 %
Patient Request	0	0.0 %	1	2.1 %
Dropped by Week 4				
Adverse event	1	1.4 %	0	0.0 %
Patient Request	0	0.0 %	2	4.2 %
Dropped by Week 8				
Poor Compliance	1	1.4 %	0	0.0 %
Patient Request	0	0.0 %	1	2.1 %
Dropped by Week 12				
Adverse event	1	1.4 %	2	4.2 %

Source: Vol. 4.2, Section 10.1

Table 7 shows the dropouts by centers, and indicates the dropout rate was not consistent across the centers. Site #4 had a statistically higher dropout rate than the other centers (Likelihood ratio test; p-value = 0.0245). Due to the small number of subjects in Sites 1, 2, and 3, it is difficult to make any conclusions about the impact this differential dropout rate may have had on the results.

Table 7: Disposition of subjects by center (Study #366)

	Site #1 (n=18)		Site #2 (n=19)		Site #3 (n=15)		Site #4 (n=68)		Total (n=120)	
	n	%	n	%	n	%	n	%	N	%
Discontinued	0	0%	0	0%	1	7%	10	15%	11	9%
Did not Disc.	18	100 %	19	100 %	14	93%	58	85%	109	91%

Source: Vol. 4.2 and 1.13; Table 10.1-2 and Apdx. 16.2.5.3.1

Applicant's Analysis

The Intent-to-treat (ITT) population is defined as all subjects randomized who completed at least 1 week of the symptom diary during the treatment period. The last observation carried forward (LOCF) approach was used for any missing time points after the first week.

The applicant's analysis plan, as described in Section 9.7.1.1 of the study report, proposed an ANOVA model with treatment, center, and treatment-by-center interaction terms be used for each of the 3 time points separately. If the treatment-by-center interaction term was not significant (alpha level not given), this term would be dropped, and the ANOVA analyses would be repeated with only the treatment and center terms. The assumptions for the ANOVA model would be tested on the residuals. If the assumptions were not met, a non-parametric approach with center as a blocking factor would be applied to each time point of interest.

The applicant followed all of the planned analysis steps. The treatment-by-center interaction terms were not statistically significant in the first ANOVA models (all p-values > 0.47), and were dropped. The residual analyses of the ANOVA models with only the treatment and center terms showed that the normality assumption was not met, but the results of the non-parametric analyses reached the same conclusions as the ANOVA models. The results of the ANOVA models appear in Table 8.

Table 8: Applicant's Results (ITT; n=117): (Study #366)

	Cenestin (n=70)	Placebo (n=47)	Diff. *	p-value: Between Group Comp.	C.I. on Diff	Meaningful Clin. Diff. (From protocol)
Efficacy Variables	Mean (SD)	Mean (SD)	Lsmeans (SE)			
Mean change in number MSVS from baseline to:						
Week 4	-68.1 (44)	-48.4 (46)	-19.9 (8.6)	0.0224	-36.9, -2.9	-28
Week 8	-78.3 (49)	-54.3 (49)	-24.6 (9.4)	0.0101	-43.2, -6.0	-28
Week 12	-80.3 (50)	-56.3 (48)	-24.7 (9.4)	0.0102	-43.4, -6.0	-28

Source: Vol. 4.2, Table 11.4.1.1-1

* A negative value for the estimated difference favors Cenestin.

In the sample size calculations (Study report, Section 9.7.2), the applicant proposed 4 MSVS per day (28 per week) as a clinically meaningful difference between the 2 groups for the mean change from baseline in the number of MSVS per week. The observed difference at all 3 time points was less than 28. However, the observed placebo effect was much greater than the applicant had anticipated (a decrease from baseline of 15 MSVS within placebo group was used for planning). The Medical Officer feels the magnitude of the observed difference between the groups, along with the statistical significance of this difference, is sufficient without meeting the clinically meaningful difference of 28 MSVS per week.

The applicant discussed the variable dosing regimen in terms of the observed regimens (Vol. 4.2; Table 11.4.1.3-1). The results were not investigated by the actual dose received, and the applicant did not discuss how changes in dose level might have impacted the efficacy results.

The applicant concludes that the ANOVA results provide sufficient evidence for the efficacy of Cenestin. Specifically, there was a statistically significant larger reduction in mean number of MSVS per week for the Cenestin group than the placebo group by week 4 on treatment, which continued through week 12.

