CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-022

STATISTICAL REVIEW(S)

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Statistical / Clinical Review and Evaluation

NDA/ Drug Class: 21-022 / 3S

Name of Drug: Loprox® (Ciclopirox) Nail Lacquer 8%

Applicant: [redacted]

Type of Report: Clinical/Statistical Review

Indication: Onychomycosis

Documents Reviewed: Volumes 1.1,13.1, 1.63 - 1.93 and diskettes containing SAS data sets from the sponsor

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1. Introduction

According to the sponsor: "Onychomycosis is a fungal disease of the nail, mostly caused by dermatophytes. The most common form is distal subungual onychomycosis. . . .[It] is more common in toenails than in fingernails. " This submission is designed to support the use of a ciclopirox lacquer for the treatment of onychomycosis of both fingernails and toenails.

The sponsor continues: "Ciclopirox is a hydroxypyridone derivative that offers a chemical class, mechanism of action, and route of administration different [from] the marketed drugs currently used for the treatment of onychomycosis in the U.S.." The sponsor further claims that "the lacquer offers several important therapeutic advantages over other treatments. These include the absence of the infrequent but very significant toxic effects of currently available systemic antifungals and its availability in situations where physiological state, administration of essential drugs, and subject preference preclude the use of systemic antifungals."

2. Experimental Designs

Four studies, two primary and two secondary endpoints were analyzed in this review to investigate statistically the effects of Loprox (ciclopirox) in the treatment of onychomycosis.

Table 1. The Studies

Protocol Number	Description
Phase II Vehicle-Controlled U.S. studies:	
211	A double-blind, parallel, U.S. multicenter trial comparing the efficacy and safety of Ciclopirox Nail Lacquer 8% with its vehicle qid 24 weeks in the treatment of distal subungual onychomycosis of the fingernails.
212	A double-blind, parallel, U.S. multicenter trial comparing the efficacy and safety of Ciclopirox Nail Lacquer 8% with its vehicle qid 24 weeks in the treatment of distal subungual onychomycosis of the fingernails..
Phase III Vehicle-Controlled U.S. studies:	
312	A double-blind, parallel, U.S. multicenter trial comparing the efficacy and safety of Ciclopirox Nail Lacquer 8% with its vehicle qid 48 weeks in the treatment of distal subungual onychomycosis of the toenails.
313	A double-blind, parallel, U.S. multicenter trial comparing the efficacy and safety of Ciclopirox Nail Lacquer 8% with its vehicle qid 48 weeks in the treatment of distal subungual onychomycosis of the toenails.

SAS data sets were provided for each of the studies above. In addition, data was provided for an open label study with protocol 111a. The latter was a small study, and its data were used only for adverse events. As noted above, the primary emphasis in this report is on the two phase III toenail studies above.

I. Response Measures (Common to all studies):

In all the studies, there was a mycological assessment at screening (pre-baseline), baseline (sponsor labeled visit 1), and at later visits. The 312 and 313 studies used both a KOH examination and culture to determine the presence of a fungal organism.

Mycological cure was defined as the occurrence of both a negative KOH and negative culture (as cultured at a later time).

In studies 312 and 313, a **Global Evaluation Score** was assessed by comparing post-baseline evaluations to the Day 1 evaluation as described below:

0 =	Cleared:	100% clearance of clinical signs of disease corroborated by absence of investigator markings on photograph.
1 =	Excellent Improvement:	75% but less than 100% clearance of clinical signs of disease
2 =	Moderate Improvement:	50% to less than 75% clearance of clinical signs of disease
3 =	Slight Improvement:	Less than 50% clearance of clinical signs of disease
4 =	No Change:	No detectable improvement from baseline evaluation
5 =	Exacerbation:	Flare of area being studied and/or increase in area of involvement

In addition, **Computerized Planimetric Measurements** were made "from standardized photographs." The affected area as a percentage of the whole nail area was used as the response.

Statistically the percentage of affected area is a very attractive endpoint. Inherently it would seem to have strong reliability and presumably good validity. It is amenable to an analysis by powerful continuous data techniques. However, as noted by the sponsor: "Computerized planimetry is reproducible: however, because areas are delineated by ink lines with a finite thickness, and because the final length of healthy nail can only be presumptive. Thus, planimetry cannot be used to distinguish minimal residual disease from cure. Hence the establishment of cure remains a clinical decision."

Complete cure (sponsor labeled **Treatment Cure**) was defined as the occurrence of a mycological cure with a score of 0 on the global evaluation scale above.

Effective treatment (sponsor labeled **Treatment Success**) was defined as the occurrence either a complete cure or a mycological cure with less than 10% involvement as expressed by a planimetric measurement.

For this analysis, response variables were defined to maximize response rate. For example, mycological cure would be defined as a success, if both KOH and culture results were found to be negative. If either culture or KOH tests were positive (i.e., indicated fungal infection), the mycological score would be defined as a failure. In particular, if either one of KOH or culture were negative, then no matter what the outcome of the other corresponding test (culture or KOH) the mycological score would still be scored as a failure. So no matter what the outcome of the corresponding test, even if results the corresponding tests were not given (say not performed, invalid, contaminated, lost, etc.), the score for mycological cure would be "failure." This leads to the matrix of defined outcomes for mycological cure as follows:

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Table 2. Response Matrix

Score for Mycological Cure		Culture		
		Negative	Positive	Missing
KOH	Negative	Success	Failure	Missing
	Positive	Failure	Failure	Failure
	Missing	Missing	Failure	Missing

This same reasoning was applied to "complete cure" (Sponsor's "treatment cure") and "effective treatment" (Sponsor's "treatment success"). Note that this can lead to some surprising results. For example: since the investigator's global evaluation was scored at numerous times when mycological results or planimetric measures were NOT computed, there are times when there are many valid responses of failure to the complete cure measure or to the effective treatment measure even when, say, there is no KOH or culture performed.

There may be a severe problem in evaluating efficacy from the occurrence of a mycological cure, and hence at all the derived end points. According to the sponsor: "Test materials were to be applied q.d. with applications approximately 24 hours apart. The test materials were to be applied evenly over the entire nail plate and the proximal and lateral nail fold areas, approximately 5mm onto folds. . . . The nail lacquer was not to be removed on a daily basis. Daily applications were to be made over the previous coat. Every seven days, subjects were to completely remove the test material with the isopropyl alcohol swabs provided (use of acetone-based nail lacquer removers by subjects was not allowed). . . . At return visits every four weeks during treatment, the nail lacquer was to be removed prior to clinical evaluations and a specimen was to be procured for mycological evaluations of the target nail (use of acetone-based nail lacquer removers by the investigator was allowed at these return visits). Once evaluations had been completed, the subject was to be instructed to reapply the nail lacquer to all toenails and the affected fingernails." According to the sponsor, isopropyl alcohol has fungicidal activity, and remnants of this remover may contribute to the apparent results of the KOH and culture tests. Note that such an outcome, though anti-conservative, could be expected to be roughly the same for each treatment arm. However, unless all of the lacquer is removed, the anti-fungal properties of any remaining ciclopirox may also invalidate the results of the mycological tests. This outcome would be expected to be anticonservative in favor of the ciclopirox lacquer treatment arm. One might guess that as studies proceed, subjects and perhaps even investigators may become increasingly careless when performing mandatory procedures. If that occurred here, one might speculate that preliminary removal of the lacquer might be less carefully done at the end of the study than at the beginning. These are exactly the times when differences are observed.

If a subject had a clinically and a mycologically cured target nail (complete cure) at any time during the 48-week treatment period, the subject was to discontinue treatment and enter a **post-treatment phase**. Initially this phase was to last for 24 weeks, but this was later amended

to 12 weeks. "Test medications and medications excluded during treatment were not to be permitted during the post-treatment phase. Post-treatment visits were not to be required for subjects who, throughout treatment, continued to show signs of disease on the target nail." Due to the problems above, it seems natural base primary results on the comparisons of subjects in this post-treatment phase. However, as noted later, very few subjects in either study, achieve this level.

3. Efficacy Results for Toenails

a. Protocol 312

This was a double-blind, randomized, multicenter, parallel group, vehicle controlled study of the safety and efficacy of ciclopirox nail lacquer 8%, applied topically once a day for 48 weeks in patients with onychomycosis of the toenails.

Patients were to return every four weeks for evaluation during the study. Days were converted to weeks according to the following transformation table (which differs slightly from that used by the sponsor):

Table 3. Day to Week Conversion

Day	Week	Day	Week	Day	Week	Day	Week
0 or 1	0	120 to 147	20	260 to 287	40	410 to 437	60
2 to 33	4	148 to 175	24	288 to 315	44	438 to 465	64
34 to 61	8	176 to 203	28	316 to 353	48	466 to 493	68
62 to 89	12	204 to 231	32	354 to 381	52	494 to 521	72
90 to 119	16	232 to 259	36	382 to 409	56		

When multiple visits occurred with the week, the response assigned to the week is the last valid, non-missing response in that period. Subjects who achieved a complete cure entered into the post-treatment evaluation phase. Responses were evaluated at nominal weeks 12 and 24 (actually weeks 10-16 and weeks 20-24, respectively.)

I. Patient Demographics:

The demographic characteristics of the baseline population are summarized in the following table. Recall that the intent-to-treat (ITT) population is defined as all subjects dispensed treatment, while the corresponding modified intent-to-treat (MITT) population is those subjects with confirmed mycological infection (as measured by KOH and culture) at baseline (sponsor's visit 1). The sponsor's analyses were performed on the ITT and the per

protocol subject groups. However, it is usual in DDDDP analyses involving fungal products to restrict the analysis to those patients randomized to treatment that have the presence of a mycological infection confirmed by KOH and culture. This is usually labeled as "The" modified intent-to-treat group in simple efficacy trials.

Table 4. Demographics

	MITT		ITT	
	Ciclopirox	Vehicle	Ciclopirox	Vehicle
Gender				
Male	60	67	85	90
Female	20	13	27	21
Race				
White	78	76	106	102
Black	0	1	1	2
Hispanic	1	3	4	7
Other	1	0	0	0
Total	84	92	119	118
Age				
Mean (Std Dev)	49.2 (12.4)	47.3 (12.7)	50.4 (12.2)	48.6 (13.2)
Range	20-70	21-70	20-70	18-70
% Area at Baseline				
Mean (Std Dev)	38.6 (9.8)	39.2 (10.3)	39.2 (10.1)	39.9 (10.5)
Range	19.2-62.4	18.0-63.0	19.2-63.4	16.8-67.0

Note that it is quite apparent that there are no statistically significant differences among treatments with respect to age, gender, race (white versus other), and/or percent baseline area of involvement.

Table 5. Disposition of Subjects

	MITT		ITT	
	Ciclopirox	Vehicle	Ciclopirox	Vehicle
Completed	68	65	89	84
Withdrawn	12	15	23	27
Violation of Protocol	2	2	5	5
Unreliability	2	2	6	5
Lost to Follow-up	4	4	7	8
Adverse Event	0	1	0	1
Laboratory	0	1	0	1
Lack of efficacy	1	2	1	3
Discontinued	2	3	3	4
Other	1	0	1	0
Total	80	80	112	111

Note there are no apparent treatment differences in either study group.

ii. Efficacy Results:

The following table was taken from the sponsor's submitted photographic and mycological data, and from Data Listing 5.2: Photography Results for Target Great Toenail. These are the patients who achieved a clear nail with negative mycology, and entered the post-treatment phase, as defined by the sponsor. At each week, an "S" denotes a "success" in all three response measures, i.e., mycological cure, complete cure, and effective treatment. An "F" represents a failure in each. An "NA" means not available or undefined.

Table 6. Patients Entering Post-treatment Phase (ITT group)

Treatment	Investigator	Subject	Results at 12 week follow-up	Results at 24 week follow-up
Loprox	26	104*	NA	F
	26	116*	S	S
	41	218*	NA	NA
	52	402	S	S
	87	926*	F	F
Vehicle	52	404	S	S

* - These subjects are also in the MITT population

Subject 402 had two culture evaluations at baseline, one negative and one positive. The results of the first, negative, evaluation were used here (and hence the subject is excluded from the MITT group). Note it makes no substantative difference if this subject is added to the MITT.

Statistical Comment:

Typically, randomization is performed within investigator. That is, each investigator follows a separate randomization schedule. One way to test treatment differences in response measures is a so-called design-based approach, where one considers the distribution of some pivotal statistic under all allowed permutations within investigator of the data. Alternatively, one can postulate a statistical distribution for the response, to get a so-called model-based approach. For such binary response data, either from a design based or from a model-based approach this reviewer would typically prefer an analysis that adjusts or stratifies on investigator. From either a design based or a model-based approach one would usually be lead to a so-called Cochrane-Mantel-Haenszel (CMH) test of treatment differences. However, both the design based and the model-based approach treat this as a so-called product hypergeometric model. Consider a typical frequency table. Note that if any marginal row or column total of frequencies is zero, we know that each cell in that row or column has zero frequency (otherwise the total would be greater than 0).

The typical CMH analysis assumes that row and column totals are fixed. For a 2x2 table, if one row or column marginal total is zero, we exactly know the values of all 4 cells in the table. That is, there is no variation associated with that table. Then effectively, the data from that particular center is ignored in the computation of the CMH statistic. In particular, when the response is success or failure, when a center has no successes in either treatment, that center is ignored by the computed CMH statistic. It affects neither the numerator nor the denominator. Yet, we know the proportion of successes (i.e., 0%) is the same across levels of treatment within the investigator, and hence the proportions of failures (i.e., 100%) is similarly constant across centers. So the information that the success rates were the same within this investigator is ignored. When a number of centers are dropped in the calculation of the CMH statistic, which is almost a certainty when there are very few successes relative to the number of investigators, it seems that an analysis that would not drop these centers, as would be given by, say, a Fisher exact test, would be more appropriate.

Tables are given for the binary response measures described above for weeks 4-48, and for weeks 12 and 24 post-treatment. Below the entries for week 48, for the last observation carried forward (LOCF) at or below week 48, or week 12 or week 24 post-treatment is the "p-value," significance level, of a test of within center homogeneity of cure over treatment, using a Mantel-Haenszel test stratified on investigator and a corresponding Fisher Exact test. As noted in the statistical comment above, it seems to this reviewer that a chi-square test of homogeneity or a Fisher exact test, ignoring investigator, would be superior to the usual model or design-based CMH test. For week 48 and the LOCF at or below week 48, success is defined as a simple mycological cure, and failure is any other valid response as explained in the response matrix described above. For the approximate week 12 and week 24 tests a success is defined as a mycological cure during the post-treatment period. A failure is defined as either a mycological failure during the post-treatment period, or failure to enter the post-treatment period. It perhaps would have been preferable to include all patients in the post-treatment period, but that was not allowed in the original design.

