CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-550/S-012

STATISTICAL REVIEW

STATISTICAL REVIEW AND EVALUATION

NDA#:	20-550, SE2-012
APPLICANT:	Glaxo Wellcome Inc.
NAME OF DRUG:	VALTREX® (valacyclovir hydrocholride) caplets
INDICATION:	Treatment of Recurrent Genital Herpes
CLINICAL STUDY #	HS2A4004
DOCUMENTS REVIEWED:	Vol. 1, 2, 5-10
MEDICAL INPUT:	HFD-530: Sumathi Nambiar, M.D.
STATISTICAL REVIEWER:	HFD-725: Rafia Bhore, Ph.D.

A. Introduction

One clinical study (HS2A4004) is being considered in this supplemental New Drug Application (sNDA) which seeks approval for a change in labeling indication for a shorter treatment course of 3 days using VALTREX 500 mg caplets b.i.d (twice daily) in the treatment of recurrent genital herpes. The originally approved treatment regimen—for the treatment of recurrent genital herpes—is VALTREX 500 mg caplets b.i.d (twice daily) for 5 days (NDA 20-550, approved December 1995).

Protocol HS2A4004 was a multicenter, randomized, double-blind, Phase IV study conducted in the United States and Canada on subjects ≥18 years of age in general good heath who had experienced "recurrent" episodes of genital herpes. This study compared the efficacy of VALTREX (valacyclovir, VACV) 500 mg bid 3 day regimen versus the standard regimen of VALTREX 500 mg bid for 5 days. The primary efficacy endpoint to determine equivalence between the 3-day versus 5-day treatment regimen was *time to lesion healing* measured in number of days.

B. Study HS2A4004

1. Study Design

Protocol Title: "A Comparison of Oral VALTREX 500 mg Twice Daily for Three or Five Days for Treatment of Recurrent Genital Herpes" (Study Period: November 1996 – June 1997).

This study was a multicenter, randomized, double-blind trial comparing the efficacy and safety of VACV for 3 days versus 5 days in the episodic treatment of recurrent genital herpes. The subjects enrolled in this study were generally healthy males and females, ≥18 years old with a history of *recurrent genital herpes* defined as either

a) at least 4 episodes in 12 months (0.33 episodes per month) assessed over a minimum of 6 months or a maximum of 12 months (i.e., 2 episodes in 6 months, or 4 episodes in 12 months), or

b) suppressive acyclovir (ACV) therapy during the past 12 months and at least 1 recurrence

within 3 months following the end of suppressive therapy and within 3 months preceding study entry.

Subjects were excluded if any of the following applied: hepatic impairment; impaired renal function; childbearing potential; pregnant females; nursing mothers; history of hypersensitivity to acyclovir or valacyclovir; immunocompromised patients; currently receiving probenecid; currently receiving or had received an investigational drug in 30 days prior to enrollment; and/or, currently receiving or had received systemic antiviral treatment in 7 days prior to starting study drug or immunomodulatory treatments in 30 days prior to starting study drug.

The target enrollment of this study was 920 subjects. At the screening visit, subjects were provided an open-label bottle containing 3-day supplies of VACV 500 mg (taken twice daily) and were asked to self-initiate treatment at the first sign or symptom of a genital herpes recurrence. Subjects were required to visit the clinic within 24 hours of initiation of therapy (Day 1). On Day 1, subjects were stratified by *gender* within that *center* and randomly assigned to one of the two treatment regimens, VACV 500 mg bid or placebo (1:1 ratio), for the final two days of dosing (see Table 1). Accordingly, subjects received a sealed bottle of 2-day supply of either VACV 500 mg or matching placebo to be taken on Days 4 and 5.

Table 1:

Treatment Assignment

		Treatment Group 1 (Test)	Treatment Group 2 (Control)
		VACV 3-days	VACV 5-days
Days 1–3	Open label (Open-label Bottle # 1)	VACV 500 mg b.i.d	VACV 500 mg b.i.d
Days 4–5	Blinded (Sealed Bottle # 2)	Matching Placebo b.i.d	VACV 500 mg b.i.d

Subjects were required to keep a diary card and record the time (date and hour) of prodrome, initiation of study medication, lesion onset, and time of each dose of study medication. Subjects also had to visit the clinic on Days 2-6 for treatment evaluations. If the lesions did not heal or the patient experienced pain/discomfort on Day 6, the patient was followed, thereafter, twice weekly until all signs and symptoms of genital herpes had resolved. Compliance was assessed by counting the number of unused tablets from each bottle at each clinic visit. Subjects were instructed not to take any concurrent antiherpetic therapies, immunomodulatory agents or other investigational drugs during the entire study period. The primary and secondary efficacy endpoints for establishing equivalence between the two treatment groups were *time to lesion healing* (number of days between initiation of therapy and complete re-epithelialization of all lesions; patients with aborted lesions excluded [i.e., those patients whose lesions did not progress past the macule/papule stage and/or who had clinical symptoms of genital herpes but did not develop lesions]) and *duration of pain* (number of days from initiation of treatment or start of pain/discomfort [whichever occurred later] to the complete cessation of pain), respectively. Other efficacy

endpoints were *length of episode* (number of days between initiation of therapy and complete resolution of all signs and symptoms) and *proportion of patients with halted progression of lesions* (i.e., aborted lesions).

Equivalence of efficacy between the two treatment regimens (5-day vs 3-day) was to be established if the 95% confidence interval on the median treatment difference in time to lesion healing was smaller than the assumed clinically significant difference of ±20% of the observed 5-day median time. If the time to event was censored then in the ITT analysis, it was imputed to be the maximum of the observed values.

The assumptions used in the estimation of sample size and the methods for establishing equivalence between the two treatment groups are summarized by the FDA Reviewer in Table 2.

Table 2:

Sample Size Estimates, Assumptions, and Methods of Analyses

	Efficacy Endpoint	Target Enrollment	Number of subjects per group	Recurrence Rate of Genital Herpes	% of Evaluable Subjects	Power	Measure	Method of Comparison†
		N	n					
Primary	**Time to Lesion Healing**	920‡	460	66% (606/920)	66% (400/606) §	80%	Median Difference	95% Hodges-Lehman confidence interval
							Hazard Ratio	95% confidence interval
Secondary	**Duration of Pain**	920††	460	66% (606/920)	100% (606/606)	>80%	Median Difference	95% Hodges-Lehman confidence interval
							Hazard Ratio	95% confidence interval
Other	**Length of Episode**	920	460	66% (606/920)	100% (606/606)	80%	Median Difference	95% Hodges-Lehman confidence interval
							Hazard Ratio	95% confidence interval
Other	**Halted progression of lesions (aborted lesions)**	920	460	66% (606/920)			Proportion of subjects	Cochran-Mantel Haenszel test controlling for center and gender
							Relative risk	95% confidence interval

† Equivalence is established if the 95% confidence limits on median treatment difference is smaller than the clinically significant difference of ±20% of the observed median of the 5-day regimen.

‡ Assumed median treatment difference of time to lesion healing is 0.7 days with variance of 6.25 for sample size evaluation.