Reviewer's Analysis

The ITT population used by the applicant is appropriate, and the applicant followed the planned analysis from the protocol. However, during this review, two questions arose which require further investigation.

The first is a request from the Medical Officer to consider how the actual dose received may have impacted the efficacy results. The applicant is requesting approval for 4 dose levels of Cenestin, although only 3 of those were included in Study #366. The Medical Officer hopes an analysis by actual dose level will provide information toward assessing the performance of the different dose levels in the submission. Subjects were not randomized to the different dose levels, so this information is only for exploratory purposes. Descriptive statistics for the actual dose received prior to each of the time points of interest are shown in Table 9 (next page) and suggest:

- There is insufficient data to assess the 0.3 mg/day dose.

- For the 0.625 mg/day dose, the reduction in mean number of MSVS per week for the Cenestin group is similar to placebo at week 4 , but somewhat higher (13 units) at weeks 8 and 12.

- The 2 x 0.625 (1.25 mg/day) dose of Cenestin shows a larger reduction in mean number of MSVS per week (25 to 28 units) than placebo at weeks 4, 8, and 12.

- It appears that placebo responders were more likely to remain on the 0.625 mg/day dose, while the placebo non-responders were more likely to receive the 2 x 0.625 (1.25 mg/day) dose. This would be expected with this type of dose-escalation study design.

Table 9: Descriptive statistics by Actual Dose (ITT; n=117): (Study #366)

		Actual Dose					
		0.3 mg/day		0.625 mg/day		2 x 0.625 mg/day (total 1.25 mg/day)	
		Cenestin	Placebo	Cenestin	Placebo	Cenestin	Placebo
Week 4 (dose level received at Week 2 Visit)	N	0	1	13	10	57	36
	Mean		-87.0	-69.7	-65.6	-67.7	-42.5
	SD			29	40	47	47
	Range			-127, -40	-126, -15	-239, 15	-239, 14
Week 8 (dose level received at Week 6 Visit)	N	1	0	13	12	56	35
	Mean	-67.5		-83.6	-70.0	-77.2	-48.9
	SD			26	35	53	53
	Range			-127, -44	-134, -15	-317, 7	-247, 34
Week 12 (dose level received at Week 10 Visit)	N	4	0	11	13	55	34
	Mean	-89.5		-86.2	-73.2	-78.4	-49.8
	SD	23		35	35	54	51
	Range	-123, -75		-161, -47	-133, -15	-326, 7	-246, 22

Source: Patient Listings in Appendix 16.2.5.3.1 (Vol. 1.13) and SAS datasets

The second item of concern relates to the unbalancedness of the baseline MSVS values across the 4 centers (see Table 10 below and Figure 1 in the Appendix). The mean MSVS per week at baseline in Site #4 is much higher than in the other 3 centers, which were similar to each other. The higher baseline MSVS in Site #4 corresponds to larger decreases in mean number MSVS per week during the treatment period. The difference in the reduction of MSVS between the Cenestin and placebo treatment groups is much larger in Site #4 than in the other centers (see Table 1 in the Appendix). Since Site #4 had 57% of the enrolled subjects, and much larger between-group differences, the results from this single center appear to be driving the overall results of this study.

Table 10: Baseline Number of MSVS per Week by Center (ITT; n-117): (Study #366)

	Site #1		Site #2		Site #3		Site #4	
	Cenestin	Placebo	Cenestin	Placebo	Cenestin	Placebo	Cenestin	Placebo
N	11	7	13	6	8	7	38	27
Mean	84.8	99.0	76.0	86.6	83.5	99.0	110.2	93.2
SD	19	14	12	26	20	21	52	42
Min	61.5	77.6	62.5	60.5	62.0	63.0	63.0	64.0
Max	125.5	119.0	95.2	137.5	122.5	133.5	325.8	254.0

Source: SAS datasets

The applicant tested for a treatment-by-center interaction in the ANOVA analyses, but concluded there was no statistically significant interaction (all p-values ≥ .47). However, with small sample sizes, particularly in 3 of the 4 centers, this study does not have the power to detect this interaction if present. Therefore, the non-significant p-values do not prove that no interaction was present in this study.