Table 7. Study 312 Mycological Cure (MITT Population)

Mycological Cure (KOH & culture negative)

	Week:										
	4	8	12	16	20	24	28	32	36	40	44
Loprox											
myco	0	0	9	3	0	21	2	0	21	4	0
N	1	0	55	16	1	53	16	1	53	15	0
%	0.0	.	16.4	18.8	0.0	39.6	12.5	0.0	39.6	26.7	.
Vehicle											
myco	0	1	7	1	0	8	1	0	8	2	0
N	1	1	62	17	0	55	16	2	44	20	5
%	0.0	100.0	11.3	5.9	.	14.5	6.3	0.0	18.2	10.0	0.0

Table 7(cont.) Study 312 Mycological Cure (MITT Population)

		Post-treatment		
	48	LOCF- (48 wks)	12 week (+ LOCF)	24 week (+ LOCF)
Loprox				
myco	17	19	1	1
N	60	78	76	77
%	28.3	24.4	1.3	1.3
Vehicle				
myco	4	7	0	0
N	51	80	80	80
%	7.8	8.8	0.0	0.0
CMH p-value	0.004	0.005	0.254	0.277
Fisher p-value	0.007	0.010	0.487	0.490

Note that at the end of the study, at week 48, the differences between the mycological cure rate of Ciclopirox lacquer and its vehicle, say roughly 24-28% to 8-9%, are statistically significant ($p \leq 0.007$ at week 48 and $p \leq 0.010$ at LOCF up to week 48). However, again, as noted above, due to slight amounts of lacquer possibly contaminating the sample, coupled with the known anti-fungal properties of Ciclopirox render these results somewhat questionable. At weeks 12 or 24 posttreatment, there is no statistically significant evidence of a difference ($p \leq 0.487$ and $p \leq 0.490$ at post-treatment week 12 or 24, respectively). As discussed above, this reviewer recommends the use of the Fisher exact test, rather the CMH test (either in an exact version or using the usual chi-square approximation).

Recall that complete cure (sponsor labeled "Treatment Cure") was defined as the occurrence of a mycological cure along with a score of 0 on the global evaluation scale above. A failure on complete cure was defined as a positive KOH or a positive culture or a response of greater than 0 on the global evaluation scale. The "N" in these tales is the total number of successes and failures, i.e., the number of evaluable cases. The following table displays these results for the MITT population:

Table 8. Study 312 Complete Cure (MITT Population)

Mycological cure plus investigator's evaluation=0

	Week:										
	4	8	12	16	20	24	28	32	36	40	44
Loprox											
cure	0	0	0	0	0	0	0	0	0	0	0
N	74	68	68	68	66	66	63	69	66	57	61
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Vehicle											
cure	0	0	0	0	0	0	0	0	0	0	0
N	70	72	65	70	66	69	70	60	61	59	61
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 8 (cont.) Study 312 Complete Cure (MITT Population)

			Post-treatment	
	48	LOCF- (48 wks)	12 week (+ LOCF)	24 week (+ LOCF)
Loprox				
cure	3	3	1	1
N	70	80	78	79
%	4.3	3.8	1.3	1.3
Vehicle				
cure	0	0	0	0
N	64	80	80	80
%	0.0	0.0	0.0	0.0
CMH p-value	0.075	0.059	0.254	0.277
Fisher p-value	0.246	0.245	0.494	0.497

Note that for complete cure, neither at the end of week 48, nor at the corresponding LOCF point, are the differences between the ciclopirox lacquer and its vehicle, say roughly 4% to 0%, statistically significant ($p \leq 0.246$ at both points). Similarly, at both time points in the post-treatment period, differences, 1% versus 0%, are not statistically significant (roughly, $p \leq 0.497$ at both points).

Effective treatment (sponsor labeled "Treatment Success") was defined as the occurrence of either a complete cure or a mycological cure with less than 10% involvement as expressed by a planimetric measurement:

Table 9. Study 312 Effective Treatment (MITT Population)

	Week:										
	4	8	12	16	20	24	28	32	36	40	44
Loprox											
eff trt	0	0	0	0	0	0	0	0	3	2	0
N	8	0	61	20	3	56	24	3	51	17	4
%	0.0	.	0.0	0.0	0.0	0.0	0.0	0.0	5.9	11.8	0.0
Vehicle											
eff trt	0	0	0	0	0	0	0	0	0	0	0
N	5	1	61	19	1	57	20	2	46	26	7
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 9 (cont.) Study 312 Effective Treatment (MITT Population)

			Post-treatment	
	48	LOCF- (48 wks)	12 week (+ LOCF)	24 week (+ LOCF)
Loprox				
eff trt	4	5	1	1
N	60	80	78	79
%	6.7	6.3	1.3	1.3
Vehicle				
eff trt	0	0	0	0
N	53	80	80	80
%	0.0	0.0	0.0	0.0
CMH p-value	0.055	0.017	0.254	0.277
Fisher p-value	0.121	0.059	0.494	0.497

For effective treatment (sponsor labeled "Treatment Success"), strictly speaking, neither at the end of week 48, nor at the corresponding LOCF point at week 48, are the differences between the ciclopirox lacquer and its vehicle, roughly 6% to 0%, statistically significant ($p \leq 0.121$ and $p \leq 0.059$, respectively). At both time points in the post-treatment period, differences, 1% versus 0%, are not statistically significant (again, roughly, $p \leq 0.497$ at both points).

Since it is quite amenable to continuous data techniques, statistically, the percent area from planimetric measurements is a very attractive endpoint. However, as noted in the discussion in the section on response measures, it is not appropriate as a primary endpoint. Response profiles for the two treatment groups (actually for the ITT population) are plotting percent area from planimetric measurement versus study day are displayed in figures 1. and 2. Profiles for the MITT population are a subset of those displayed here, but are equally messy. Clearly as presented these are difficult to interpret. One technique to help discover structure is local smoothing. Strictly speaking, most local smoothers assume simple random samples and ignore correlation structure among observations. But since one is only interested in mean structures little information should be lost. Figures 3 and 4 display a so-called "Lowess" smooth for each treatment group (again, actually for the ITT data). Figure 5 overlays the two smooths for each treatment group. Note that the ciclopirox mean is smaller, but the difference is not apparently large relative to the amount of variation. Figure 6.0 overlays the two smooths for the MITT patients. Note it is very similar to the smooths for the ITT patients.

An omnibus test of treatment differences over time might be helpful. Note that if treatment were effective, near the end of the experiment we would expect statistically significant differences. However, just due to randomization, at baseline we would expect no statistically significant differences. One way to investigate omnibus treatment differences would be to compute mean area under the curves for each subject over the entire duration of the experiment. To avoid biases due to early termination, the last observed value could be carried forward to the end of the study. Though not displayed here, the areas under the resulting

curves (AUC) were used as response variables in an ANCOVA with age as a covariate and investigator and treatment group as factors. No statistically significant differences were found. An alternative approach to an omnibus test of treatment differences is to use so-called "generalized estimating equations" (GEE) technology. This was done, though also not displayed here. Assuming normal errors with an identity link and a provisional exchangeable correlation structure, and with the same factors as in the ANCOVA above, treatment differences were not statistically significant for the ITT population ($p \leq 0.2026$) but were statistically significant for the MITT population ($p \leq 0.0157$). So our omnibus tests over time (AUC for both and GEE for ITT versus GEE for MITT) seem to give inconsistent results. This reviewer has some evidence that such GEE results may be anticonservative, but the generality of these results is not known.

If treatment effects are relatively small, these may be masked by the pooling over time. Plus tests at each time point should be more powerful, although they may run into multiplicity problems. Thus, it may make sense to look at these results at selected time points:

The following table displays least squares means and p-values from a Type 3 analysis of variance with mean percent area as response and investigator, treatment group, and interaction as factors. The p-value is from the test of differences in these least squares means (i.e., type III sums of squares).

Table 10. Study 312 Mean Percent Area from Planimetric Measurements (MITT Population)

Week:	12	LOCF(12 wks)	24	LOCF(24 wks)	36	LOCF(36 wks)	48	LOCF(48 wks)	LOCF(60 wks)
Loprox									
LS Mean	43.6	41.9	39.2	41.1	39.4	41.1	39.0	38.8	38.8
Std Err	2.5	1.8	2.4	1.9	2.9	2.0	2.7	2.1	2.1
N	59	80	52	80	49	80	54	80	80
Vehicle									
LS Mean	39.7	40.3	44.3	44.3	43.0	44.8	44.8	44.5	45.4
Std Err	2.5	1.9	2.4	2.0	3.2	2.0	3.0	2.2	2.2
N	60	80	54	80	42	80	46	80	80
p-value*	0.2719	0.5437	0.1402†	0.2419	0.4022	0.1973	0.1481	0.0628	0.0327

* - From ANOVA test of treatment differences (Type 3 SSQ)
† - Contrasts defining LS Means redefined (effectively investigator 75 deleted)

Note that week 48 represents the end of the study and cases in that group essentially correspond to a per protocol group. Usually one would like to see consistency between this week 48 group and the corresponding week 48 LOCF group. Here, strictly speaking neither is significant, though the LOCF group is close ($p \leq 0.1481$ and $p \leq 0.0628$, respectively). Again, a problem with interpreting tests at each time point, as opposed to the omnibus tests above, is that the tests become multiple decision problems, where due to the multiplicity of tests, the

probability of making a type I error increases above the typically specified 0.05 level.

Statistical Comment:

One caveat is that these tests use type 3 sums of squares. One of several ways to look at such an analysis is to note that when adjusting terms for other effects, the number of cases involved in estimating that effect is ignored. That means that the contrasts used to define type 3 sums of squares are not independent. However, in terms of simple cell means these contrasts are very easy to interpret. But cells with 1 observation are treated the same as cells with 10 or 20. The analysis above deletes singleton cells, namely that associated with investigator 75.

The FDA ITT population consists of all patients given treatment, and is equivalent to the sponsor's ITT group. Again, for each patient at or before week 48, success is defined as a simple mycological cure, and failure is any other valid response as explained in the response matrix above. For the approximate week 12 and week 24 tests a success is defined as a mycological cure during the post-treatment period. A failure is defined as either a mycological failure during the post-treatment period, or failure to enter the post-treatment period. For this ITT population the table of mycological cures appears below:

Table 11. Study 312 Mycological Cure (ITT Population)

		Week: 4	8	12	16	20	24	28	32	36	40	44
Loprox	myco	0	0	13	8	0	30	3	1	26	6	0
	N	2	1	73	23	1	72	21	3	69	21	0
	%	0.0	0.0	17.8	34.8	0.0	41.7	14.3	33.3	37.7	28.6.	
Vehicle	myco	0	1	10	1	0	14	2	1	13	3	0
	N	2	1	78	28	1	70	23	4	56	26	5
	%	0.0	100.0	12.8	3.6	0.0	20.0	8.7	25.0	23.2	11.5	0.0

				Post-treatment	
		48	LOCF- (48 wks)	12 week (+ LOCF)	24 week (+ LOCF)
Loprox	myco	25	31	2	2
	N	79	106	104	105
	%	31.6	29.2	1.9	1.9
Vehicle	myco	9	13	1	1
	N	67	108	108	108
	%	13.4	12.0	0.9	0.9
CMH p-value		0.003	0.001	0.503	0.516
Fisher p-value		0.011	0.002	0.616	0.618

At the completion of the treatment period (week 48), differences in mycological cure rate between ciclopirox lacquer and its vehicle in the ITT sample, say roughly 30% to 13%, are statistically significant ($p \leq 0.011$ and $p \leq 0.002$, at week 48 and LOCF week 48 respectively).

However, again, these results may be considered suspect due to the possibility of slight amounts of lacquer possibly contaminating the sample. At week 12 or 24 posttreatment, there is no statistically significant evidence of a difference (roughly $p \leq 0.618$ for both time points).

As noted above, complete cure (sponsor labeled "Treatment Cure") was defined as the occurrence of a mycological cure with a score of 0 on the global evaluation scale above. The following table displays these results for the ITT population:

Table 12. Study 312 Complete Cure (ITT Population)

Week:		4	8	12	16	20	24	28	32	36	40	44
Loprox	cure	0	0	0	0	0	0	0	0	1	0	0
	N	102	92	91	89	89	88	86	91	86	76	78
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.2	0.0	0.0
Vehicle	cure	0	0	0	0	0	0	0	1	1	0	0
	N	93	99	88	94	90	88	88	80	79	77	77
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.3	1.3	0.0	0.0

		Post-treatment		
	48	LOCF- (48 wks)	12 week (+ LOCF)	24 week (+ LOCF)
Loprox cure	4	4	2	2
N	91	112	110	111
%	4.4	3.6	1.8	1.8
Vehicle cure	1	1	1	1
N	83	110	110	110
%	1.2	0.9	0.9	0.9
CMH p-value	0.231	0.184	0.559	0.573
Fisher p-value	0.370	0.369	1.000	1.000

Note that for complete cure, neither at the end of week 48, nor at the corresponding LOCF point are the differences between the ciclopirox lacquer and its vehicle, say roughly 4%-5% to 1%-2%, statistically significant (roughly $p \leq 0.370$ at both points). Similarly, at both time points in the post-treatment period, differences, 2% versus 1%, are not statistically significant ($p \leq 1.000$ at both time points).

Again, effective treatment (sponsor labeled "Treatment Success") was defined as the occurrence either a complete cure or a mycological cure with less than 10% involvement as expressed by a planimetric measurement:

Table 13. Study 312 Effective Treatment (ITT Population)

Week:		4	8	12	16	20	24	28	32	36	40	44
Loprox	eff trt	0	0	0	0	0	1	0	0	4	2	0
	N	12	2	80	28	6	75	29	5	66	25	5
	%	0.0	0.0	0.0	0.0	0.0	1.3	0.0	0.0	6.1	8.0	0.0
Vehicle	eff trt	0	0	1	0	0	1	0	1	1	0	0
	N	7	4	78	31	2	72	28	4	59	32	8
	%	0.0	0.0	1.3	0.0	0.0	1.4	0.0	25.0	1.7	0.0	0.0

				Post-treatment	
		48	LOCF- (48 wks)	12 week (+ LOCF)	24 week (+ LOCF)
Loprox	eff trt	6	7	2	2
	N	80	108	106	107
	%	7.5	6.5	1.9	1.9
Vehicle	eff trt	1	1	1	1
	N	69	109	109	109
	%	1.4	0.9	0.9	0.9
CMH p-value		0.090	0.028	0.559	0.573
Fisher p-value		0.123	0.035	0.618	0.620

For effective treatment (sponsor labeled "Treatment Success"), at the end of week 48 differences are not statistically significant ($p \leq 0.123$), while differences at the corresponding LOCF point at week 48, are just barely statistically significant ($p \leq 0.035$). Of course, as noted earlier, due to contamination from the Loprox treatment, these comparisons are of debatable importance. At both time points in the post-treatment period, differences, roughly 2% versus 1%, are not statistically significant (roughly, $p \leq 0.620$ at both points).

As noted above for ITT population the response profiles of percent area cleared computed from planimetric measurements appear in figures 1 and 2 of the appendix. Figures 3 and 4 display a so-called "Lowess" smooth for each treatment group. Figure 5 overlays the two smoothers for each treatment group. Note that the ciclopirox mean is smaller, but the difference is fairly small relative to the amount of variation in the data.

Again two omnibus tests of treatment differences were performed, but the details are not presented. First areas under the response profiles (AUC) were used as response variables in an ANCOVA with age as a covariate and investigator and treatment group as factors. No statistically significant differences were found. Second, an omnibus test of treatment differences was made using a GEE approach with normal errors, an identity link, and a provisional exchangeable correlation structure, and with the same factors as in the ANCOVA above. Again, no statistically significant differences between treatment groups was found.