§ It is assumed that 34% of subjects will not develop a vesicular lesion, hence 66% of 606 subjects (i.e., 400 subjects) will be evaluable.

†† Assumed median treatment difference of duration of pain is 0.5 days with variance of 5.0 for sample size evaluation.

C. Applicant's Results

1. Subject Accounting

The clinical study report of Protocol HS2A4004 is based on subjects enrolled in 48 centers—34 centers in the United States and 14 centers in Canada—conducted during the study period November 1996–June 1997. Of the 1,170 subjects enrolled, 800 subjects were randomized to one of the two treatment groups and 370 subjects were not randomized. Table 3 below gives an accounting of the subjects in this study in terms of number of subjects randomized, those who completed the study and those who discontinued the study.

Table 3:

Subject Accounting

Number of Subjects	VALTREX 5-day (Control Group)	VALTREX 3-day (Test Group)	Total Randomized
Randomized to Treatment	398	402	800
Completed study	362	359	721 (90.1%)
Discontinued study	36	43	79 (9.9%)
due to consent withdrawn	2	2	4 (0.5%)
due to loss-to-follow-up	3	6	9 (1.1%)
due to protocol violation	31	35	66 (8.3%)

Number of study centers = 48
Number of subjects enrolled (N) = 1,170
Number of subjects randomized to treatment = 800 (68% of 1170) †
Number of subjects not randomized to treatment = 370 (32% of 1170)
Percentages in table are calculated based on the sample size in each group.
† Of the 1,170 enrolled subjects, 68% of the subjects satisfied the criteria of a "recurrent" episode of genital herpes along with other study eligibility criteria.

Reviewer's Comments:

As shown in Table 3, of the 800 subjects randomized to treatment, 721 (90.1%) subjects completed the study and the remaining 79 (9.9%) were classified as discontinuations. A high number of these discontinuations were due to protocol violations (66/79 = 83.5%). The FDA reviewer notes that, of the 66 subjects, 49 subjects developed lesions and contributed to the ITT population (45 with complete observations on the primary endpoint of time to lesion healing and 4 with censored observations) while the remaining 17 subjects had aborted lesions and were excluded from the ITT population. Further details on discontinued subjects contributing to the ITT population are discussed in Section 3a Analysis Population—Intent-to-Treat.

2. Demographics and Baseline Characteristics

The distribution of subjects in the two treatment groups (5-day regimen vs 3-day regimen) were generally similar in terms of the demographics such as age, sex, and race. These demographics are summarized in Table 4.

Overall, the study had more women subjects (~63%), and the predominant ethnic origin of the subjects was Caucasian (~85%).

Table 4:

Demographics

Characteristic	VALTREX 5-day (Control Group)	VALTREX 3-day (Test Group)	Total Randomized
	n=398	n=402	N=800
Age (Yrs)			
Mean (Std. Dev.)	36 (10.3)	36 (11.2)	36 (10.7)
Median	34	35	34
Range	18 to 74	18 to 82	18 to 82
Sex			
Female	252 (63.3%)	253 (62.9%)	505 (63.1%)
Male	146 (36.7%)	149 (37.1%)	295 (36.9%)
Race			
Caucasian/White	335 (84.2%)	343 (85.3%)	678 (84.7%)
Black	36 (9.0%)	32 (8.0%)	68 (8.5%)
Other	27 (6.8%)	27 (6.7%)	54 (6.8%)

Other baseline characteristics included the history of HSV infections such as the number of recurrent episodes of herpes in the previous 12 months, hours from first sign or symptom to initiation of treatment, and number of subjects with previous suppressive therapy (see Table 5 and Figure 1).

Table 5:

History of Herpes Simplex Virus (HSV) Infections

Characteristic		VALTREX 5-day (Control Group) n=398		VALTREX 3-day (Test Group) n=402		Total Randomized N=800	
		n	(%)	n	(%)	N	(%)
Recurrences in past 12 months	Previous Antiherpes Treatment?						
1-3	Yes	4	(1.0%)	7	(1.7%)	11	(1.4%)
	No	17	(4.3%)	14	(3.5%)	31	(3.9%)
	Total	21	(5.3%)	21	(5.2%)	42	(5.3%)
≥4	Yes	34	(8.5%)	25	(6.2%)	59	(7.4%)
	No	343	(86.2%)	356	(88.6%)	699	(87.4%)
	Total	377	(94.7%)	381	(94.8%)	758	(94.8%)
Total		398	(100.0%)	402	(100.0%)	800	(100.0%)
Hours since 1st sign/symptom to first treatment							
Mean (Std. Dev.)		8.8	(13.2) hrs	7.2	(10.1) hrs	8.0	(11.8) hrs
Median		3.5	hrs	3.0	hrs	3.3	hrs
Range		0 to 82 hrs		0 to 70 hrs		0 to 82 hrs	

Reviewer's Comments:

The FDA reviewer examined whether the 800 randomized subjects met the definition of recurrent genital herpes as stated in the protocol. Majority of the subjects (769/800 = 96.1%) met the criteria of recurrent genital herpes (758 subjects had 4 or more recurrent episodes of genital herpes in the 12 months prior to enrollment in the study and approximately 11 subjects who had <4 episodes in the previous 12 months also had prior suppressive antiherpes therapy). However, 31 (~3.9%) subjects who had <4 recurrent episodes did not have any prior suppressive antiherpes treatment. These 31 subjects did not satisfy the definition of "recurrent genital herpes" as given by the Sponsor in the protocol.

Regarding initiation of therapy by the subjects at the first sign or symptom of genital herpes, the distribution of hours to initiate therapy was generally similar in both treatment groups (see Figure 1). The median

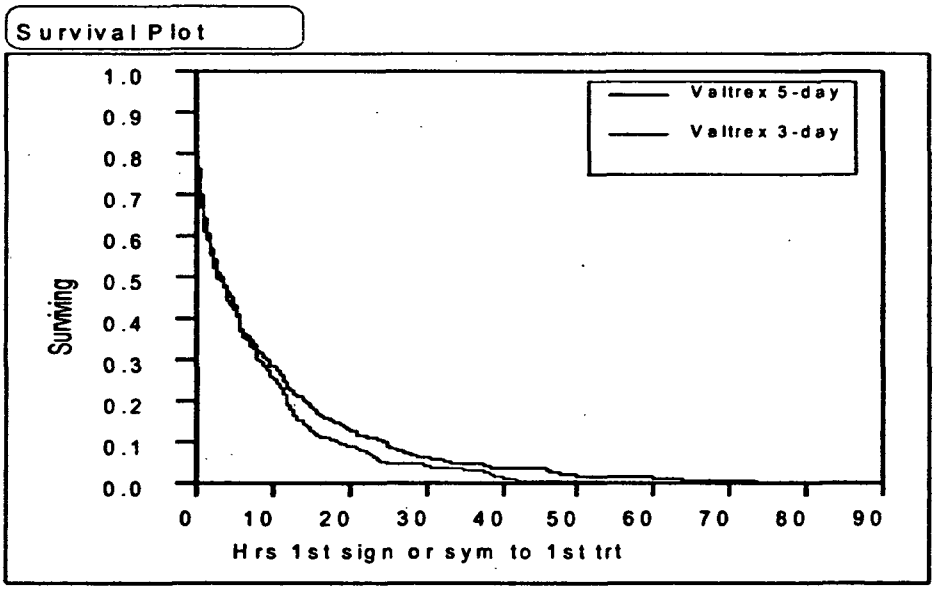
hours to initiation of treatment were similar (3.5 hrs [5-day] vs 3.0 hrs [3-day]), but the mean hours to initiation of treatment were significantly different (8.8 hrs [5-day] vs 7.2 hrs [3-day]). According to the protocol, patients were required to self-initiate treatment within 24 hours after the onset of a recurrent episode of genital herpes. However, approximately 10% of the patients started therapy after that window (see Figure 1).