Site #4 is the one that does not resemble the rest of the centers at baseline, and which has the majority of the subjects in this study. The subjects with the higher baseline MSVS values observed in Site #4 correspond to larger reductions on treatment. Since the results from this center may be driving the conclusions in the overall analyses, this reviewer investigated how the results would differ if Site #4 was removed from the analyses. Site #4 was dropped from the data set and this reviewer reran the ANOVA analyses performed by the applicant. The results indicate there was not a statistically significant difference between Cenestin and placebo in the reduction in mean number of MSVS per week at any of the time points of interest (all p-values ≥ 0.31). However, this analysis had a very small sample size (total n=52) which means the results are inconclusive. Table 1 in the Appendix presents the efficacy results by center. It is not possible to conclude that the results from Sites 1-3 do not support the efficacy of Cenestin, but only that there were not enough subjects in these 3 centers to provide sufficient evidence.

Thirteen subjects from Site #4 (10 in Cenestin group, 3 in placebo group) had baseline values for the mean number of MSVS per week which were higher (140 or above) than the largest value (137.5) from any of the other 3 centers (see Table 3 in the Appendix). The Medical Officers identified a value of 200 MSVS per week as a cut-off for extreme baseline scores. There were 3 subjects in Site #4 with a baseline value above 200, all of whom had correspondingly large reductions in MSVS per week. As an exploratory analysis, these 3 subjects were dropped from the data set and the ANOVA model was rerun. The mean MSVS per week by center for the data set without the 3 subjects is shown in Table 2 of the Appendix (page 15). The ANOVA results, using the same model as the applicant used, indicate there is a statistically significant difference in the reduction of mean number of MSVS per week between the 2 treatment groups at all 3 time points of interest (all p-values ≤ .01). These results suggest that the strength of the evidence from the subjects who were not extreme at baseline is sufficient to support the applicant's conclusions.

Conclusions - Study #366

The baseline mean number of MSVS per week is significantly higher in Site #4 than in the other 3 centers combined. Site #4 had 57% of the subjects enrolled, and the between-group differences in the reduction in mean number of MSVS per week was much greater in that center than in the other 3 centers. It appears that Site #4 is driving the overall results. For example, at Week 12, the treatment effect at Site 4 showed a 36.1 MSVS per week larger reduction for the Cenestin group than for the placebo group. At the other 3 sites, the treatment effect at Week 12 was 18.6, 5.7, and 4.4 (see Table 1 in Appendix).

The applicant did not discuss the difference between the centers in baseline mean number of MSVS per week, and did not investigate the impact of this imbalance on the efficacy results. The applicant concluded that there was a statistically significant larger reduction in mean number of MSVS per week for the Cenestin group than the placebo group by week 4 on treatment, which continued through week 12.

Exploratory analyses by this reviewer suggest that, without the subjects at Site #4, there is not sufficient evidence to conclude a statistically significant difference between the Cenestin and placebo treatment groups for the reduction in mean number of MSVS per week at any of the 3 time points of interest. However, if only the 3 subjects with extremely high baseline values for mean MSVS per week (>200 per week) are dropped from the analyses, there is sufficient evidence to support a statistically significant difference between the Cenestin and placebo treatment groups at weeks 4, 8 and 12 on treatment. These are exploratory analyses only, and suggest the need for further investigation of the relationship between baseline patient status and the efficacy of Cenestin versus placebo.

Summary

Overall, patients randomized to Cenestin had significantly greater reductions in MSVS per week than did patients randomized to placebo. The efficacy results, however, are being driven by one large center that had 57% of the enrolled subjects. Some subjects at this center (Site #4) had baseline values for the mean number of MSVS per week which were much higher than any subjects at the other 3 centers. These issues, especially the relative size of Site #4, raise concerns about the representativeness of the patients enrolled at Site #4 to the target population, and therefore the overall results as well.

Exploratory analyses were used to investigate the impact of Site #4, and in particular that of the subjects with high baseline values, on the efficacy results. These exploratory analyses suggest:

- If Site #4 is excluded, there is not sufficient evidence from the remaining 3 centers in this study to support a difference in the reduction in mean number of MSVS per week between the 2 treatment groups.

- If only the subjects with extreme values at baseline for mean number of MSVS per week (> 200) are excluded from the analysis, there is sufficient evidence to support a difference in the reduction in mean number of MSVS per week between the 2 treatment groups. This relies on the assumption that, by dropping the 3 subjects with the most extreme baseline values, Site #4 then represents the same patient population at baseline as the other 3 centers.