The following table displays least squares means and p-values from a Type 3 analysis of variance with mean percent area as response and investigator, treatment group, and interaction as factors. The p-value is from the test of differences in these least squares means (i.e., type III sums of squares).

Table 14. Study 312 Mean Percent Area from Planimetric Measurements (ITT Population)

Week:	12	LOCF(12 wks)	24	LOCF(24 wks)	36	LOCF(36 wks)	48	LOCF(48 wks)	LOCF(60 wks)
Loprox									
LS Mean	44.4	42.7	40.4	41.7	42.7	42.7	37.9	39.4	39.3
Std Err	2.1	1.6	2.2	1.7	2.7	1.8	2.3	1.9	1.9
N	78	106	70	107	61	107	72	107	107
Vehicle									
LS Mean	39.9	40.6	43.5	43.2	42.0	44.3	43.6	43.9	44.7
Std Err	2.1	1.5	2.2	1.7	2.9	1.8	2.5	1.9	1.9
N	76	107	69	107	55	107	62	107	107
p-value*	0.1479	0.3324	0.3140†	0.5408	0.8599	0.5231	0.0954	0.0886	0.0454

* - From ANOVA test of treatment differences (Type 3 SSQ)
† - Contrasts defining LS Means redefined (effectively investigator 75 deleted)

Again, week 48 represents the end of the study and cases in that group essentially correspond to a per protocol group. Strictly speaking, at the usual 0.05 level, neither this test or the test for the corresponding LOCF group are statistically significant ($p \leq 0.0954$ and $p \leq 0.0886$, respectively). Again, a problem with interpreting tests at each time point, as opposed to the omnibus tests above, is that the tests become multiple decision problems, where due to the multiplicity of tests, the probability of making a type I error increases above the usually specified 0.05 level. This problem is exacerbated by testing in both the MITT and the ITT populations.

iii. Subgroup Results:

The following tables display results by gender and age group (less than 50 years versus greater than or equal to 50 years). There are too few non-white subjects to make a breakdown by race interpretable.

Table 15a. Study 312 Response Measures by Gender (MITT Population)

Mycological Cure:	4	8	12	16	20	24	28	32	36	40	44	48	LOCF (48 wks)	+12 wks	+24 wks
Loprox Male															
Myco	0	.	7	2	.	14	1	0	12	3	.	10	11	0	0
N	1	.	40	11	.	38	12	1	37	12	.	43	58	58	58
%	0.0	.	17.5	18.2	.	36.8	8.3	0.0	32.4	25.0	.	23.3	19.0	0.0	0.0
Female															
Myco	.	.	2	1	0	7	1	.	9	1	.	7	8	1	1
N	.	.	15	5	1	15	4	.	16	3	.	17	20	18	19
%	.	.	13.3	20.0	0.0	46.7	25.0	.	56.3	33.3	.	41.2	40.0	5.6	5.3
Vehicle Male															
Myco	0	1	7	0	.	8	1	0	7	1	0	4	7	0	0
N	1	1	54	12	.	44	14	2	38	15	4	43	67	67	67
%	0.0	100.0	13.0	0.0	.	18.2	7.1	0.0	18.4	6.7	0.0	9.3	10.4	0.0	0.0
Female															
Myco	.	.	0	1	.	0	0	.	1	1	0	0	0	0	0
N	.	.	8	5	.	11	2	.	6	5	1	8	13	13	13
%	.	.	0.0	20.0	.	0.0	0.0	.	16.7	20.0	0.0	0.0	0.0	0.0	0.0

Comparing the proportions, there may be weak evidence that Ciclopirox lacquer is somewhat more efficacious in female patients than with male patients. However, it is this reviewer's opinion that the data are too sparse to make tests very meaningful.

The following table displays similar results for complete cure and for effective treatment. Note that there were no successes in the vehicle group for either response measure, so the vehicle group would have 0% at each time point.

Table 15b. Study 312 Response Measures by Gender (MITT Population)

Complete Cure & Effective Treatment	4	8	12	16	20	24	28	32	36	40	44	48	LOCF (48 wks)	+12 wks	+24 wks
Loprox Male															
Cure	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0
N	57	52	49	50	48	50	46	51	49	41	46	52	60	60	60
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.9	1.7	0.0	0.0
Female															
Cure	0	0	0	0	0	0	0	0	0	0	0	2	2	1	1
N	17	16	19	18	18	16	17	18	17	16	15	18	20	18	19
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11.1	10.0	5.6	5.3
Loprox Male															
Eff trt	0	.	0	0	0	0	0	0	0	2	0	1	2	0	0
N	6	.	46	14	2	40	20	3	35	14	4	42	59	59	59
%	0.0	.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14.3	0.0	2.4	3.4	0.0	0.0
Female															
Eff trt	0	.	0	0	0	0	0	.	3	0	.	3	3	1	1
N	2	.	15	6	1	16	4	.	16	3	.	16	19	17	18
%	0.0	.	0.0	0.0	0.0	0.0	0.0	.	18.8	0.0	.	18.8	15.8	5.9	5.6

For both response variables there may be weak evidence of greater efficacy among females, but gender differences are slight. The following table displays similar results for the ITT population:

Table 16a. Study 312 Response Measures by Gender (ITT Population)

Mycological Cure:	4	8	12	16	20	24	28	32	36	40	44	48	LOCF (48 wks)	Post-treatment +12 wks	Post-treatment +24 wks
Loprox Male															
Myco	0	0	11	6	.	22	1	1	16	5	.	16	21	1	1
N	1	1	55	17	.	55	16	3	51	17	.	59	81	81	81
%	0.0	0.0	20.0	35.3	.	40.0	6.3	33.3	31.4	29.4	.	27.1	25.9	1.2	1.2
Female															
Myco	0	.	2	2	0	8	2	.	10	1	.	9	10	1	1
N	1	.	18	6	1	17	5	.	18	4	.	20	25	23	24
%	0.0	.	11.1	33.3	0.0	47.1	40.0	.	55.6	25.0	.	45.0	40.0	4.3	4.2
Vehicle Male															
Myco	0	1	9	0	0	12	2	0	11	2	0	6	10	0	0
N	2	1	66	19	1	55	19	2	48	18	4	55	87	87	87
%	0.0	100.0	13.6	0.0	0.0	21.8	10.5	0.0	22.9	11.1	0.0	10.9	11.5	0.0	0.0
Female															
Myco	.	.	1	1	.	2	0	1	2	1	0	3	3	1	1
N	.	.	12	9	.	15	4	2	8	8	1	12	21	21	21
%	.	.	8.3	11.1	.	13.3	0.0	50.0	25.0	12.5	0.0	25.0	14.3	4.8	4.8

From simply scanning the observed proportions, it does appear that for this population group there is no particular evidence of gender based differences in efficacy for either Ciclopirox lacquer or its vehicle. Again, it is this reviewer's opinion that the data are too sparse to make tests very meaningful.

The following table displays results for complete cure and for effective treatment (i.e., sponsor labeled treatment cure and treatment success)..

Table 16b. Study 312 Response Measures by Gender (ITT Population)

Complete Cure & Effective Treatment:

	4	8	12	16	20	24	28	32	36	40	44	48	LOCF (48 wks)	Post-treat +12 wks	Post-treat +24 wks
Loprox Male															
Cure	0	0	0	0	0	0	0	0	1	0	0	2	2	1	1
N	78	72	69	68	68	69	66	70	66	57	60	70	85	85	85
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.5	0.0	0.0	2.9	2.4	1.2	1.2
Female															
Cure	0	0	0	0	0	0	0	0	0	0	0	2	2	1	1
N	24	20	22	21	21	19	20	21	20	19	18	21	27	25	26
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9.5	7.4	4.0	3.8
Vehicle Male															
Cure	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	76	79	74	76	73	69	73	63	63	61	64	67	89	89	89
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Female															
CURE	0	0	0	0	0	0	0	1	1	0	0	1	1	1	1
N	17	20	14	18	17	19	15	17	16	16	13	16	21	21	21
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.9	6.3	0.0	0.0	6.3	4.8	4.8	4.8

	4	8	12	16	20	24	28	32	36	40	44	48	wks)	LOCF)	LOCF)
Loprox Male															
Eff trt	0	0	0	0	0	1	0	0	1	2	0	2	3	1	1
N	9	2	62	21	4	57	25	4	48	21	5	59	82	82	82
%	0.0	0.0	0.0	0.0	0.0	1.8	0.0	0.0	2.1	9.5	0.0	3.4	3.7	1.2	1.2
Female															
Eff trt	0	.	0	0	0	0	0	0	3	0	.	4	4	1	1
N	3	.	18	7	2	18	4	1	18	4	.	19	24	22	23
%	0.0	.	0.0	0.0	0.0	0.0	0.0	0.0	16.7	0.0	.	21.1	16.7	4.5	4.3
Vehicle Male															
Eff trt	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	7	3	66	22	2	57	24	2	50	23	7	56	87	87	87
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Female															
Eff trt	.	0	1	0	.	1	0	1	1	0	0	1	1	1	1
N	.	1	12	9	.	15	4	2	9	9	1	12	21	21	21
%	.	0.0	8.3	0.0	.	6.7	0.0	50.0	11.1	0.0	0.0	8.3	4.8	4.8	4.8

Again, for both response variables, from a simple visual comparison of observed proportions it seems that there may be weak evidence of greater efficacy among females, but success rates are too low for any statistically significant differences to become apparent.

Recall that mean age was 50.4 and 48.6 years in the Ciclopirox and vehicle treatment groups, with ranges 20-70 and 18-70 respectively. Age was dichotomized into two roughly equal groups, those less than 50 years of age and those greater than or equal to 50 years. To reduce space, the similar results for the MITT population are not displayed. The age group tables for the ITT population has more cases and is displayed below:

Table 17. Study 312 Response Measures by Age Group (ITT Population)

Mycological Cure, Complete Cure, & Effective Treatment:

	4	8	12	16	20	24	28	32	36	40	44	48	LOCF (48 wks)	Post-treat. +12 wks	Post-treat. +24 wks
Loprox Age<50															
Myco	0	0	5	2	0	16	2	1	13	2	.	13	17	1	1
N	1	1	33	9	1	31	10	1	32	7	.	33	50	48	49
%	0.0	0.0	15.2	22.2	0.0	51.6	20.0	100.0	40.6	28.6	.	39.4	34.0	2.1	2.0
Age 50+															
Myco	0	.	8	6	.	14	1	0	13	4	.	12	14	1	1
N	1	.	40	14	.	41	11	2	37	14	.	46	56	56	56
%	0.0	.	20.0	42.9	.	34.1	9.1	0.0	35.1	28.6	.	26.1	25.0	1.8	1.8
Vehicle Age<50															
Myco	.	.	6	0	.	10	1	1	7	1	0	4	7	1	1
N	.	.	39	15	.	40	8	3	26	15	2	33	53	53	53
%	.	.	15.4	0.0	.	25.0	12.5	33.3	26.9	6.7	0.0	12.1	13.2	1.9	1.9
Age 50+															
Myco	0	1	4	1	0	4	1	0	6	2	0	5	6	0	0
N	2	1	39	13	1	30	15	1	30	11	3	34	55	55	55
%	0.0	100.0	10.3	7.7	0.0	13.3	6.7	0.0	20.0	18.2	0.0	14.7	10.9	0.0	0.0
Loprox Age<50															
Cure	0	0	0	0	0	0	0	0	0	0	0	2	2	1	1
N	49	44	45	44	39	39	40	40	39	34	36	40	54	52	53
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.0	3.7	1.9	1.9
Age 50+															
Cure	0	0	0	0	0	0	0	0	1	0	0	2	2	1	1
N	53	48	46	45	50	49	46	51	47	42	42	51	58	58	58
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1	0.0	0.0	3.9	3.4	1.7	1.7
Vehicle Age<50															
CURE	0	0	0	0	0	0	0	1	1	0	0	1	1	1	1
N	50	50	42	48	44	49	45	42	37	40	36	42	54	54	54
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.4	2.7	0.0	0.0	2.4	1.9	1.9	1.9
Age 50+	All percentages are 0.0														
Loprox Age<50															
Eff trt	0	0	0	0	0	0	0	0	2	1	0	3	4	1	1
N	4	1	40	13	2	32	15	2	30	9	3	31	49	47	48
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6.7	11.1	0.0	9.7	8.2	2.1	2.1
Age 50+															
Eff trt	0	0	0	0	0	1	0	0	2	1	0	3	3	1	1
N	8	1	40	15	4	43	14	3	36	16	2	47	57	57	57
%	0.0	0.0	0.0	0.0	0.0	2.3	0.0	0.0	5.6	6.3	0.0	6.4	5.3	1.8	1.8
Vehicle Age<50															
Eff trt	0	0	1	0	0	1	0	1	1	0	0	1	1	1	1
N	2	1	39	17	1	41	12	3	27	19	4	35	54	54	54
%	0.0	0.0	2.6	0.0	0.0	2.4	0.0	33.3	3.7	0.0	0.0	2.9	1.9	1.9	1.9
Age 50+	All percentages are 0.0														

Again, for all response variables, just descriptively there no particular evidence of differential treatment effects across age groups.

b. Protocol 313

The protocol for this study was virtually identical to the preceding study 312.

I. Patient Demographics:

The demographic characteristics of the baseline population are summarized in the following table. Again, the ITT population is defined as all subjects dispensed treatment, while the MITT is those subjects with confirmed mycological infection (as measured by both KOH and culture) at baseline.

Table 18. Demographics

	MITT		ITT	
	Ciclopirox	Vehicle	Ciclopirox	Vehicle
Gender				
Male	69	71	94	89
Female	15	21	25	29
Race				
White	73	82	103	104
Black	3	4	4	6
Oriental	3	0	4	0
Hispanic	4	4	6	6
Other	1	2	2	2
Total	84	92	119	118
Age				
Mean (Std Dev)	51.0 (10.8)	49.2 (12.2)	49.6 (11.9)	50.1 (12.2)
Range	28-70	23-70	19-70	23-70
% Area at Baseline				
Mean (Std Dev)	37.7 (10.9)	37.8 (9.8)	38.2 (11.0)	37.6 (9.4)
Range	19.6-64.5	9.6-61.8	19.6-64.5	9.6-61.8

Again, though not displayed here, it is apparent that there are no statistically significant differences among treatments with respect to age. gender, race (white versus other), or percent area at baseline.

Table 19. Disposition of Subjects

	MITT		ITT	
	Ciclopirox	Vehicle	Ciclopirox	Vehicle
Completed	75	74	96	94
Withdrawn	9	18	23	24
Violation of Protocol	2	6	7	7
Unreliability	2	4	5	6
Lost to Follow-up	3	2	3	2
Adverse Event	0	1	0	1
Lack of efficacy	0	3	1	3
Discontinued	2	3	7	5
Total	84	92	119	118

In the ITT population there are clearly no treatment related differences within each classification. The differences in the MITT group are a bit more problematic, but are not considered to be of importance.

ii. Efficacy Results:

The following patients achieved a clear nail with negative mycology, and entered the post-treatment phase, where an "S" denotes a "success" and "F" a failure for the indicated response variable. When only "S" or "F" is indicated it refers to all three response measures, i.e., mycological cure, complete cure, and effective treatment. An "NA" means not available or undefined.