Figure 1:

Proportion of Patients who Initiated Treatment at 1st Sign or Symptom
Comparison by Treatment Groups

Product-Limit Survival Estimates

Time Variable: Hours since 1st sign or symptom to 1st treatment



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	3.7252	1	0.0536
Wilcoxon	1.3380	1	0.2474

3. Efficacy Results

a. Analysis Population—Intent-to-Treat

Of the 800 subjects who were randomized to treatment, 592 subjects developed lesions and contributed to the intent-to-treat (ITT) analysis for the primary efficacy endpoint of *time to lesion healing*. The remaining 208 subjects had aborted episodes of lesions (or halted progression of lesions). These 208 subjects were excluded from the intent-to-treat primary efficacy analysis. Table 6 shows a breakdown of the intent-to-treat population for the primary efficacy analysis.

Among the ITT population of 592 subjects who had lesions, 532 subjects completed the study and 60 subjects (1 had a missing endpoint) were classified by the Sponsor as discontinuations.

Table 6:

Intent-to-Treat Population for
Primary Efficacy Analysis on Time to Lesion Healing
(Aborted Lesions Excluded)

			VALTREX 5-day (Control Group) n = 292	VALTREX 3-day (Test Group) n = 300	Total N = 592
Lesion Episode	Completed Study?	Censor Status for Lesions			
With Lesions	Yes		267	265	532
	No	Missing ‡	0	1	1
		Yes	2	6	8
		No	23	28	51
		Total	25	35	60
	Total		292	300	592†

† Primary efficacy analysis was performed on 591 subjects who developed lesions while 1 subject had a missing endpoint. Censored observations were imputed with the maximum of the observed values and missing observation was dropped from the ITT analysis.

‡ No post-randomization data available.

Reviewer's Comments:

Although there appears to be a high percentage of discontinuations (60/592 = 10%), only 8 subjects in the ITT population had censored observations, 1 had a missing endpoint and the remaining 51 subjects had complete observations on the primary endpoint of *time to lesion*

healing. The eight censored observations were discontinuations due to the following reasons—1 due to withdrawn consent, 3 due to loss-to-follow, and 4 due to protocol violations. The censored observations were imputed to be the maximum of the observed values and the 1 missing observation was dropped from the ITT analysis.

In summary, the ITT population for primary efficacy analysis on *time to lesion healing* had 583 subjects with complete observations, 8 subjects with censored observations, and 1 with a missing endpoint.

b. Efficacy Endpoints

Time to Lesion Healing

Primary efficacy analysis on time to lesion healing was performed on the median difference between the two treatment groups and the hazard ratio of the two treatment groups (see Table 7).

Table 7:

Intent-to-Treat Efficacy Analyses on
Median Treatment Difference

	Efficacy Endpoint	VACV 5-day (Control) Number of Subjects	VACV 3-day (Test) Number of Subjects	VACV 5-day (Control) Median	VACV 3-day (Test) Median	Median Difference VACV 5-day vs VACV 3-day	95% Confidence Interval on Median Difference
Primary	Time to Lesion Healing	292	299	4.7 days	4.4 days	0.1 days	(-0.1, 0.4)
Secondary	Duration of Pain	398	401	2.5 days	2.9 days	-0.1 days	(-0.5, 0.0)
Other	Length of Episode	398	401	4.4 days	4.3 days	0.0 days	(-0.2, 0.2)

The median time to lesion healing for the VALTREX 5-day treatment group was 4.7 days versus 4.4 days for the VALTREX 3-day treatment group. The median treatment difference between the two groups (5 day – 3 day) was 0.1 days with a 95% confidence interval on the median difference being (-0.1 days, 0.4 days). The lower bound of 0.1 days on the median difference (5 day – 3 day) in *time to lesion healing* was less than the prespecified clinically equivalent lower bound of approximately 1 day (i.e., -20% of the median of the 5-day treatment group).

Reviewer's Comments:

Note that median treatment difference is not the same as difference in medians for the 2 treatment groups. Median difference is calculated by computing differences in all possible pair of observations from the 2 treatment groups and then finding the median (50^{th} percentile) of that distribution. Difference in medians makes a comparison of the population in one treatment group versus another, while median difference (although difficult to interpret) may give a measure of central tendency for the difference in healing time if an individual was randomly assigned to one group versus another.

In addition, a Cox's Proportional Hazards model was developed for the primary endpoint of *time to lesion healing* with treatment groups (5-day vs 3-day), gender (males vs females), and center (larger centers vs a collection of small centers) as covariates. (See Table 8.) This model included only the main effects.

Table 8:

Intent-to-Treat Efficacy Analyses on Hazard Ratios

	Efficacy Endpoint	Hazard Ratio	95% Confidence Interval on Hazard Ratio	p-value
Primary	Time to Lesion Healing			
	Valtrex 5-day vs Valtrex 3-day	0.95	(0.81, 1.13)	0.586 †
	Males vs Females	0.84	(0.70, 1.00)	0.050 * †
Secondary	Duration of Pain	1.15	(0.99, 1.33)	0.056 ‡
Other	Length of Episode			
	Valtrex 5-day vs Valtrex 3-day	1.05	(0.91, 1.22)	0.472 §
	Males vs Females	0.81	(0.69, 0.95)	0.010 ** §

† Based on Cox's proportional hazards model with main effects of treatment, gender and center.
‡ Based on Cox's proportional hazards model stratified by gender and covariates of treatment groups and center. Since the assumption of proportional hazards for males vs females was not satisfied in terms of duration of pain, stratification was done based on gender.
§ Based on Cox's proportional hazards model with treatment, gender and center as covariates.
* P-value = 0.05 is marginally statistically significant at 0.05 level.
** P-value = 0.01 is statistically significant at 0.05 level.

Reviewer's Comments:

The FDA reviewer confirmed that the proportional hazards assumptions of the model for time to lesion healing were satisfied and the Applicant's

results were consistent with the analysis done by the FDA reviewer.

The hazard ratio of VALTREX 5-day vs 3-day for *time to lesion healing* was 0.95 with a 95% confidence interval of (0.81, 1.13) and a *p-value* of 0.586, further showing consistency of the efficacy results using the endpoint for median difference.