Because the results are being driven by one center which differs from the other centers in both the baseline values and the size of the treatment effect, this reviewer would prefer to use caution before reporting statistical conclusions in the label. The Medical Officer has proposed the label use wording such as "results indicate Cenestin produced a reduction" in MSVS, rather than a statistically significant reduction.

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Mathematical Statistician

Concur: Dr. Nevius 2/23/99
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cc:
Archival NDA 20-992
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HFD-580/TvanderVlugt, MMann, LRarick
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HFD-715/ENevius, LKammerman, KMeaker, Division File, Chron

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APPENDIX

Table 1: Efficacy Results by Site (ITT; n=117) Study #366

Mean MSVS per week	Site 1			Site 2			Site 3			Site4		
	Cenestin (n=11)	Placebo (n=7)		Cenestin (n=13)	Placebo (n=6)		Cenestin (n=8)	Placebo (n=7)		Cenestin (n=38)	Placebo (n=27)	
	Mean (SD)	Mean (SD)	Diff (C-P)	Mean (SD)	Mean (SD)	Diff (C-P)	Mean (SD)	Mean (SD)	Diff (C-P)	Mean (SD)	Mean (SD)	Diff (C-P)
Baseline	84.8 (19)	99.0 (14)		76.0 (12)	86.6 (27)		83.5 (20)	99.0 (21)		110.2 (53)	93.2 (42)	
Change: Week 4	-69.3 (23)	-59.1 (32)	-10.2	-61.9 (20)	-58.3 (39)	-3.6	-63.8 (36)	-64.1 (45)	0.4	-70.8 (55)	-39.3 (51)	-31.5
Change: Week 8	-77.7 (26)	-55.7 (60)	-22.0	-64.9 (21)	-61.5 (32)	-3.4	-74.3 (30)	-70.1 (46)	-4.1	-83.8 (62)	-48.2 (51)	-35.6
Change: Week 12	-78.1 (26)	-59.5 (55)	-18.6	-66.1 (20)	-60.5 (36)	-5.7	-76.1 (29)	-71.7 (46)	-4.4	-86.6 (64)	-50.5 (50)	-36.1

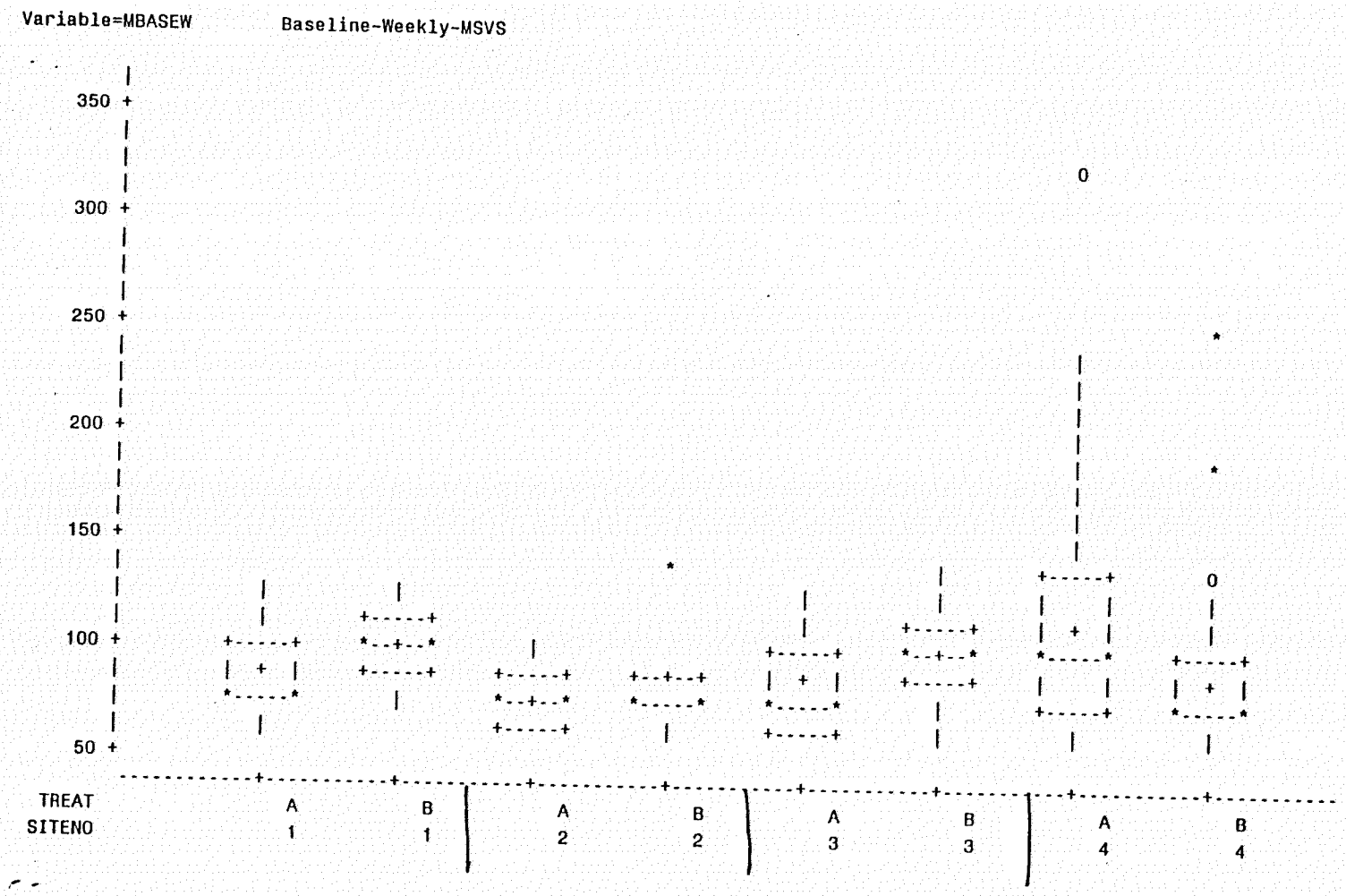
Table 2: Efficacy Results by Site (Drop 3 subjects with baseline MSVS >200; n=114) Study #366