Table 20. Patients Entering Post-treatment Phase (ITT group)

Treatment	Investigator	Subject	Results at 12 week follow-up	Results at 24 week follow-up
Loprox	28	1116*	F	F
	36	1202*	Cure F Oth NA	NA
	36	1211	S	S
	36	1220*	S	NA
	36	1224	Myco S Oth NA	NA
	47	1422	S	S
	63	1509*	F	NA
	88	1802*	Myco S Oth F	NA

* - These subjects are also in the MITT population

As in the 312 study, for mycological cure, tables are given for weeks 4-48, and for weeks 12 and 24 post-treatment. Below the entries for week 48, for the last observation carried forward (LOCF) at or below week 48, or week 12 or week 24 post-treatment is the "p-value," significance level, of a test of within center homogeneity of cure over treatment, using a Mantel-Haenszel test and a corresponding Fisher Exact test. As described above, the Fisher Exact test is preferred by this reviewer for this particular analysis.. For week 48 and the LOCF at or below week 48, success is defined as a simple mycological cure, and failure is any other valid response as explained in the response matrix above. For the approximate week 12 and week 24 tests a success is defined a mycological cure during the post-treatment period. A failure is defined as either a mycological failure during the post-treatment period, or as failure to enter the post-treatment period. One might suspect that it would have been preferable to include all patients in the post-treatment period, but that was not allowed in the original design.

Table 21. Study 313 Mycological Cure (MITT Population)

	Week: 4	12	16	20	24	28	32	36	40	44
Loprox										
mycological	0	19	5	0	20	5	0	27	7	1
N	0	64	19	1	53	22	1	53	23	2
%	.	29.7	26.3	0.0	37.7	22.7	0.0	50.9	30.4	50.0
Vehicle										
mycological	0	8	1	0	10	0	0	5	2	0
N	1	70	18	3	59	20	2	56	16	4
%	0.0	11.4	5.6	0.0	16.9	0.0	0.0	8.9	12.5	0.0

			Post-treatment 12 week (+ LOCF)	24 week (+ LOCF)
	48	LOCF-(48 wks)		
Loprox				
mycological	26	30	2	0
N	66	84	82	79
%	39.4	35.7	2.4	0.0
Vehicle				
mycological	5	6	0	0
N	67	91	91	91
%	0.0	0.0	0.0	0.0
CMH p-value	0.001	0.001	0.107	NA
Fisher p-value	>0.001	>0.001	0.226	NA

At the completion of the treatment period (week 48), differences in mycological cure rate between ciclopirox lacquer and its vehicle, say roughly 36% to 39% versus 0% is highly statistically significant ($p \leq 0.001$ at both week 48 and LOCF week 48 respectively). However, as commented above, these results may be considered suspect due to the possibility of slight amounts of Ciclopirox lacquer possibly contaminating the sample. At week 12 or 24 posttreatment, there is no statistically significant evidence of a difference ($p \leq 0.226$). At week 24, both proportions are the same, namely zero. However, since there is no variance, neither the CMH nor the Fisher Exact test statistic is defined.

Again, complete cure (sponsor labeled "Treatment Cure") was defined as the occurrence of a mycological cure with a score of 0 on the global evaluation scale above. The following table displays these results for the MITT population:

Table 22. Study 313 Complete Cure (MITT Population)

	Week: 4	8	12	16	20	24	28	32	36	40	44	48
Loprox												
cure	0	0	0	0	0	0	0	0	0	0	1	5
N	77	76	72	73	72	70	69	76	73	68	70	75
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.4	6.7
Vehicle												
cure	0	0	0	0	0	0	0	0	0	0	0	0
N	85	83	79	81	81	73	72	70	71	67	68	75
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

	48	LOCF-(48 wks)	Post-treatment 12 week (+ LOCF)	24 week (+ LOCF)
Loprox				
cure	5	5	1	0
N	75	84	83	79
%	6.7	6.0	1.2	1.2
Vehicle				
cure	0	0	0	0
N	75	92	92	92
%	0.0	0.0	0.0	0.0
CMH p-value	0.019	0.012	0.254	NA
Fisher p-value	0.058	0.023	0.477	NA

For complete cure at week 48, treatment differences are barely statistically nonsignificant ($p \leq 0.058$) while at the LOCF point at the end of study day treatment differences are barely statistically significant ($p \leq 0.023$). However, at both time points in the post-treatment period, differences, 1% or 0% versus 0%, are not statistically significant (roughly, $p \leq 0.477$ at the 12 week endpoint).

Effective treatment (sponsor labeled "Treatment Success") was defined as the occurrence of either a complete cure or a mycological cure with less than 10% involvement as expressed by a planimetric measurement:

Table 23. Study 313 Effective Treatment (MITT Population)

	Week: 4	8	12	16	20	24	28	32	36	40	44
Loprox											
eff trt	0	0	0	0	0	1	0	0	5	1	1
N	9	0	64	25	2	55	28	5	53	27	5
%	0.0	.	0.0	0.0	0.0	1.8	0.0	0.0	9.4	3.7	20.0
Vehicle											
eff trt	0	0	0	0	0	1	0	0	0	0	0
N	12	3	74	30	6	62	26	3	59	18	5
%	0.0	0.0	0.0	0.0	0.0	1.6	0.0	0.0	0.0	0.0	0.0

	48	LOCF- (48 wks)	Post-treatment 12 week (+ LOCF)	24 week (+ LOCF)
Loprox				
eff trt	7	8	1	0
N	66	84	82	79
%	10.6	9.5	2.4	0.0
Vehicle				
eff trt	1	1	0	0
N	72	92	92	92
%	1.4	1.1	0.0	0.0
CMH p-value	0.030	0.012	0.229	NA
Fisher p-value	0.028	0.014	0.474	NA

Note that for effective treatment (sponsor labeled "Treatment Success"), at the end of week 48, and at the corresponding LOCF point at week 48, the differences between the ciclopirox lacquer and its vehicle, roughly 10% to 1%, are statistically significant ($p \leq 0.028$ and $p \leq 0.014$, respectively). However, at the 12 week endpoint differences, 2% versus 0%, are not statistically significant ($p \leq 0.224$). At week 24, both proportions are the same, namely zero. However, since there is no variance, neither test statistic is defined.

As noted above, statistically, the percent area from planimetric measurements is a very attractive endpoint. However, as also discussed above, it is, unfortunately, not appropriate as a primary endpoint. Response profiles for the two treatment groups look similar to those in Figures 1.0 and 2.0. Again, profiles for the MITT population are a subset of those displayed here, but are equally messy. Clearly these are difficult to interpret. Again, we overlay Lowess local smoothers for each treatment group to display mean structure in figure 7 (again, actually for the ITT data). Data for the MITT population would be similar.

Again omnibus test of treatment differences over time were computed using "area under the curve" (AUC) and "generalized estimating equations" (GEE) techniques. Though not displayed here, the AUC approach showed no statistically significant treatment differences between treatments, while the GEE approach did ($p \leq 0.002$). As noted earlier, tests at each

week will have more power, but tend to inflate Type I error due to the multiplicity of tests. For the MITT population these tests of treatment differences in mean percent area from planimetric measurements appear below, i.e., the following table displays least squares means and p-values from a Type 3 analysis of variance with mean percent area as response and investigator, treatment group, and interaction as factors. The p-value is from the test of differences in these least squares means (i.e., type III sums of squares).

Table 24. Study 313 Mean Percent Area from Planimetric Measurements (MITT Population)

Week:	12	LOCF(12 wks)	24	LOCF(24 wks)	36	LOCF(36 wks)	48	LOCF(48 wks)	LOCF (60 wks)
Loprox									
LS Mean	41.5	40.2	35.7	40.9	31.5	36.7	36.9	37.2	37.6
Std Err	2.4	1.9	2.7	2.2	2.7	2.3	2.7	2.4	2.4
N	59	84	53	84	50	84	61	84	84
Vehicle									
LS Mean	40.1	39.5	41.4	41.0	44.0	42.6	45.4	44.1	44.2
Std Err	2.1	1.7	2.6	2.1	2.6	2.2	2.8	2.3	2.3
N	71	91	55	91	52	91	61	91	91
p-value*	0.6568	0.7958	0.1323	0.9861	0.0014	0.0689	0.0268	0.0396	0.0482

* - From ANOVA test of treatment differences (Type 3 SSQ)

Note at week 48 and its corresponding LOCF point, differences are statistically significant ($p \leq 0.0268$ and $p \leq 0.0396$, respectively), though the evidence is not exactly overwhelming..

Again, the ITT population consists of all patients given treatment, and corresponds to the sponsor's ITT group. For each patient at or before week 48, success is defined as a simple mycological cure, and failure is any other valid response as explained in the response matrix above. For the approximate week 12 and week 24 tests a success is defined a mycological cure during the post-treatment period. A failure is defined as either a mycological failure during the post-treatment period, or as failure to enter the post-treatment period. For this ITT population the table of mycological cures appears below:

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Table 25. Study 313 Mycological Cure (ITT Population)

Mycological Cure (KOH & culture negative)

Week:		4	12	16	20	24	28	32	36	40	44
Loprox	myco cure	0	24	7	0	28	7	0	37	12	1
	N	1	89	26	3	73	28	2	71	30	2
	%	0.0	27.0	26.9	0.0	38.4	25.0	0.0	52.1	40.0	50.0
Vehicle	myco cure	0	10	2	0	15	0	0	14	3	0
	N	1	86	22	3	76	25	2	72	20	4
	%	0.0	11.6	9.1	0.0	19.7	0.0	0.0	19.4	15.0	0.0

		48	LOCF- (48 wks)	Post-treatment 12 week (+ LOCF)	Post-treatment 24 week (+ LOCF)
Loprox	myco cure	34	42	5	2
	N	85	119	114	110
	%	40.0	36.2	3.4	2.6
Vehicle	myco cure	10	11	0	0
	N	86	114	114	114
	%	11.6	9.6	0.0	0.0
CMH p-value		0.001	0.001	0.020	0.132
Fisher p-value		<0.001	<0.001	0.060	0.242

At the completion of the treatment period (week 48), differences in mycological cure rate between ciclopirox lacquer and its vehicle in the ITT sample, say roughly 36-40% versus 9-12%, are statistically significant ($p \leq 0.001$, at both week 48 and LOCF week 48 respectively). At week 12 or 24 posttreatment, there is no statistically significant evidence of a difference (roughly $p \leq 0.060$ or $p \leq 0.242$, respectively).

As noted above, complete cure (sponsor labeled "Treatment Cure") was defined as the occurrence of a mycological cure with a score of 0 on the global evaluation scale above. The following table displays these results for the ITT population:

Table 26. Study 313 Complete Cure (ITT Population)

Week:		4	8	12	16	20	24	28	32	36	40	44
Loprox	cure	0	0	0	0	0	2	0	0	2	1	1
	N	106	104	100	101	98	96	90	98	93	87	87
	%	0.0	0.0	0.0	0.0	0.0	2.1	0.0	0.0	2.2	1.1	1.1
Vehicle	cure	0	0	0	0	0	0	0	0	0	0	0
	N	105	106	100	100	103	92	93	88	91	87	87
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 26 (cont.) Study 313 Complete Cure (ITT Population)

				Post-treatment	
		48	LOCF- (48 wks)	12 week (+ LOCF)	24 week (+ LOCF)
Loprox	cure	8	10	3	2
	N	95	118	115	111
	%	8.4	8.5	3.5	2.7
Vehicle	cure	0	0	0	0
	N	85	117	117	117
	%	0.0	0.0	0.0	0.0
CMH p-value		0.004	0.001	0.066	0.134
Fisher p-value		0.007	0.002	0.122	0.240

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For complete cure at week 48 and its corresponding LOCF point, treatment differences are statistically significant ($p \leq 0.007$ and $p \leq 0.002$, respectively). However, at both time points in the post-treatment period, differences, 3% versus 0%, are not statistically significant (roughly, at the nominal 12 and 24 week posttreatment evaluations, $p \leq 0.122$ and $p \leq 0.240$ respectively).

Effective treatment (sponsor labeled "Treatment Success") was defined as the occurrence either a complete cure or a mycological cure with less than 10% involvement as expressed by a planimetric measurement:

Table 27. Study 313 Effective Treatment (ITT Population)

		4	8	12	16	20	24	28	32	36	40	44
Loprox	eff trt	0	0	1	0	0	3	0	0	10	2	1
	N	14	0	89	36	5	76	35	6	70	34	6
	%	0.0	.	1.1	0.0	0.0	3.9	2.9	0.0	14.3	5.9	16.7
Vehicle	eff trt	0	0	0	0	0	1	0	0	1	0	0
	N	14	4	92	36	6	80	32	3	75	22	6
	%	0.0	0.0	0.0	0.0	0.0	1.3	0.0	0.0	1.3	0.0	0.0

				Post-treatment	
		48	LOCF- (48 wks)	12 week (+ LOCF)	24 week (+-LOCF)
Loprox	eff trt	11	14	3	2
	N	86	116	113	111
	%	12.8	12.1	3.5	2.7
Vehicle	eff trt	1	1	0	0
	N	92	115	115	115
	%	1.2	0.9	0.0	0.0
CMH p-value		0.003	0.001	0.058	0.125
Fisher p-value		0.002	0.001	0.122	0.240

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For effective treatment (sponsor labeled "Treatment Success"), at the end of week 48 and its corresponding LOCF point, differences are statistically highly significant ($p \leq 0.002$ or $p \leq 0.001$, respectively). At both time points in the post-treatment period, differences, roughly 3% versus 0%, are not statistically significant (roughly, $p \leq 0.122$ at week 12 and $p \leq 0.240$ at week 24).

As described above for the ITT population the response profiles of percent area cleared computed from planimetric measurements appear in figures 6 and 7 of the appendix. Figures 8 and 9 display a so-called "Lowess" smooth for each treatment group. Figure 10 overlays the two smoothers for each treatment group. As in the 312 study, we can see that the ciclopirox mean is smaller, but the difference is fairly small relative to the amount of variation in the data.

Again omnibus tests of treatment differences over time were computed using "area under the curve" and "generalized estimating equations" techniques. Though not displayed here, neither approach showed statistically significant treatment differences between treatments. . The p-value below is from the test of differences in the least squares means (i.e., type III sums of squares) of treatment group.

Table 28. Study 313 Mean Percent Area from Planimetric Measurements (ITT Population)

Week:	12	LOCF(12 wks)	24	LOCF(24 wks)	36	LOCF(36 wks)	48	LOCF(48 wks)	LOCF(60 wks)
Loprox									
LS Mean	41.5	40.4	36.8	41.4	32.6	37.9	36.5	37.9	38.4
Std Err	2.0	1.6	2.2	1.9	2.5	2.0	2.4	2.1	2.1
N	81	115	74	115	67	115	80	115	115
Vehicle									
LS Mean	39.7	38.9	40.3	40.7	42.7	42.2	45.8	44.0	44.4
Std Err	2.0	1.6	2.3	1.9	2.4	2.0	2.4	2.1	2.1
N	87	110	71	112	69	112	78	112	112
p-value*	0.5369	0.4998	0.2667	0.8043	0.0039	0.1252	0.0076	0.0405	0.0433

* - From ANOVA test of treatment differences (Type 3 SSQ)

Differences at the end of treatment, i.e., week 48, or its corresponding LOCF point, are statistically significant, though barely for the LOCF endpoint ($p \leq 0.0076$ and $p \leq 0.0405$, respectively).