Reviewer's Comments:

Two separate analyses on time to lesion healing were also performed by the FDA reviewer, namely, a) a Cox's proportional hazards model with the main effects of treatment, gender, and center, and a treatment by gender interaction, and b) a Cox's proportional hazards model stratified by gender with treatment and center as covariates. There was no significant treatment by gender interaction effect (p-value = 0.959) and both models led to the same conclusions given above.

Table 9:

Subgroup Efficacy Analyses within Gender on
Median Treatment Difference
Intent-to-Treat Population

	Efficacy Endpoint	Subgroup	VACV 5-day (Control) Median	VACV 3-day (Test) Median	Median Difference VACV 5-day vs VACV 3-day †	95% Confidence Interval on Median Difference
Primary	Time to Lesion Healing	Males	4.9 days	4.6 days	0.2 days	(-0.2, 0.7)
		Females	4.5 days	4.1 days	0.1 days	(-0.2, 0.5)
Secondary	Duration of Pain	Males	2.0 days	2.5 days		
		Females	2.9 days	3.0 days		

† Subgroup analysis using Hodges-Lehman confidence interval was computed only for the primary endpoint, not for the secondary endpoint.

Table 9 shows subgroup analysis for *time to lesion healing* within each gender with respect the median treatment differences. Also, see **Figure 2** for an overall distribution of proportion of patients not healed for males vs females.

Reviewer's Comments:

There was a marginally significant difference in time to lesion healing between males vs females. Males generally took longer to heal than females. Even though the primary analysis was not stratified by

gender, the subgroup analysis for males and females showed that the lower bound for median difference in *time to lesion healing* (5-day – 3 day) was no worse than 0.2 days, which is not different from the results of the primary analysis of 0.1 days. Both of the lower bounds are less than the prespecified clinically equivalent lower bound of approximately 1 day (i.e., -20% of the median of the 5-day treatment group).

The Applicant has incorrectly interpreted the hazard ratios for males vs females throughout the clinical study report. For example, on page 21 of the Clinical Study Report (i.e., page 53 of Vol. 2 of 11), the Applicant incorrectly says, "The hazard ratio for gender suggested that males may tend to heal sooner than females (hazard ratio 0.84; 95% CI [0.70, 1.00]; p=0.05)." A lower hazard ratio for males implies longer survival rate or longer time to heal. This can also be seen from the treatment medians in Table 9.

Duration of Pain and Length of Episode

Table 7 and Table 8 also show efficacy results for the secondary endpoint of *duration of pain* and for the other endpoint of *length of episode.* There was no statistically significant difference between the VALTREX 5-day treatment group and VALTREX 3-day treatment group with respect to these endpoints.

In addition, **Figure 4**, **Figure 5**, **Figure 6**, and Figure 7 show the survival distributions for *duration of pain* and *length of episode* by treatment groups and by gender (i.e., proportion of patients in the intent-to-treat population who were *still experiencing pain* or whose *lesions had not completely resolved* as compared across treatment groups or across gender).

Reviewer's Comments:

Although *duration of pain* between the two treatment regimens (5-day vs 3-day) was not statistically significant, there appeared to be a trend of shorter *duration of pain* in the patients who took VALTREX for the standard regimen of 5-days versus those patients who took VALTREX for only 3-days. Also, males generally had a shorter *duration of pain* as compared to females. However, after stratifying for gender, the Cox's proportional hazards model showed no statistically significant difference between VALTREX 5-day regimen vs 3-day regimen.

The FDA reviewer also evaluated the pain endpoint that is mentioned in the label for VALTREX, namely, *time to cessation of pain.* The Applicant did not describe this endpoint in the clinical study report. *Time to cessation of pain* is defined as the number of days from the start of therapy to the complete cessation of pain. The median *time to cessation of pain* in both treatment groups was about 3 days in both

treatment groups (5-day vs 3-day) as shown in Table 10.

Table 10:

Median Duration of Pain vs Time to Cessation of Pain
Intent-To-Treat Population

	VACV 5-day (Control) n=398	VACV 3-day (Test) n=401
Duration of Pain	2.5 days	2.9 days
Time to Cessation of Pain	2.7 days	3.0 days

With respect to the *length of episode*, the effect of *gender* (males vs females) was statistically significant with a hazard ratio of 0.81, 95% CI of (0.70, 0.95) and *p-value* of 0.01 (also see **Figure 6**). Since males had a lower hazard or longer survival than females, this indicated that males had a longer length of episode compared to females. Once again the FDA reviewer notes that the Sponsor has incorrectly interpreted this hazard ratio on page 56, Vol. 2 of 11 of the NDA, by saying that "...suggesting that males may have a shorter length of episode than females".

Aborted Lesions

The proportion of patients with *aborted lesions* (i.e., halted progression of lesions) in the VALTREX 5-day treatment group were not statistically significantly different from those in the VALTREX 3-day treatment group. The relative risk ratio of 5-day vs 3-day groups was 1.04 with a 95% CI of (0.83, 1.32) and *p-value* of 0.728. This was based on the Cochran-Mantel-Haenszel test controlling for center and gender effects.

However, the proportion of patients with aborted lesions was higher in females vs males in both treatment groups (31% and 29% of females in the 5-day vs 3-day group and 19% and 20% males in the 5-day vs 3-day group had aborted lesions).

D. Applicant's Conclusions

The efficacy of the VALTREX 500mg twice daily for 3-days regimen is equivalent to the approved treatment regimen of VALTREX 500 mg twice daily for 5-days in terms of the primary efficacy endpoint, *time to lesion healing*. With respect to the secondary endpoints of *duration of pain*, *length of episode*, and *proportion of patients with aborted lesions* the two treatment groups (5-day vs 3-day) were numerically similar and statistically not significant.

E. Statistical Reviewer's Summary

Study HS2A4004 compares VALTREX 500 mg bid for 3-days versus the standard regimen of VALTREX 500 mg bid for 5-days for the treatment of recurrent genital herpes. This study showed the following.

1. When treatment duration is reduced from 5 days to 3 days, median time to lesion healing is increased by no more than 0.1 days based on the 95% confidence interval for median difference.

2. There was marginal evidence that 5 day treatment reduces duration of pain compared to 3 day regimen. However, when examined by the endpoint of time to pain relief the difference is less.

3. Proportion of patients with aborted lesions (i.e., halted progression of lesions) was evaluated for the two treatment arms. There was no statistically significant difference between the two treatment regimens in terms of proportion of patients with aborted lesions.

4. There appeared to be some gender differences in this study with respect to the efficacy endpoints.

   a) Although not statistically significant, males generally had a longer *time to lesion healing* than females.

   b) Although not statistically significant, males generally had a shorter *duration of pain* as compared to females.

   c) A significant difference was found between males vs females in terms of the *length of the episode*. Males had a longer length of episode as compared to females.

   d) The *proportion of patients with aborted lesions* was higher in females vs males in both treatment groups.

   e) Finally, there was no interaction effect between gender and treatment with respect to the primary endpoint of *time to lesion healing*. In other words, gender had no effect on the treatment difference between the 5-day group vs 3-day group.