Mean MSVS per week	Site 1			Site 2			Site 3			Site4		
	Cenestin (n=11)	Placebo (n=7)		Cenestin (n=13)	Placebo (n=6)		Cenestin (n=8)	Placebo (n=7)		Cenestin (n=38)	Placebo (n=27)	
	Mean (SD)	Mean (SD)	Diff (C-P)	Mean (SD)	Mean (SD)	Diff (C-P)	Mean (SD)	Mean (SD)	Diff (C-P)	Mean (SD)	Mean (SD)	Diff (C-P)
Baseline	84.8 (19)	99.0 (14)		76.0 (12)	86.6 (27)		83.5 (20)	99.0 (21)		100.8 (33)	87.0 (27)	
Change: Week 4	-69.3 (23)	-59.1 (32)	-10.2	-61.9 (20)	-58.3 (32)	-3.6	-63.8 (36)	-64.1 (45)	0.4	-64.3 (47)	-31.6 (32)	-32.7
Change: Week 8	-77.7 (26)	-55.7 (60)	-22.0	-64.9 (21)	-61.5 (32)	-3.4	-74.3 (30)	-70.1 (46)	-4.1	-74.6 (46)	-40.6 (33)	-34.0
Change: Week 12	-78.1 (26)	-59.5 (55)	-18.6	-66.1 (20)	-60.5 (36)	-5.7	-76.1 (29)	-71.7 (46)	-4.4	-76.3 (46)	-43.0 (32)	-33.3

Table 3: Results for subjects in Site #4 with unusual baseline values for MSVS per week

Pt. No.	Trmt. Group	Baseline MSVS per week	Reduction in number of MSVS per week		
			Week 4	Week 8	Week 12
062	Cenestin	325.8	-238.8	-316.8	-325.8
067	Placebo	254.0	-239.0	-247.0	-246.0
036	Cenestin	232.0	-136.0	-185.0	-219.0
127	Placebo	182.0	-25.0	-78.0	-71.2
075	Cenestin	168.5	-94.5	-99.5	-88.5
073	Cenestin	163.5	-53.5	-78.5	-75.5
069	Cenestin	160.5	-160.5	-160.5	-160.5
032	Cenestin	155.5	-132.5	-140.5	-142.7
039	Cenestin	146.5	-146.5	-146.5	-146.5
066	Cenestin	145.5	-144.5	-145.5	-145.5
078	Cenestin	142.0	-120.0	-142.0	-142.0
126	Cenestin	141.0	-127.0	-127.0	-125.8
080	Placebo	140.0	+11.0	+6.0	+3.0

Figure 1: Baseline MSVS per Week by Treatment Group and Center



TREAT = Treatment group: A=Cenestin B=Placebo