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iii. Subgroup Results:

The following tables display results by gender and age group (less than 50 years versus greater than or equal to 50 years). Again, it is this reviewer's opinion that there are too few non-white subjects to make a breakdown by race readily interpretable.

Table 29. Study 313 Response Measures by Gender (MITT Population)

Mycological Cure, Complete Cure, & Effective Treatment:	4	12	16	20	24	28	32	36	40	44	48	LOCF (48 wks)	Post-treatmenr +12 wks	+24 wks
Loprox Male														
Myco	.	14	5	0	18	4	0	20	6	0	20	24	1	0
N	.	49	19	1	44	18	1	42	20	1	53	69	69	67
%	.	28.6	26.3	0.0	40.9	22.2	0.0	47.6	30.0	0.0	37.7	34.8	1.4	0.0
Female														
Myco	.	5	.	.	2	1	.	7	1	1	6	6	1	0
N	.	15	.	.	9	4	.	11	3	1	13	15	13	12
%	.	33.3	.	.	22.2	25.0	.	63.6	33.3	100.0	46.2	40.0	7.7	0.0
Vehicle Male														
Myco	.	8	0	0	8	0	0	4	1	0	5	6	0	0
N	.	56	12	1	45	16	2	42	15	2	52	70	70	70
%	.	14.3	0.0	0.0	17.8	0.0	0.0	9.5	6.7	0.0	9.6	8.6	0.0	0.0
Female														
Myco	0	0	1	0	2	0	.	1	1	0	0	0	0	0
N	1	14	6	2	14	4	.	14	1	2	15	21	21	21
%	0.0	0.0	16.7	0.0	14.3	0.0	.	7.1	100.0	0.0	0.0	0.0	0.0	0.0
Loprox Male														
Cure	0	0	0	0	0	0	0	0	0	0	0	2	2	1	0
N	63	62	57	63	60	58	58	63	59	55	57	61	69	69	67
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.3	2.9	1.4	0.0
Female														
Cure	0	0	0	0	0	0	0	0	0	0	1	3	3	0	0
N	14	14	15	10	12	12	11	13	14	13	13	14	15	14	12
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.7	21.4	20.0	0.0	0.0
Vehicle														
Cure	All proportions are 0.0 for both genders													
Loprox Male														
Eff trt	0	.	0	0	0	1	0	0	1	1	0	3	4	1	0
N	6	.	49	24	1	45	23	3	42	24	4	52	67	67	65
%	0.0	.	0.0	0.0	0.0	2.2	0.0	0.0	2.4	4.2	0.0	5.8	6.0	1.5	0.0
Female														
Eff trt	0	.	0	0	0	0	0	0	4	0	1	4	4	0	0
N	3	.	15	1	1	10	5	2	11	3	1	11	14	12	11
%	0.0	.	0.0	0.0	0.0	0.0	0.0	0.0	36.4	0.0	100.0	36.4	28.6	0.0	0.0
Vehicle														
Eff trt	All proportions are 0.0 for both genders													

Again, for all response variables, just descriptively there no particular evidence of differential treatment effects of gender. Similar conclusions hold for the ITT population.

Table 30. Study 313 Response Measures by Gender (ITT Population)

Mycological Cure, Complete Cure, & Effective Treatment:

	4	12	16	20	24	28	32	36	40	44	48	LOCF (48 wks)	Post-treat. +12 wks	Post-treat. +24 wks
Loprox Male														
Myco	0	18	7	0	23	5	0	26	10	0	27	34	3	1
N	1	67	25	3	57	23	2	54	25	1	67	93	93	90
%	0.0	26.9	28.0	0.0	40.4	21.7	0.0	48.1	40.0	0.0	40.3	36.6	3.2	1.1
Female														
Myco	.	6	0	.	5	2	.	11	2	1	7	8	2	0
N	.	22	1	.	16	5	.	17	5	1	18	23	21	19
%	.	27.3	0.0	.	31.3	40.0	.	64.7	40.0	100.0	38.9	34.8	9.5	0.0
Vehicle Male														
Myco	.	9	1	0	13	0	0	11	1	0	8	9	0	0
N	.	65	16	1	58	19	2	52	18	2	65	86	86	86
%	.	13.8	6.3	0.0	22.4	0.0	0.0	21.2	5.6	0.0	12.3	10.5	0.0	0.0
Female														
Myco	0	1	1	0	2	0	.	3	2	0	2	2	0	0
N	1	21	6	2	18	6	.	20	2	2	21	28	28	28
%	0.0	4.8	16.7	0.0	11.1	0.0	.	15.0	100.0	0.0	9.5	7.1	0.0	0.0

Complete Cure, & Effective Treatment:

	4	8	12	16	20	24	28	32	36	40	44	48	LOCF (48 wks)	Post-treat. +12 wks	Post-treat. +24 wks
Loprox Male															
Cure	0	0	0	0	0	1	0	0	0	0	0	4	5	2	1
N	84	83	77	83	78	77	73	80	73	69	70	76	94	93	91
%	0.0	0.0	0.0	0.0	0.0	1.3	0.0	0.0	0.0	0.0	0.0	5.3	5.3	2.2	1.1
Female															
Cure	0	0	0	0	0	1	0	0	2	1	1	4	5	1	0
N	22	21	23	18	20	19	17	18	20	18	17	19	24	23	20
%	0.0	0.0	0.0	0.0	0.0	5.3	0.0	0.0	10.0	5.6	5.9	21.1	20.8	4.3	0.0
Vehicle															
Cure	All proportions are 0.0 for both genders														
Loprox Male															
Eff trt 0	.	1	0	0	2	0	0	4	1	0	6	8	2	1	
N	11	.	67	33	4	59	29	4	53	29	5	67	91	90	88
%	0.0	.	1.5	0.0	0.0	3.4	0.0	0.0	7.5	3.4	0.0	9.0	8.8	2.2	1.1
Female															
Eff trt 0	.	0	0	0	1	1	0	6	1	1	5	6	1	0	
N	3	.	22	3	1	17	6	2	17	5	1	16	22	20	18
%	0.0	.	0.0	0.0	0.0	5.9	16.7	0.0	35.3	20.0	100.0	31.3	27.3	5.0	0.0
Vehicle Male															
Eff trt 0	0	0	0	0	1	0	0	1	0	0	1	1	0	0	
N	10	2	71	28	2	61	26	2	55	19	3	69	86	86	86
%	0.0	0.0	0.0	0.0	0.0	1.6	0.0	0.0	1.8	0.0	0.0	1.4	1.2	0.0	0.0
Female															
Eff trt	All proportions are 0.0														

Again, for all response variables, just descriptively there no particular evidence of differential treatment effects of gender.

Table 31. Study 313 Response Measures by Age Group (ITT Population)

Mycological Cure

	4	2	16	20	24	28	32	36	40	44	48	LOCF (48 wks)	Post-treat. +12 wks	Post-treat. +24 wks
Loprox Age<50														
Myco	0	13	3	0	11	5	0	17	9	1	16	21	3	0
N	1	48	12	2	34	16	2	29	21	2	41	59	57	53
%	0.0	27.1	25.0	0.0	32.4	31.3	0.0	58.6	42.9	50.0	39.0	35.6	5.3	0.0
Age 50+														
Myco	.	11	4	0	17	2	.	20	3	.	18	21	2	1
N	.	41	14	1	39	12	.	42	9	.	44	57	57	56
%	.	26.8	28.6	0.0	43.6	16.7	.	47.6	33.3	.	40.9	36.8	3.5	1.8
Vehicle Age<50														
Myco	.	3	2	0	7	0	.	4	2	0	2	3	0	0
N	.	42	10	1	37	13	..	31	12	3	40	55	55	55
%	.	7.1	20.0	0.0	18.9	0.0	.	12.9	16.7	0.0	5.0	5.5	0.0	0.0
Age 50+														
myco	0	7	0	0	8	0	0	10	1	0	8	8	0	0
N	1	44	12	2	39	12	2	41	8	1	46	59	59	59
%	0.0	15.9	0.0	0.0	20.5	0.0	0.0	24.4	12.5	0.0	17.4	13.6	0.0	0.0

Complete Cure, & Effective Treatment:

	4	8	12	16	20	24	28	32	36	40	44	48	LOCF (48 wks)	Post-treat. +12 wks	Post-treat. +24 wks
Loprox Age<50															
Cure	0	0	0	0	0	2	0	0	2	1	1	6	8	1	0
N	55	53	51	48	48	46	41	46	43	43	45	46	61	59	55
%	0.0	0.0	0.0	0.0	0.0	4.3	0.0	0.0	4.7	2.3	2.2	13.0	13.1	1.7	0.0
Age 50+															
Cure	0	0	0	0	0	0	0	0	0	0	0	2	2	2	1
N	51	51	49	53	50	50	49	52	50	44	42	49	57	57	56
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.1	3.5	3.5	1.8
Vehicle															
Cure	All Proportions are 0.0 for both age groups														
Loprox Age <50															
Eff trt	0	.	1	0	0	3	1	0	6	2	1	8	10	1	0
N	7	.	48	16	4	35	19	5	30	22	6	41	58	55	52
%	0.0	.	2.1	0.0	0.0	8.6	5.3	0.0	20.0	9.1	16.7	19.5	17.2	1.8	0.0
Age 50+															
Eff trt	0	.	0	0	0	0	0	0	4	0	.	3	4	2	1
N	7	.	41	20	1	41	16	1	40	12	.	42	55	55	54
%	0.0	.	0.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0	.	7.1	7.3	3.6	1.9
Vehicle Age <50															
Eff trt	All proportions are 0.0														
Age 50+															
Eff trt	0	0	0	0	0	1	0	0	1	0	0	1	1	0	0
N	8	2	47	21	5	42	17	2	42	9	2	48	59	59	59
%	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.0	2.4	0.0	0.0	2.1	1.7	0.0	0.0

Once more, for all response variables, just descriptively there no particular evidence of differential treatment effects of age

c. Study No. 211

This was a double-blind, randomized, multicenter trial comparing the efficacy and safety of Ciclopirox (Loprox) nail lacquer 8% versus its vehicle in patients with dermatophytic onychomycosis of the fingernails. Patients were seen on a monthly basis, the maximum treatment period consisting of six consecutive months. Thus visit 1 corresponds to the baseline measure, visits 2 through 7 correspond to the monthly visits, at weeks 4, 8, 12, 16, 20, and 24. Visit 8 was posttreatment, 4-8 weeks posttreatment. Mycological evaluations were scheduled to be performed at visit 1 (baseline), visit 3 (week 8), visit 7 (week 24), and visit 8 (week 28-32). The tables reflect the actual time of observation.

Mycological cure was defined as in the previous studies. In addition, an investigator's global assessment of the target nail was scored as:

0 = Cure 100%
1 = Improvement: 50 to <100%
2 = Poor or No Improvement: <50%

Complete cure was defined as the occurrence of a mycological cure with a score of 0 on the global assessment above.

ii. Efficacy Results:

Tables are given for the binary response measures described above for visits 1-8, and for the last observation carried forward (LOCF) at or below week 28-32. Below each of these visits is the "p-value," significance level, of a test of within center homogeneity of mycological cure over treatment, using a Mantel-Haenszel test stratified on investigator and a corresponding Fisher Exact test. As noted in the statistical comment above, it seems to this reviewer that a chi-square test of homogeneity or a Fisher exact test, ignoring investigator, would be superior to the usual model or design-based CMH test.

Table 32. Study 211 Mycological Cure (MITT Population)

	Visit Number								
	01	02	03	04	05	06	07	08	LOCF
Ciclopirox									
Myco. Cure	0	0	.	.	0	4	5	3	3
N	20	2	.	.	20	20	19	19	20
%	0.0	0.0	.	.	0.0	20.0	26.3	15.8	15.0
Vehicle									
Myco. Cure	0	0	0	0	0	6	3	2	3
N	24	3	1	1	24	22	18	14	24
%	0.0	0.0	0.0	0.0	0.0	27.3	16.7	14.3	12.5
CMH p-value	NA	NA	NA	NA	NA	0.591	0.397	0.823	0.793
Exact p-value	NA	NA	NA	NA	NA	0.723	0.693	1.000	1.000

Note there are some discrepancies between the results reported here and the results given by the sponsor in their reports (particularly volumes 1.63 and 1.66). However, they do seem to reflect the data sets as provided to this reviewer.

Even without performing any statistical test it is clear that the proportions of mycological cure show no difference between Ciclopirox lacquer 8% and its corresponding vehicle (In fact, p-values for tests of difference posttreatment and LOCF are extremely nonsignificant p≤1.000). Similar results hold for complete cure:

Table 33. Study 211 Complete Cure (MITT Population)

	Visit Number								
	01	02	03	04	05	06	07	08	LOCF
Ciclopirox									
Complete Cure	0	0	.	.	0	0	0	1	1
N	20	2	.	.	20	20	19	19	20
%	0.0	0.0	.	.	0.0	0.0	0.0	5.3	5.0
Vehicle									
Complete Cure	0	0	0	0	0	0	0	0	0
N	24	3	1	1	24	22	19	15	24
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CMH p-value	NA	NA	NA	NA	NA	NA	NA	0.439	0.371
Exact p-value	NA	NA	NA	NA	NA	NA	NA	1.000	0.465

Again, even without performing any statistical test it is clear that the proportions of complete cure show no statistically significant differences between Ciclopirox lacquer 8% and its corresponding vehicle. (p≤1.000 and p≤0.465 at week 8 and LOCF). Similar results hold for the ITT population:

Table 34. Study 211 Mycological Cure (ITT Population)

	Visit Number								
	01	02	03	04	05	06	07	08	LOCF
Ciclopirox									
Myco. Cure	3	1	0	.	0	9	8	6	7
N	42	22	6	.	42	42	39	31	42
%	7.1	4.5	0.0	.	0.0	21.4	20.5	19.4	16.7
Vehicle									
Myco. Cure	2	0	0	0	0	6	6	3	5
N	43	19	6	1	44	41	36	26	44
%	4.7	0.0	0.0	0.0	0.0	14.6	16.7	11.5	11.4
CMH p-value	0.581	0.414	NA	NA	NA	0.463	0.581	0.732	0.406
Exact p-value	0.676	1.000	NA	NA	NA	0.570	0.771	0.488	0.545

Again, even though success rates in the Ciclopirox group tend to dominate those in the corresponding vehicle group, without performing any statistical test it is clear that the proportions of mycological cure show no difference between Ciclopirox lacquer 8% and its

vehicle. (In fact, p-values for tests of difference posttreatment and LOCF are extremely nonsignificant: p≤0.545).