Rafia Bhore, Ph.D.
Mathematical Statistician

Concur: Greg Soon, Ph.D., Statistics Team Leader

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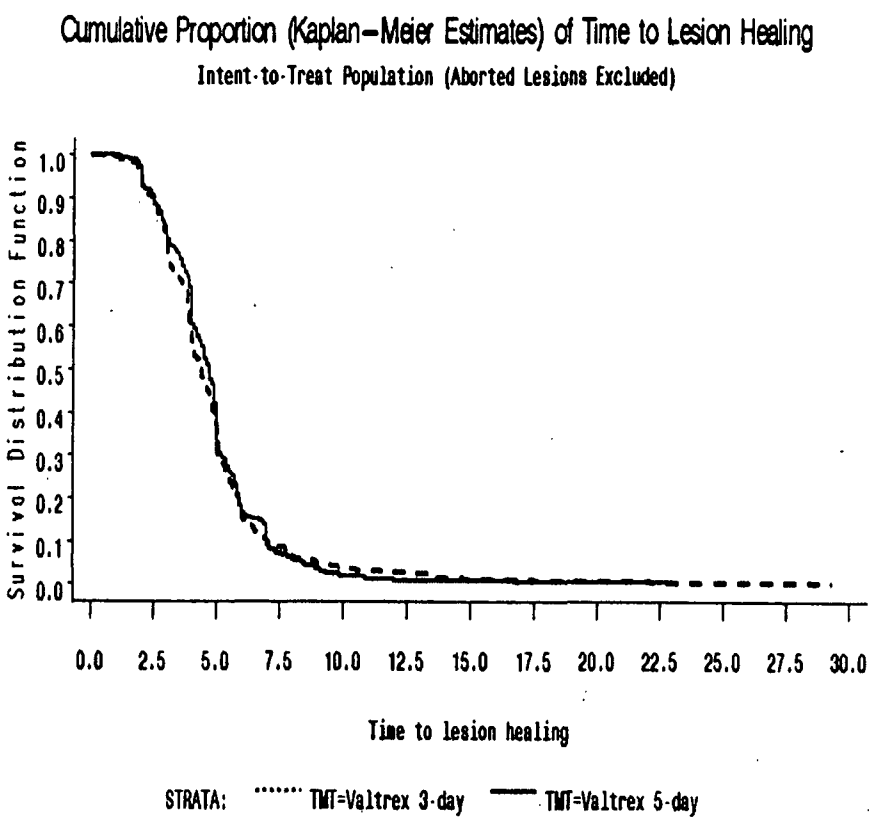
APPENDIX

Figures

Figure 2:
Proportion of Patients Not Healed
Comparisons by Treatment Groups and Gender



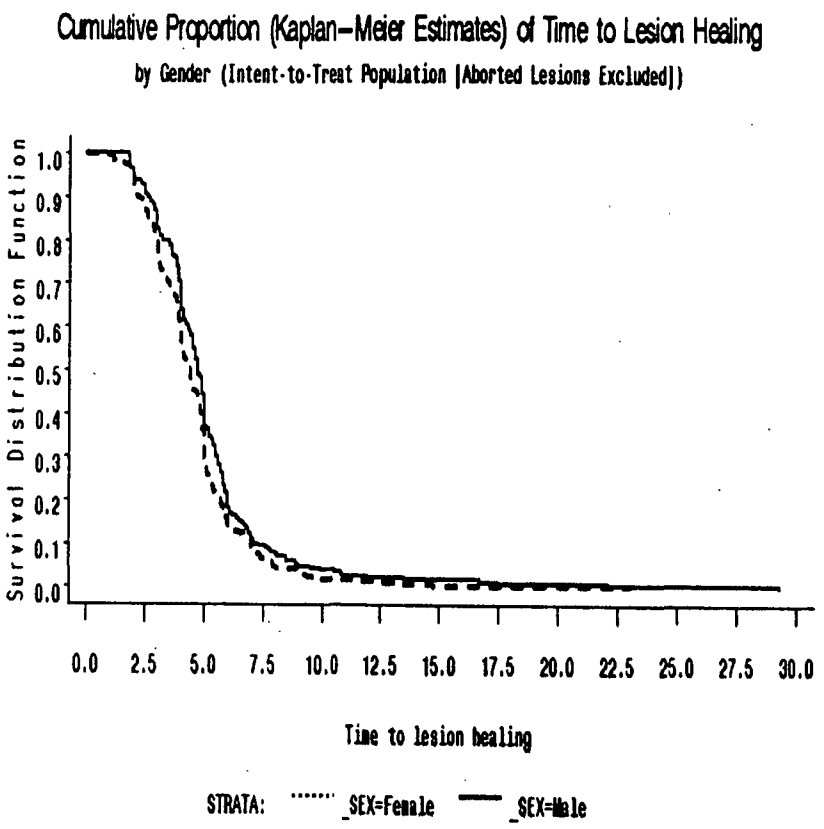
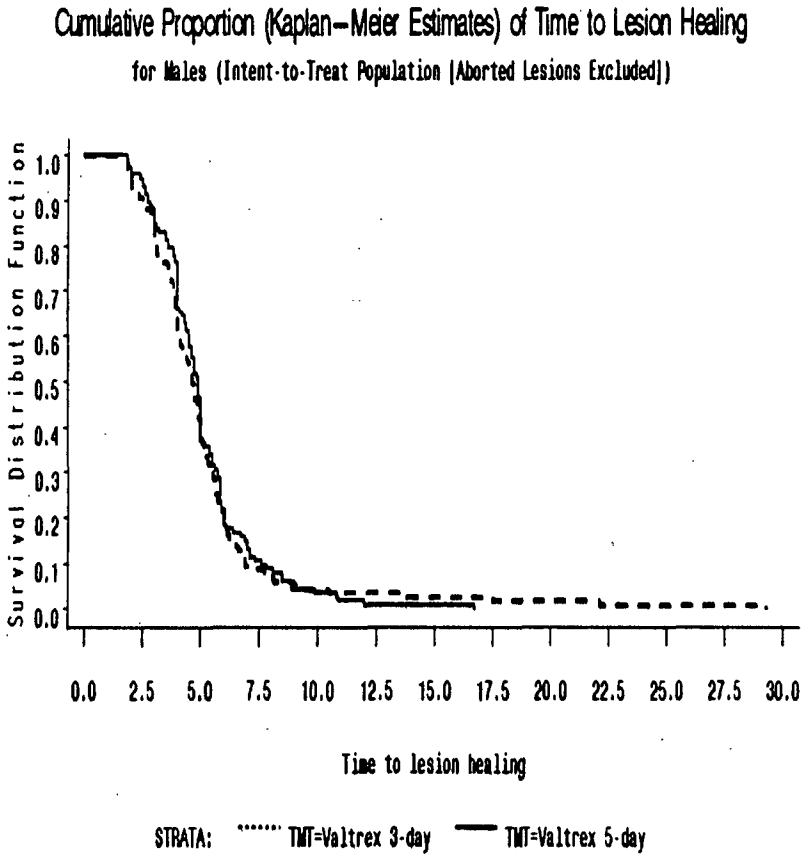


Figure 3:
Proportion of Patients Not Healed
Comparisons of Treatment Groups within each Gender



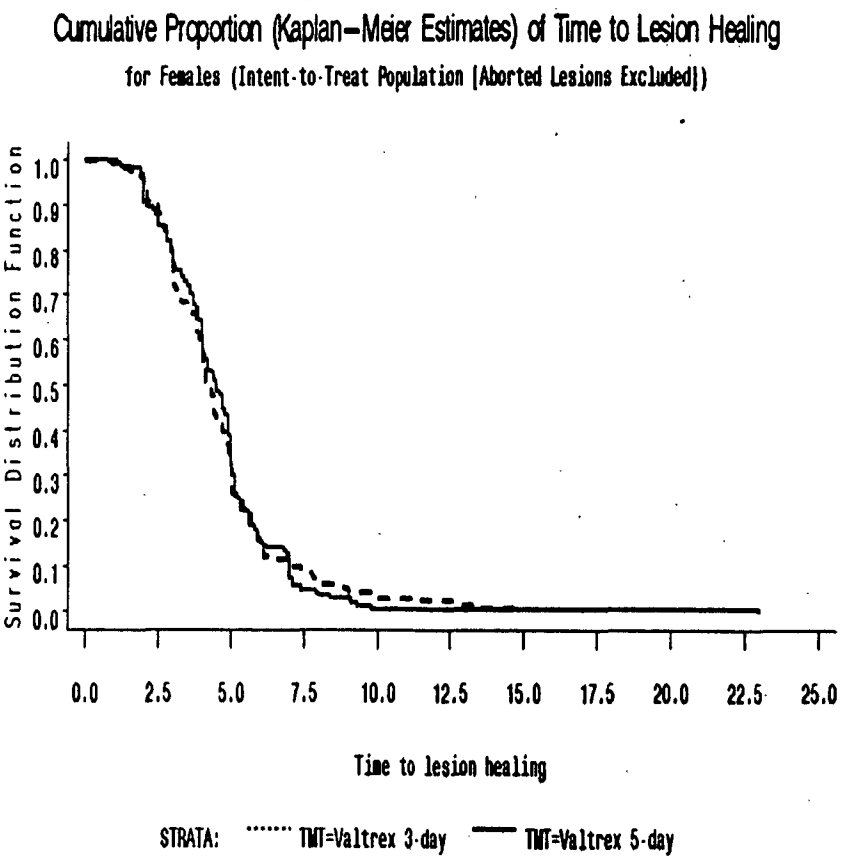
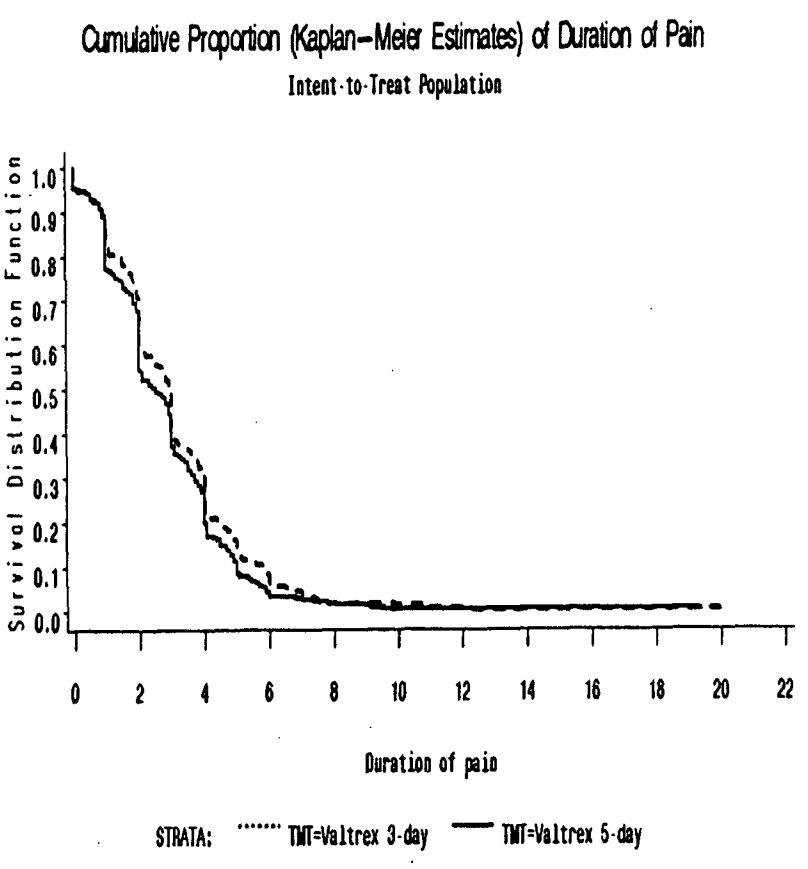


Figure 4:
Proportion of Patients Still Experiencing Pain
Comparisons by Treatment Groups and Gender