Results for complete cure in the ITT population virtually coincide with those for the MITT population:

Table 35. Study 211 Complete Cure (ITT Population)

	Visit Number								
	01	02	03	04	05	06	07	08	LOCF
Ciclopirox									
Complete Cure	0	0	0	.	0	0	0	1	1
N	39	22	6	.	42	42	40	32	39
%	0.0	0.0	0.0	.	0.0	0.0	0.0	3.1	2.7
Vehicle									
Complete Cure	0	0	0	0	0	0	1	0	1
N	41	19	6	1	44	41	37	28	41
%	0.0	0.0	0.0	0.0	0.0	0.0	2.7	0.0	2.5
CMH p-value	NA	NA	NA	NA	NA	NA	0.317	0.361	0.808
Exact p-value	NA	NA	NA	NA	NA	NA	0.481	1.000	1.000

Again, even without performing any statistical test it is clear that the proportions of complete cure show no statistically significant differences between Ciclopirox lacquer 8% and its corresponding vehicle (p≤1.000 at week 8 and LOCF).

d. Study No. 212

For the endpoints considered here, this study was virtually identical to the 211 study.

ii. Efficacy Results:

Again, results for the MITT population are displayed first:

Table 36. Study 212 Mycological Cure (MITT Population)

	Visit Number							
	01	02	03	05	06	07	08	LOCF
Ciclopirox								
Myco. Cure	0	0	.	0	10	8	7	7
N	37	1	.	36	35	34	31	37
%	0.0	0.0	.	0.0	28.6	23.5	22.6	18.9
Vehicle								
Myco. Cure	0	0	1	0	5	5	7	7
N	40	5	1	39	39	35	35	40
%	0.0	0.0	100.0	0.0	12.8	14.3	20.0	17.5
CMH p-value	NA	NA	NA	NA	0.097	0.362	0.882	0.935
Exact p-value	NA	NA	NA	NA	0.147	0.371	1.000	1.000

Again, even without performing any statistical test it is clear that the proportions of mycological cure show no statistically significant differences across treatment groups (p≤1.000 at both week 8 and LOCF).

Table 37. Study 212 Complete Cure (MITT Population)

	Visit Number							
	01	02	03	05	06	07	08	LOCF
Ciclopirox								
Complete Cure	0	0	.	0	0	1	3	3
N	37	1	.	37	34	35	31	37
%	0.0	0.0	.	0.0	0.0	2.9	9.7	8.1
Vehicle								
Complete Cure	0	0	0	0	0	0	2	2
N	40	5	1	39	38	36	36	40
%	0.0	0.0	0.0	0.0	0.0	0.0	5.6	5.0
CMH p-value	NA	NA	NA	NA	NA	0.414	0.673	0.704
Exact p-value	NA	NA	NA	NA	NA	0.493	0.656	0.667

As easily observed in the table above, the proportions of complete cures were virtually identical across visits (p≤0.667 at week 8 and LOCF).

Results for the ITT population follow:

Table 38. Study 212 Mycological Cure (ITT Population)

	Visit Number								
	01	02	03	04	05	06	07	08	LOCF
Ciclopirox									
Myco. Cure	2	0	0	0	0	14	12	9	9
N	51	12	5	1	53	52	49	45	54
%	3.9	0.0	0.0	0.0	0.0	26.9	24.5	20.0	16.7
Vehicle									
Myco. Cure	0	0	1	0	0	8	7	9	9
N	55	19	4	1	55	55	50	50	56
%	0.0	0.0	25.0	0.0	0.0	14.5	14.0	18.0	16.1
CMH p-value	0.146	NA	NA	NA	NA	0.087	0.184	0.721	0.890
Exact p-value	0.229	NA	0.444	NA	NA	0.152	0.211	1.000	1.000

Again, even without performing any statistical test it is clear that the proportions of mycological cure will show no statistically significant differences between Ciclopirox lacquer 8% and its corresponding vehicle. (p≤1.000 at week 8 and LOCF). Results for complete cure are similar:

Table 39. Study 212 Complete Cure (ITT Population)

	Visit Number								
	01	02	03	04	05	06	07	08	LOCF
Ciclopirox									
Complete Cure	0	0	0	0	0	0	3	4	4
N	49	12	5	1	54	51	50	45	53
%	0.0	0.0	0.0	0.0	0.0	0.0	6.0	8.9	7.5
Vehicle									
Complete Cure	0	0	0	0	0	0	1	3	3
N	55	19	4	1	55	54	51	51	56
%	0.0	0.0	0.0	0.0	0.0	0.0	2.0	5.9	5.4
CMH p-value	NA	NA	NA	NA	NA	NA	0.295	0.499	0.596
Exact p-value	NA	NA	NA	NA	NA	NA	0.362	0.702	0.711

Again, even without performing any statistical test it is apparent that the proportions of complete cure show no statistically significant differences across treatment groups ($p \leq 0.711$ at week 8 and LOCF).

4. Adverse Events

a. Pooled Studies 312 and 313

The following table presents both a count of adverse events and a count of the individuals experiencing adverse events, at least according to the data provided by the sponsor (Disclaimer: The sponsor's data set had numerous text descriptions with each adverse event code. These descriptions were summarized and consolidated by this reviewer, without particular input from the Medical Officer.)

To test the statistical significance of any differences in adverse events between Loprox lacquer 8% and its vehicle, first adverse events were screened for those with four or more three subjects experiencing the event. The number four was arbitrary, but reduces the number of adjustments required, and hence should increase power in the tests adjusted for multiplicity. Note that only the following comparisons were statistically significant (prior to adjusting for multiplicity of tests):

AE Code	Description	Unadjusted p-value	Adjusted p-value
3100	Laryngitis	0.0302	0.6982
4530	Allergies	0.0144	0.3116.

The unadjusted p-value is the p-value from a Fisher Exact test of differences between Loprox lacquer and its vehicle. Note that 71 of these adverse events involved four or more subjects. Adjusting the tests for this multiplicity of comparisons using the techniques of Westfall and Young (1993) gives the "Adjusted p-value" above. After adjusting for the multiplicity of tests, no comparisons are statistically significant (although the approriateness of the adjustment is arguable.).

Table 40. Adverse Events (Studies 312 and 313)

Adverse Event Code	Description	Loprox n indiv.	Vehicle n indiv.	Loprox n event	Vehicle n event
40	Abscessed Tooth	7	5	7	5
47	Sting,bite,injury	33	35	42	41
80	Rosacea	3	6	3	6
195	Allergic Reaction	3	3	3	3
200	Alopecia	.	2	.	2
205	Blurred Vision	.	3	.	3
300	Iron Deficiency Anemia	.	1	.	1
337	Aneurysm	.	1	.	2
340	Angina	2	.	2	.
384	Congenital Kidney Obstruction	.	1	.	1
430	Stress	4	3	6	5
457	Burning Left Toe	3	3	3	6
465	Heart Fibrillation	.	1	.	1
505	Musculoskeletal Pain	19	12	22	18
510	Arthritis	1	5	1	5
525	Inflammed Hip Joint	.	1	.	1
540	Fatigue	1	3	1	3
545	Asthma	2	2	2	4
550	Disturbed Balance	.	1	.	1
630	Second Degree Wenckebach Av Blck	.	1	.	1
685	Gilberts Syndrome	.	1	.	1
745	Bone Spur	2	2	3	2
765	Sinus Bradycardia	.	1	.	1
810	Bronchitis	9	11	11	15
835	Branch Block	1	.	1	.
840	Bursitis	3	.	3	.
860	Seminoma	.	1	.	1
865	Carcinoma	1	.	1	.
870	Cancer Right Breast	1	.	1	.
905	Prostate Cancer	2	2	3	2
910	Basal Cell Carcinoma	4	1	4	1
925	Heart Disease	.	3	.	3
1015	Cholecystitis	2	.	3	.
1185	Conjunctivitis	2	3	2	3
1190	Constipation	.	1	.	1
1240	Coronary Artery Disease	1	.	1	.
1250	Cough	1	3	1	5
1252	Muscle Spasms	2	1	2	1
1310	Skin Cyst	2	3	2	3
1317	Ovarian Cyst	1	.	1	.
1390	Depression	5	5	5	5
1400	Contact Dermatitis	5	12	6	13
1410	Tinea Pedis/Cruris/Corporis	32	43	41	49
1430	Diabetes	3	1	3	1
1435	Diarrhea	8	5	8	6
1470	Lightheaded	1	.	1	.
1525	Menstrual Cramps	.	2	.	2

Table 40 (cont.) Adverse Events (Studies 312 and 313)

Adverse Event Code	Description	Loprox n indiv.	Vehicle n indiv.	Loprox n event	Vehicle n event
1535	Indigestion	6	4	6	7
1560	Inflamed Tympanic Membranes	1	3	1	3
1562	Bruise	2	3	2	3
1580	Eczema	2	4	4	5
1600	Swollen Jaw	1	.	1	.
1630	Edema	1	.	1	.
1665	Ejaculatory Problems	.	1	.	2
1805	Epididymitis	.	2	.	3
1820	Epistaxis	1	.	2	.
1855	Esophageal Reflux	1	3	1	3
1900	Prem. Vent. Complexes	.	1	.	1
1910	Eye Infection	1	3	2	3
1945	Fever	1	1	1	1
1950	Atrial Fibrillation	1	.	1	.
2025	Plantar Fascitis	1	.	2	.
2032	Flu	20	19	23	25
2046	Broken bone	5	3	5	3
2047	Bloating	.	1	.	1
2055	Boil	2	.	2	.
2085	Gastritis	.	2	.	2
2095	Gastroenteritis	4	6	4	8
2100	Diverticulitis	5	6	5	7
2110	Periodontal Disease	2	.	2	.
2150	Glossitis	.	2	.	2
2230	Gout	3	4	5	5
2266	Gum Infection	2	.	2	.
2285	Headache	29	22	66	47
2295	Herniated Incision	.	1	.	1
2320	Congestive Heart Failure	1	.	1	.
2330	Skin Hemorrhage	3	1	3	1
2415	Rectal Bleeding	1	1	1	1
2433	Hematoma	2	1	2	1
2455	Microscopic Hematuria	1	.	1	.
2530	Hernia	1	6	1	6
2535	Herpes	2	4	2	4
2540	Shingles	1	1	1	1
2610	Hypercholeterolernia	2	.	2	.
2620	Elevated glucose	.	1	.	1
2675	Hypertension	5	7	5	7
2710	Actinic Keratosis	8	6	9	6
2715	Hyperupidemia	1	.	1	.
2895	Decreased Bladder Control	.	1	.	1
2925	Infection	9	9	9	10
2932	Cold/URI	75	76	109	112
2935	Pseudomonas	1	.	1	.

Table 40 (cont.) Adverse Events (Studies 312 and 313)

Adverse Event Code	Description	Loprox n indiv.	Vehicle n indiv.	Loprox n event	Vehicle n event
2940	Urinary Tract Infection	6	6	8	7
2950	Reaction To Allergy Shot	1	.	1	.
2955	Insomnia	2	.	2	.
3025	Damaged joint	4	3	5	3
3045	Kidney Stones	2	2	2	2
3077	Tear Gland Infection	1	1	1	1
3100	Laryngitis	6	.	6	.
3240	Fatty infil. Liver	.	1	.	1
3245	Elevated Lfts	.	1	.	1
3255	Crepitus Lungs	.	1	.	1
3265	Swollen Lymph Node	2	.	2	.
3295	General Malaise	1	.	1	.
3355	Blood In Stool	1	.	1	.
3375	Menopause	1	.	1	.
3385	Irregular Menses	.	1	.	1
3405	Breakthru Vag. Bleeding	1	1	1	1
3410	Migraine Headache	2	4	3	12
3455	Vaginal Yeast Infect.	1	.	1	.
3470	Muscle Soreness	6	8	6	12
3520	Rhaldomyolysis	.	1	.	1
3530	Toenail Problems	16	12	19	13
3535	G I Upset	5	4	7	4
3550	Stiff Neck	2	2	2	2
3610	Nodule /Polyp	1	1	1	1
3625	Breast Mass	1	.	1	.
3635	Warts/Lipoma	8	4	8	4
3637	Vulva Tumor	.	1	.	1
3670	Pinched Nerve	.	3	.	4
3695	Motor Nerve Problem	1	.	1	.
3745	Small Bowel Obstruct.	1	.	1	.
3760	Coronary Artery Occ.	1	.	2	.
3840	Otitis Externa	3	.	3	.
3845	Otitis Media	1	3	1	3
3875	Body Aches	5	5	7	6
3880	Abdominal Pain	1	3	1	3
3885	Back Pain	11	12	11	15
3905	Chest Pains	3	2	4	2
3915	Earache	1	1	1	1
3918	Arm Pain	5	9	5	9
3919	Sun Exposure	1	.	1	.
3921	Stomach Spasm	1	.	1	.
3922	Groin pain	1	1	1	1
3935	Neck Pain	2	2	2	2
3937	Orthodontial Pain	1	.	1	.
3940	Cramps (uterus)	.	1	.	2
3942	Burning Toe/Hallux	1	1	1	2
3944	Sore Throat	7	6	7	7
3955	Palpitations	.	1	.	1

Table 40 (cont.) Adverse Events (Studies 312 and 313)

Adverse Event Code	Description	Loprox n indiv.	Vehicle n indiv.	Loprox n event	Vehicle n event
4050	Finger Numbness	1	1	1	1
4075	Tight Foreskin	1	.	1	.
4115	Pharyngitis	2	2	2	3
4185	Pleurisy	1	.	1	.
4190	Pneumonia	2	1	2	1
4305	Prostatitis	6	4	7	5
4320	Puritis	2	.	3	.
4323	Guttate Psoriasis Flare	.	1	.	1
4360	Fine Pigmented Purpura	2	.	2	.
4415	Dermatitis/Erythema	26	16	27	18
4425	Papule/Rash	3	7	5	8
4445	Blisters	1	1	1	1
4470	Anal/Rectal Fistula	1	1	1	1
4475	Decreased Dtrs	.	1	.	1
4480	Increased Dtrs	1	.	1	.
4490	Chest Congestion	1	1	1	1
4505	Detached Retina	1	.	2	.
4530	Allergies	29	13	36	16
4595	Seborrhic Dermatitis	.	2	.	2
4600	Septicemia	1	.	1	.
4655	Sinus Infection	27	18	42	19
4660	Arcuate Purple Line	1	1	1	1
4668	Irritated toes/fingr	7	5	7	6
4805	Aphtrous Stomatitis	.	1	.	1
4832	Minor Surgery	4	8	4	9
4845	Syncope	1	.	1	.
4910	Tendonitis	4	4	5	4
4945	Intraluminal Thrombus	.	1	.	1
5010	Thrombocy Topenia	1	.	1	.
5040	Inc.Thyroid Levels	1	.	1	.
5050	Hearing Pulse	.	1	.	1
5060	Dental Caries	2	1	2	1
5065	Dental Work	4	6	6	8
5080	Tremors in Extremities	1	.	1	.
5125	Duodenal Ulcer	1	1	1	1
5185	Cold Sore	1	1	1	1
5215	Skin Sores	.	2	.	2
5220	Stomach Ulcers	2	.	2	.
5280	Urethral Stenosis	1	.	1	.
5305	Hives	1	2	1	2
5350	Yeast Vaginitis	.	1	.	1
5410	Vertigo	.	1	.	1
5420	Spots in Vision	.	1	.	1
5435	Raspy Throat	1	.	1	.
5440	Vomiting	1	.	1	.
9998	Extreme Lab values	1	3	1	3
Overall		630	608	785	755

It is apparent that no treatment related differences are statistically significant.

b. Studies 211 and 213

The following frequency tables display the number of subjects showing irritation around the nail and skin surrounding the target nail. Unfortunately such data apparently was not collected in the 312 and 313 studies.