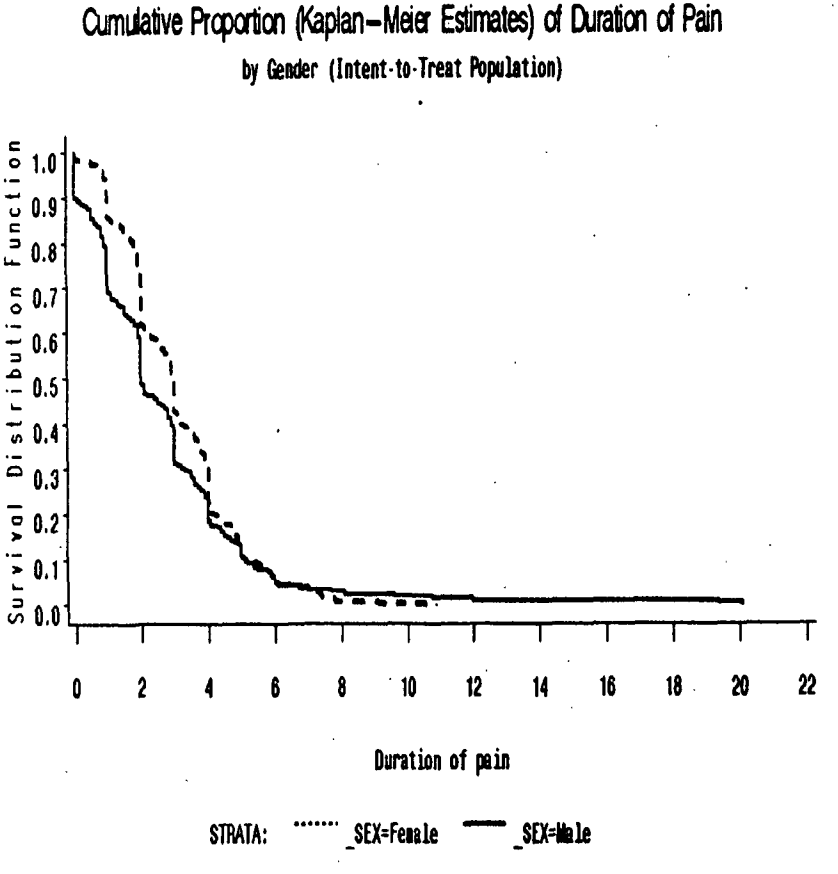
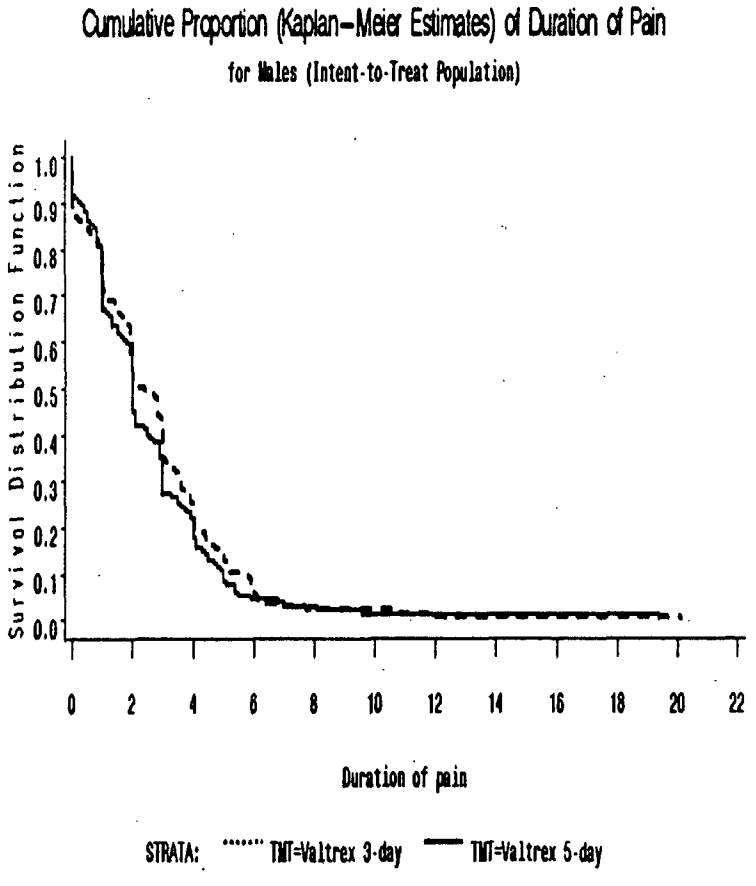


Figure 5:
Proportion of Patients Still Experiencing Pain
Comparisons of Treatment Groups within each Gender



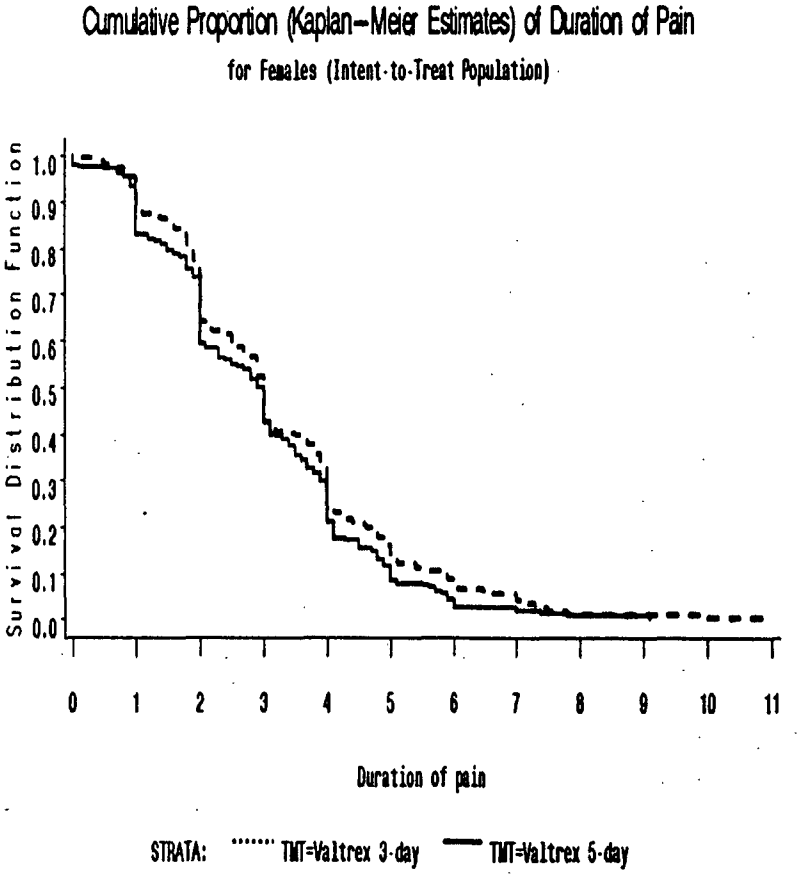
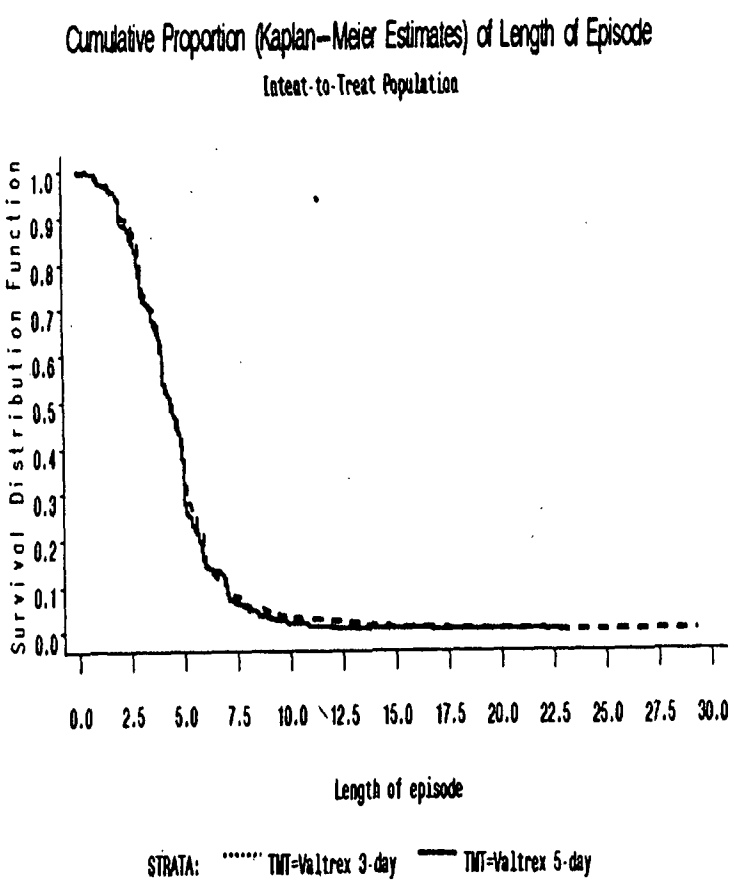


Figure 6:
Proportion of Patients Not Completely Resolved
Comparisons by Treatment Groups and Gender



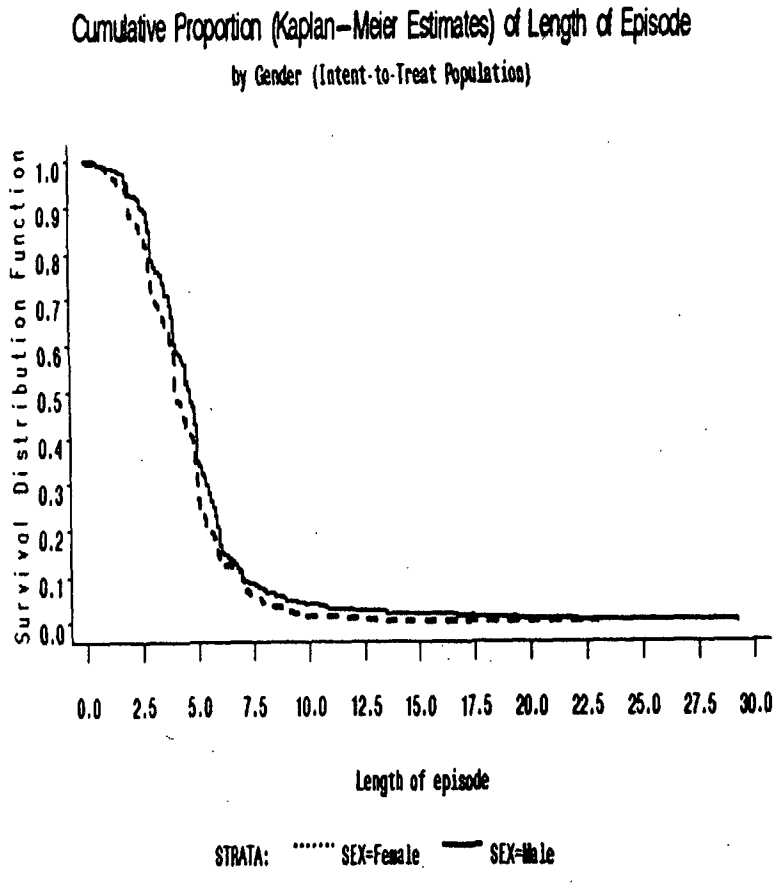
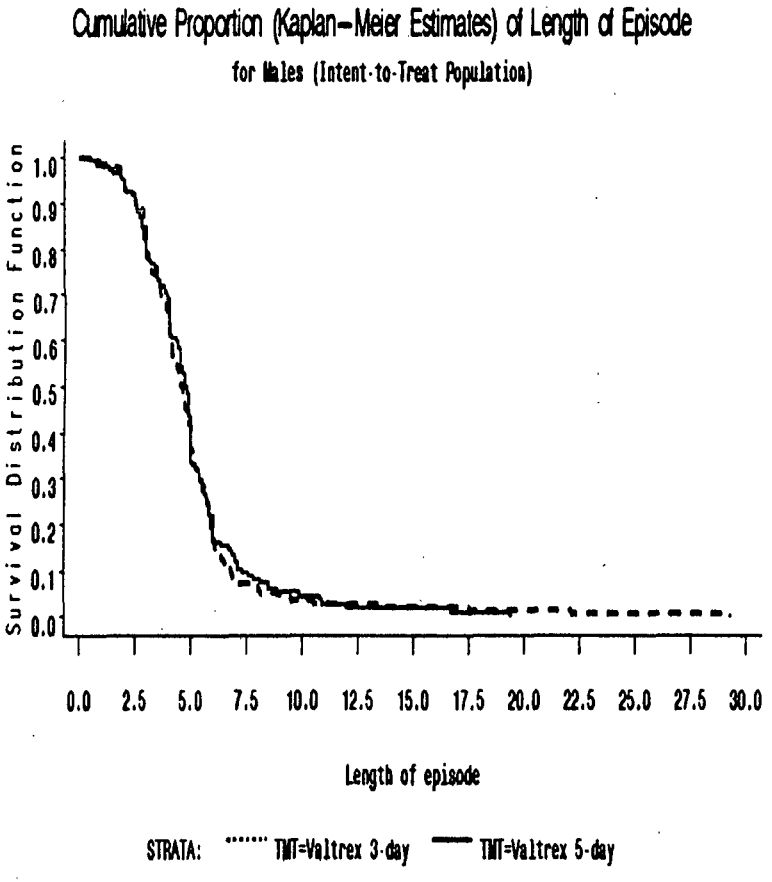
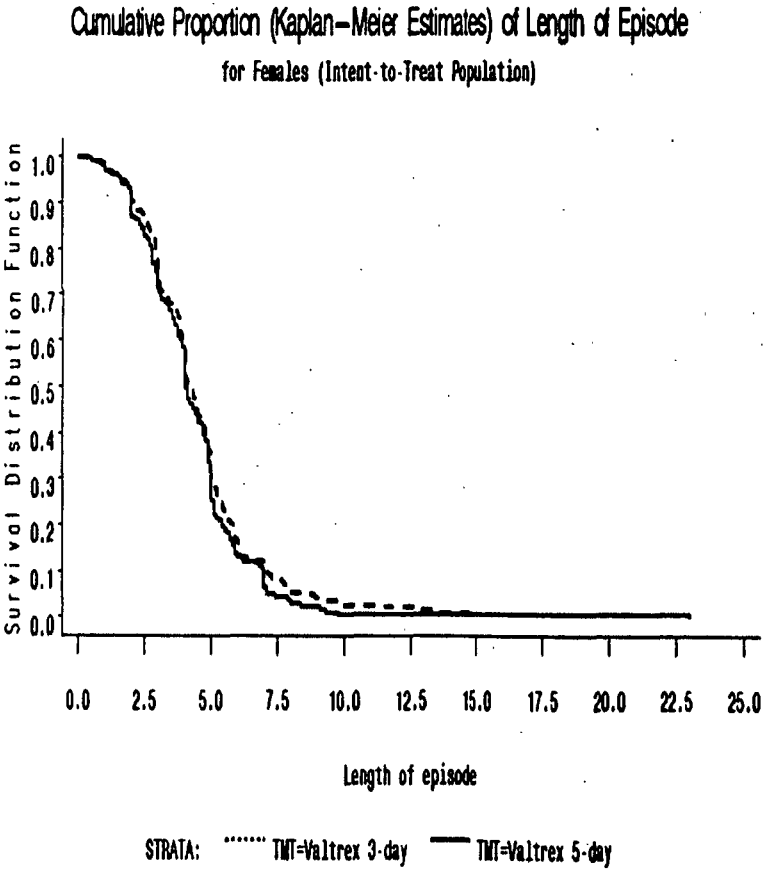


Figure 7:
Proportion of Patients Not Completely Resolved
Comparisons of Treatment Groups within each Gender





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/s/

Rafia Bhore
4/12/01 10:35:47 AM
BIOMETRICS

Greg: Does anyone else need to sign off besides you and me? -Rafia

Greg Soon
5/10/01 01:55:30 PM
BIOMETRICS