Table 41. Skin and Nail Irritation (Studies 211)

	Visit Number													
Skin Irritation	01	02	03	04	05	06	07	08	09	10	11	12	13	14
Ciclopirox														
No Irritation	39	33	36	36	38	37	37	35	6	5	6	6	6	6
Eryth. & Skin Irr.														
No Indur.	3	8	6	5	4	1	3	2	.	1	.	.	.	.
Vehicle														
No Irritation	38	37	35	35	38	35	36	33	6	5	5	5	5	4
Eryth. & Skin Irr.														
No Indur.	5	5	5	3	1	4	.	.	.	.	.	.	.	.
Intense Skin Irr.														
Eyrth. with Indur.	1	.	1	.	.	.	1	.	.	.	.	.	.	.
Nail Irritation														
Ciclopirox														
Absent	40	39	40	40	40	38	38	36	6	6	6	6	6	6
Present	2	2	2	1	2	.	2	1	.	.	.	.	.	.
Vehicle														
Absent	42	40	39	35	37	36	36	32	6	5	5	5	5	4
Present	2	2	2	3	2	3	1	1	.	.	.	.	.	.

Table 42. Skin and Nail Irritation (Studies 212)

	Visit Number													
Skin Irritation	01	02	03	04	05	06	07	08	09	10	11	12	13	14
Ciclopirox														
No Irritation	54	50	47	42	45	45	48	46	1	1	1	1	1	1
Eryth. & Skin Irr.														
No Indur.	.	2	5	6	3	2	.	.	.	.	.	.	.	.
Vehicle														
No Irritation	52	54	54	51	50	48	49	51	.	.	.	.	.	.
Eryth. & Skin Irr.														
No Indur.	4	1	1	2	1	2	1	.	.	.	.	.	.	.
Intense Skin Irr.														
Eyrth. with Indur.	.	.	.	.	.	.	1	.	.	.	.	.	.	.
Nail Irritation														
Ciclopirox														
Absent	54	52	52	48	48	47	48	46	1	1	1	1	1	1
Vehicle														
Absent	55	55	55	53	51	50	50	51	.	.	.	.	.	.
Present	1	.	.	.	.	.	1	.	.	.	.	.	.	.

Note that descriptively there seem to be no apparent differences in irritation between Ciclopirox and its vehicle.

The following table is also both a count of adverse events and a count of the individuals experiencing adverse events, at least according to the data provided by the sponsor:

Table 43. Adverse Events (Studies 211 and 212)

Adverse Event Code	Description	Loprox n indiv.	Vehicle n indiv.	Loprox n event	Vehicle n event
47	Injury	2	5	2	5
165	Alcohol Detoxification	1	.	1	.
240	Mild Anemia	1	1	1	1
430	Anxiety	1	.	1	.
465	Irregular Heart Beat	.	1	.	1
505	Joint Pain	1	1	1	1
510	Arthritis Pain	2	.	2	.
545	Asthma Flare	.	1	.	1
810	Bronchitis	2	4	2	4
905	Prostatic Cancer	1	.	1	.
910	Skin Cancer	1	1	1	1
935	Cataractectomy	1	1	1	1
1250	Cough	1	.	1	.
1310	Sebaceous Cyst On Neck	.	1	.	1
1320	Cystitis	.	1	.	2
1400	Asteatotic Ecz./contact	.	1	.	1
1430	Diabetes Out Of Control	1	.	1	.
1435	Diarrhea	1	1	1	1
1470	Dizziness from study med.	2	.	2	.
1535	Stomach Discomfort	1	.	1	.
1545	Dyspnea	1	1	1	1
1555	Dysuria	.	1	.	1
1580	Eczema	.	1	.	1
1945	Fever	1	.	2	.
2032	Influenza	2	2	2	2
2100	GI Upset/Food Poisoning	1	2	1	2
2266	Gum Disease	.	1	.	1
2285	Headache	5	1	7	3
2330	Bleeding Of Nail Beds	1	1	1	1
2360	Subconj. Hemorrhage	.	1	.	1
2415	Rectal Bleeding	.	1	.	1
2482	Hemorrhoidectomy	.	1	.	1
2610	Hypercholesterolemia	1	1	1	1
2710	Facial Act. Keratoses	2	.	2	.
2925	Infection	4	6	4	6
2932	Upper Resp. Infection	12	9	14	10
2940	Urinary Tract Infection	8	4	10	4
3045	Kidney Stones	.	1	.	1
3050	Complete Kidney Failure	.	1	.	1
3071	Lab Abnormalties	.	1	.	1
3265	Lymphadenitis	.	1	.	1
3410	Migraine	.	1	.	5
3470	Muscle Soreness	1	.	1	.

Table 43 (cont.) Adverse Events (Studies 211 and 212)

Adverse Event Code	Description	Loprox n indiv.	Vehicle n indiv.	Loprox n event	Vehicle n event
3530	Paronychia	1	2	1	4
3535	Nausea	1	.	1	.
3625	Breast Mass	.	1	.	1
3635	Excised Nevus	1	2	1	2
3845	Otitis Media	1	1	1	1
3875	Pain Beneath Nails	.	3	.	5
3880	Abdominal Pain	2	.	2	.
3885	Low Back Pain	1	.	1	.
3905	Chest Pain	1	.	1	.
3918	Aching Pain L Thumb	1	.	2	.
3920	Eye Burning	1	.	1	.
3930	Pain In Right Kidney	.	1	.	1
3942	Burn in Periungual Skin	.	1	.	1
3944	Sore Throat	.	1	.	1
3955	Palpitations	2	.	2	.
3970	Possible Pancreatitis	1	.	1	.
4010	Bell's Palsy	.	1	.	1
4050	Paresthesias	1	1	1	1
4115	Pharyngitis	.	1	.	1
4305	Prostatism	2	2	2	3
4320	Pruritus	2	1	2	1
4415	Rash	2	3	2	3
4530	Runny Nose/Sneezing	1	1	1	1
4590	Multiple Sclerosis	.	1	.	1
4600	Septicemia	1	.	1	.
4635	Elevated Sgot	.	1	.	1
4655	Sinus Infection	2	2	2	2
4660	Redness In Nail Folds	2	.	2	.
4665	Cracked Fingertips	2	.	2	.
4668	Tinea Manuism/Corp.	4	4	4	4
4959	Seborrheic Keratoses	1	.	1	.
5040	Abn Thyroid Funct.	1	.	1	.
5065	Tooth Aches	3	.	3	.
5215	Ulcer On Thigh	.	1	.	1
5305	Hives	1	1	1	1
5432	Large Vitreous Detachment	.	1	.	1
5435	Intermittent Hoarseness	1	.	1	.
	Overall	97	90	105	103

It is apparent that no treatment related differences are statistically significant, even prior to an adjustment for multiplicity..

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Table 42 Adverse Events (Studies 111a)

Adverse Event Code	Description	Loprox n indiv.	Loprox n event
1365	Dehydration	1	1
2032	Flu	2	2
2095	Diarrhea, Nausea, Vomiting, Fever	1	1
2285	Headache etc.	1	1
3921	Stomach Pain (nausea, etc.)	1	1
3944	Sore Throat	1	1
4835	Diaphoresis	1	1
7001	Nausea, Vomiting	1	1
	Overall	9	9

Again, it is apparent that no treatment related differences are statistically significant.

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REFERENCE:
Westfall, P.H. and Young, S.S. (1993) *Resampling-Based Multiple Testing: Examples and Methods for p-value Adjustment*, New York: John Wiley & Sons, Inc.

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Conclusions (Which may be conveyed to the Sponsor):

1. The sponsor provided the results from two pivotal phase 3 studies and two phase 2 studies to support the claim of efficacy and safety for the use of Ciclopirox lacquer 8% in the treatment of onychomycosis of fingernails and toenails. In these studies, *Mycological Cure* was defined as the occurrence of both a negative KOH and negative culture. In studies 312 and 313, a *Global Evaluation Score* was assessed by comparing post-Baseline evaluations to the Day 1 evaluation on a scale of 0 (cleared) to 5 (Exacerbation). *Complete cure* (sponsor labeled *Treatment Cure*) was defined as the occurrence of a mycological cure with a score of 0 on the global evaluation scale above. Complete Cure in the 211 and 212 studies was defined similarly.

2. In addition, Computerized Planimetric Measurements were made "from standardized photographs." The affected area as a percentage of the whole nail area was used as the response. Statistically this is a very attractive endpoint. However, as noted by the sponsor: "Computerized planimetry is reproducible: however, because areas are delineated by ink lines with a finite thickness, and because the final length of healthy nail can only be presumptive. Thus, planimetry cannot be used to distinguish minimal residual disease from cure. Hence the establishment of cure remains a clinical decision."

3. The final endpoint chosen was based on constructing a variable that should reflect an "almost cure." *Effective treatment* (sponsor labeled *Treatment Success*) was defined as the occurrence either a complete cure or a mycological cure with less than 10% involvement as expressed by a planimetric measurement. It was felt that complete cure and effective treatment would generally define "regressing subsets," with effective treatment being essentially the next, natural, least restrictive endpoint after a complete cure.

4. The sponsor's analyses were performed on the intent-to-treat (ITT) subject group. However, it is usual in DDDDP analyses involving fungal products to restrict the analysis to those patients randomized to treatment that have the presence of a mycological infection confirmed by KOH and culture. This is usually labeled as "The" modified intent-to-treat (MITT) group in simple efficacy trials.

5. Typically the endpoints above would be tested using Cochrane-Mantel-Haenszel tests stratified on investigator. However, one problem with such CMH tests is that investigators with a zero marginal, as would occur when there were no successes, are essentially deleted from the analysis. For such cases this reviewer would recommend the use of Fisher Exact tests, not adjusting for the stratification on investigator.

6. Evaluations were performed during treatment, and, according to the protocol, post treatment for those subjects who achieved a complete cure. An apparent problem with these evaluations is that while the subject was being treated, the procedure for

removing the lacquer may not have removed all of the lacquer, and, as was noted by the sponsor, the removers themselves may have some antifungal effects. That makes it very difficult to interpret the mycologically based evaluations during treatment. Thus it makes the most sense to define the primary endpoints, complete cure and effective treatment, at posttreatment evaluations. However, again, according to the protocol, these were only performed for subjects who achieved complete cure. For this review, a "success" in this posttreatment period was scored among those patients who entered the post-treatment follow-up versus either a "failure" in the posttreatment period or as failure to enter the posttreatment portion of the study. This is a conservative endpoint, but should be a good indicator of success.

7. At the nominal 12 week post-treatment time point, in the MITT samples, neither study showed statistically significant differences in complete cure ($p \leq 0.494$ and $p \leq 0.477$, for the 312 and 313 studies respectively). At the nominal 24 week posttreatment endpoint, there were no successes in either treatment group in the 313 study, while differences in the 312 study were not significant ($p \leq 0.497$). For effective treatment results are similar. At the nominal 12 week post-treatment point, in the MITT samples neither study showed statistically significant differences in complete cure ($p \leq 0.494$ and $p \leq 0.474$, for the 312 and 313 studies respectively). At the nominal 24 week posttreatment endpoint, again, there were no successes in either treatment group in the 313 study, while differences in the 312 study were not significant ($p \leq 0.497$). Results for the ITT population were similar.

8. While not displayed here it is this reviewer's opinion that results from the computerized nail planimetry do tend to show that the nail lacquer has some effect. However, as noted by the sponsor in point 2, above, this effect is presumably not sufficient to suggest clinical efficacy.

9. Adjusting for the large number of comparisons there is no particular statistically significant difference across treatments in terms of adverse events.

10. It is also this reviewer's opinion that the pivotal studies (312 and 313) fail to demonstrate statistically significant differences in complete cure or effective treatment when comparing Ciclopirox Nail Lacquer 8% to the vehicle lacquer. However, there is no particular evidence of a statistically significant difference between Ciclopirox Nail Lacquer 8% and its vehicle with respect to the overall occurrence of adverse events.

Figure 1.0 ITT Population:

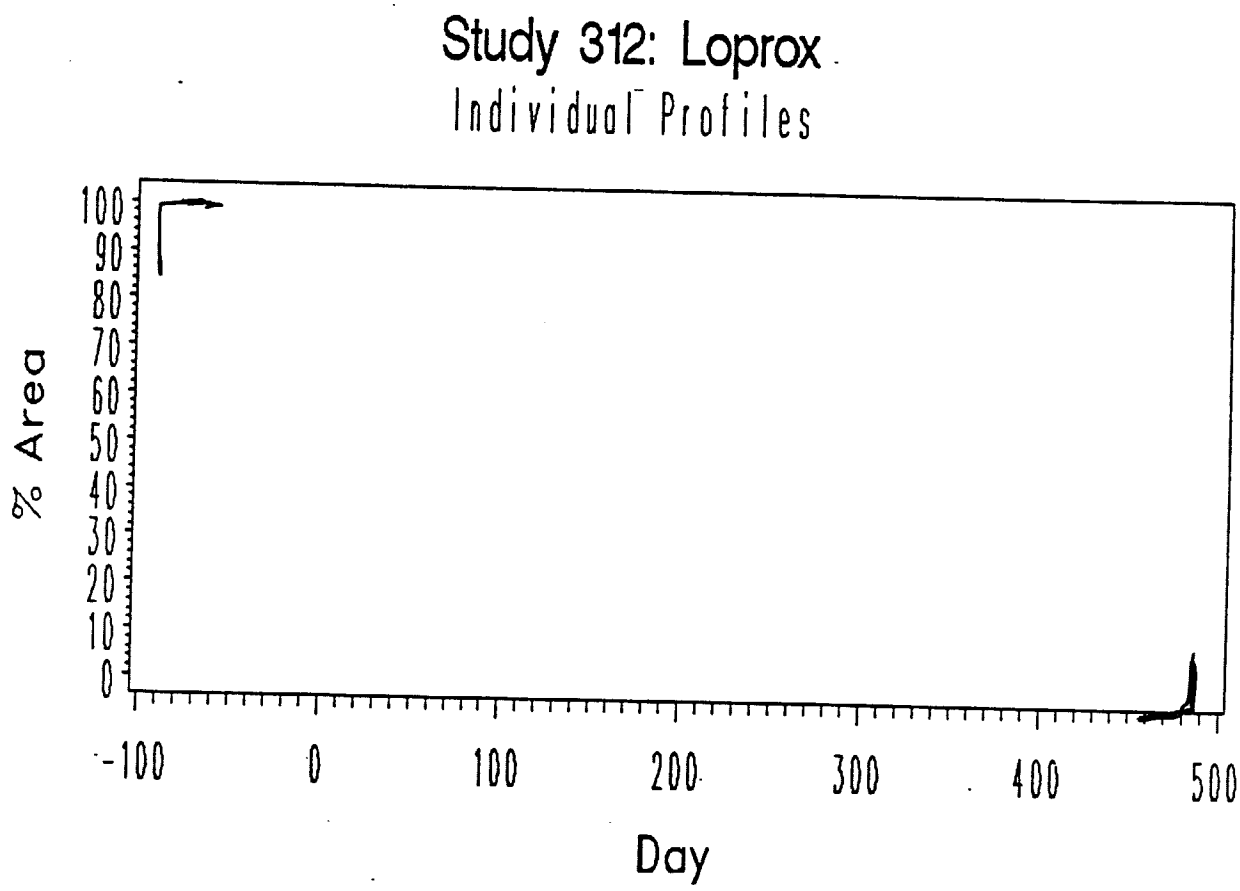

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Figure 2. ITT Population:

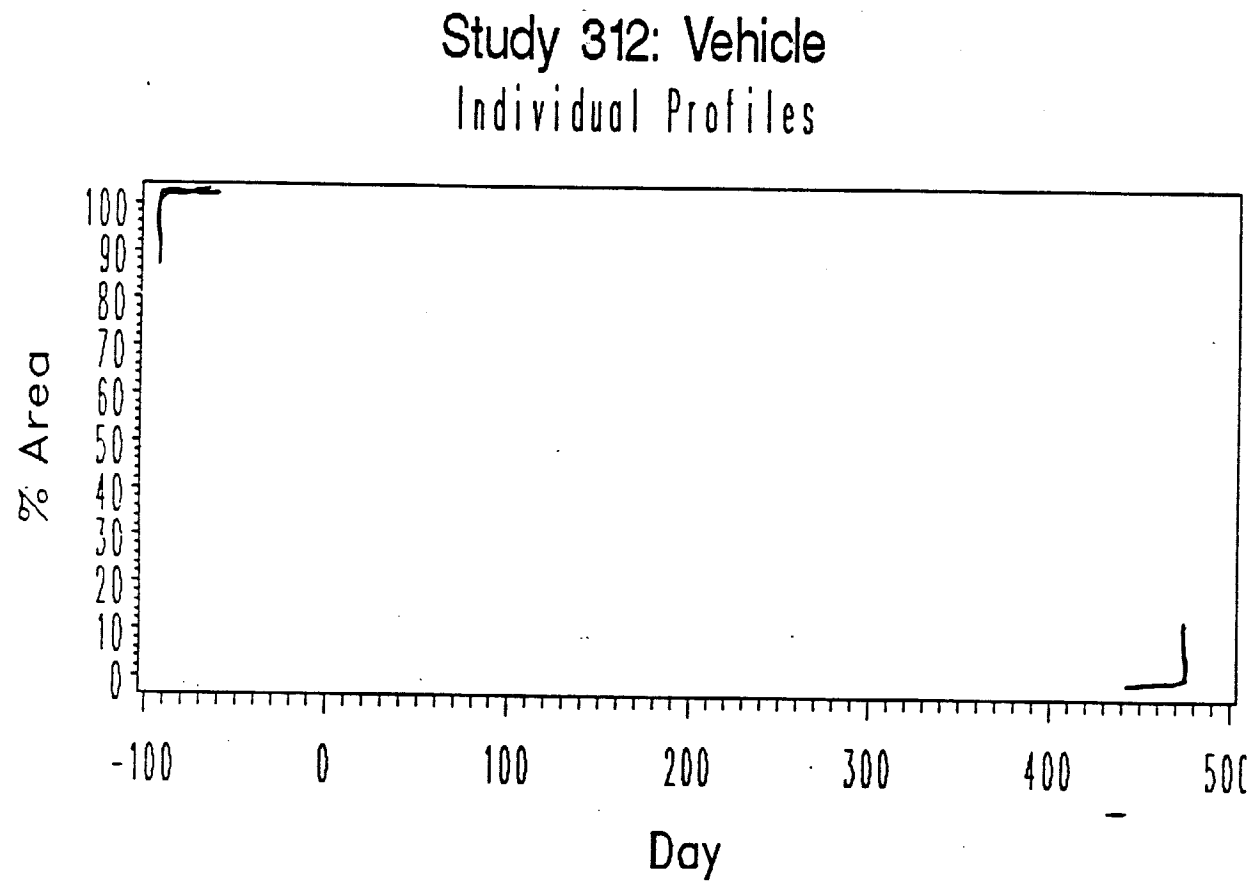

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Figure 3. ITT Population:

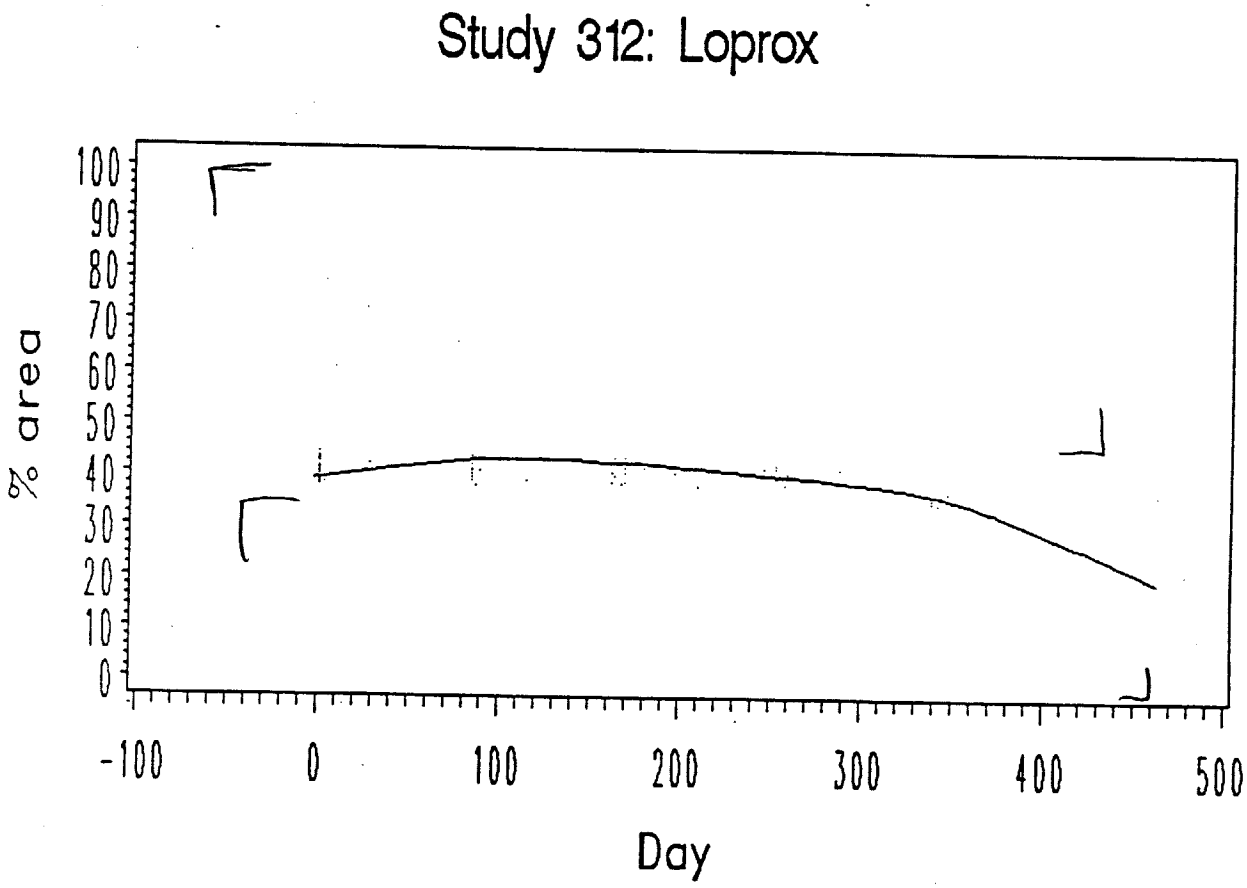

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Figure 4. ITT Population:

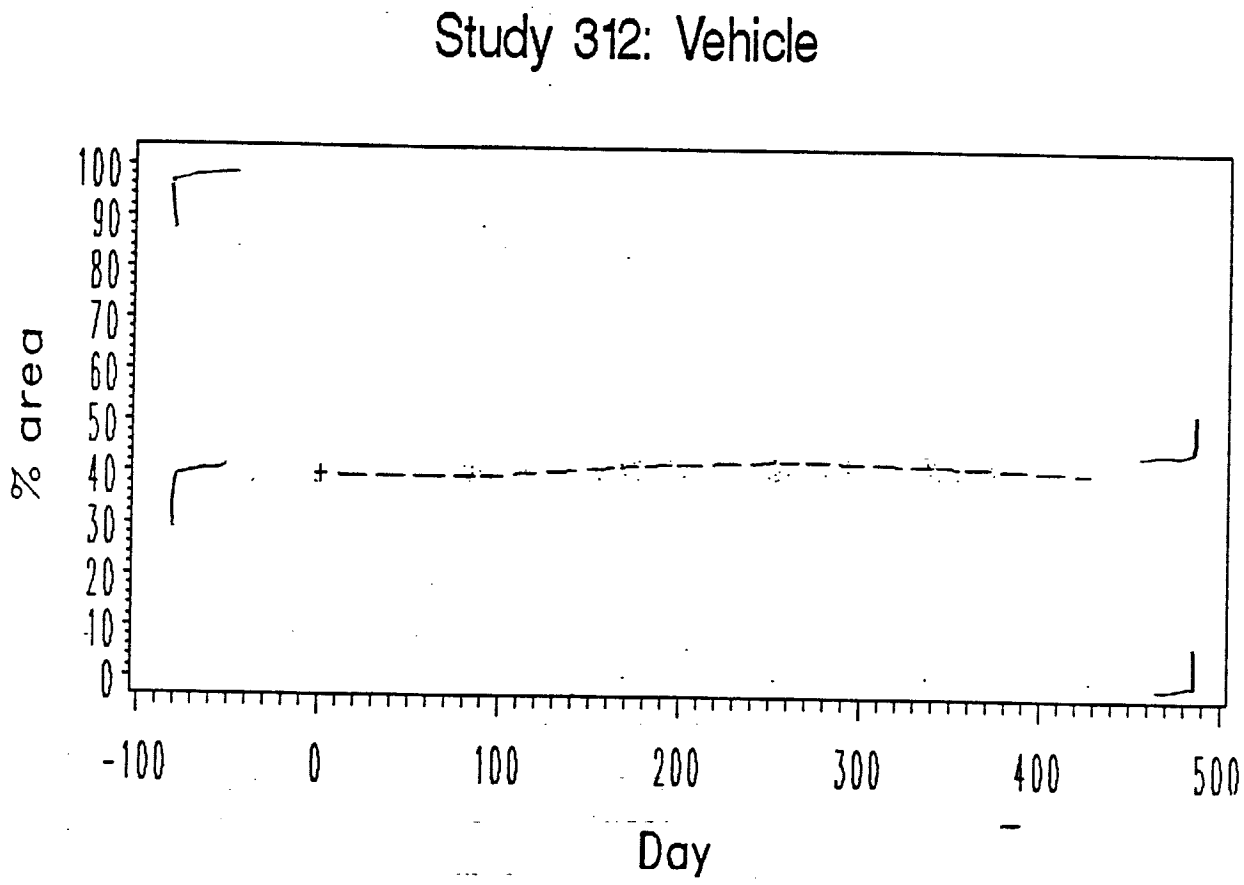

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Figure 5. ITT Population:

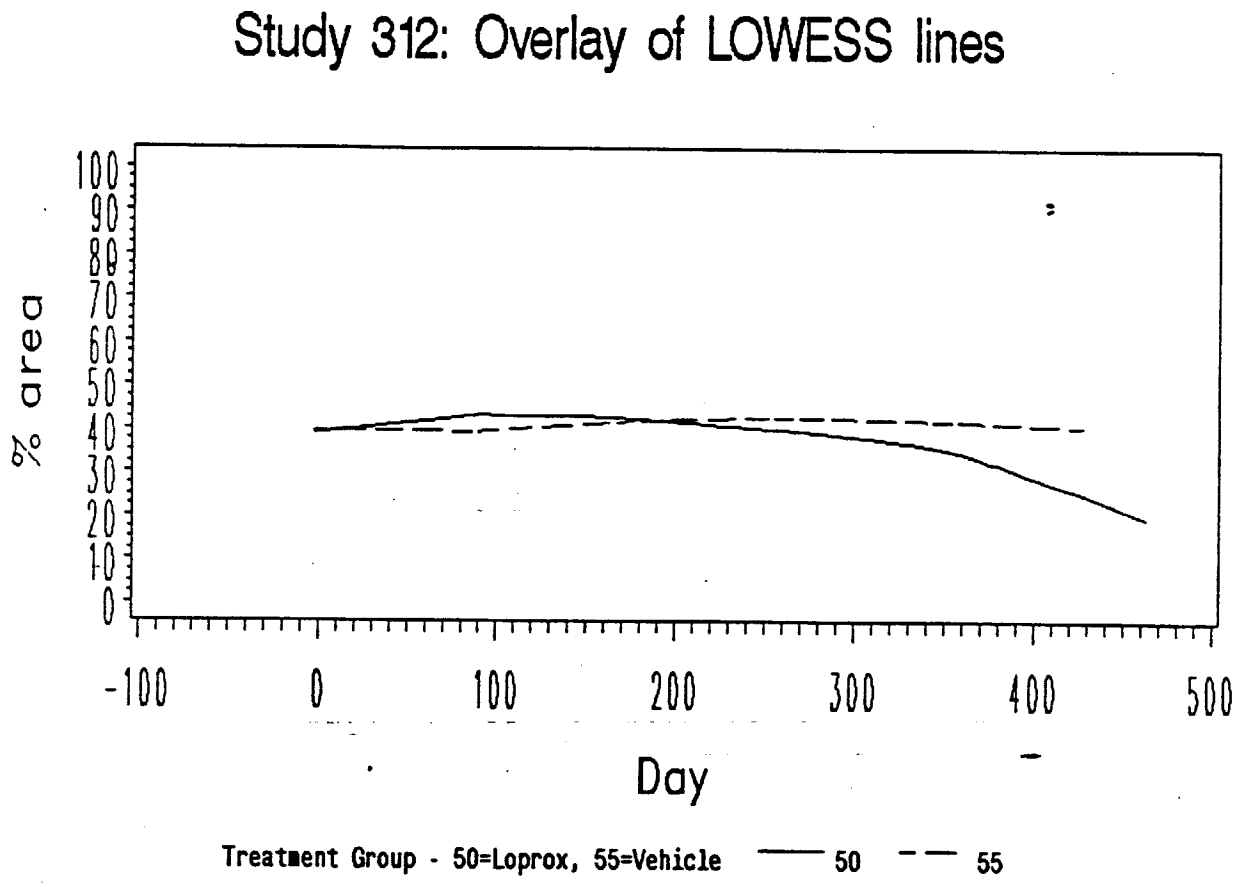

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Figure 6.0 MITT population:

Note when interpreting these lines that the curves in the right tail are based on very few data points and are not reliable.

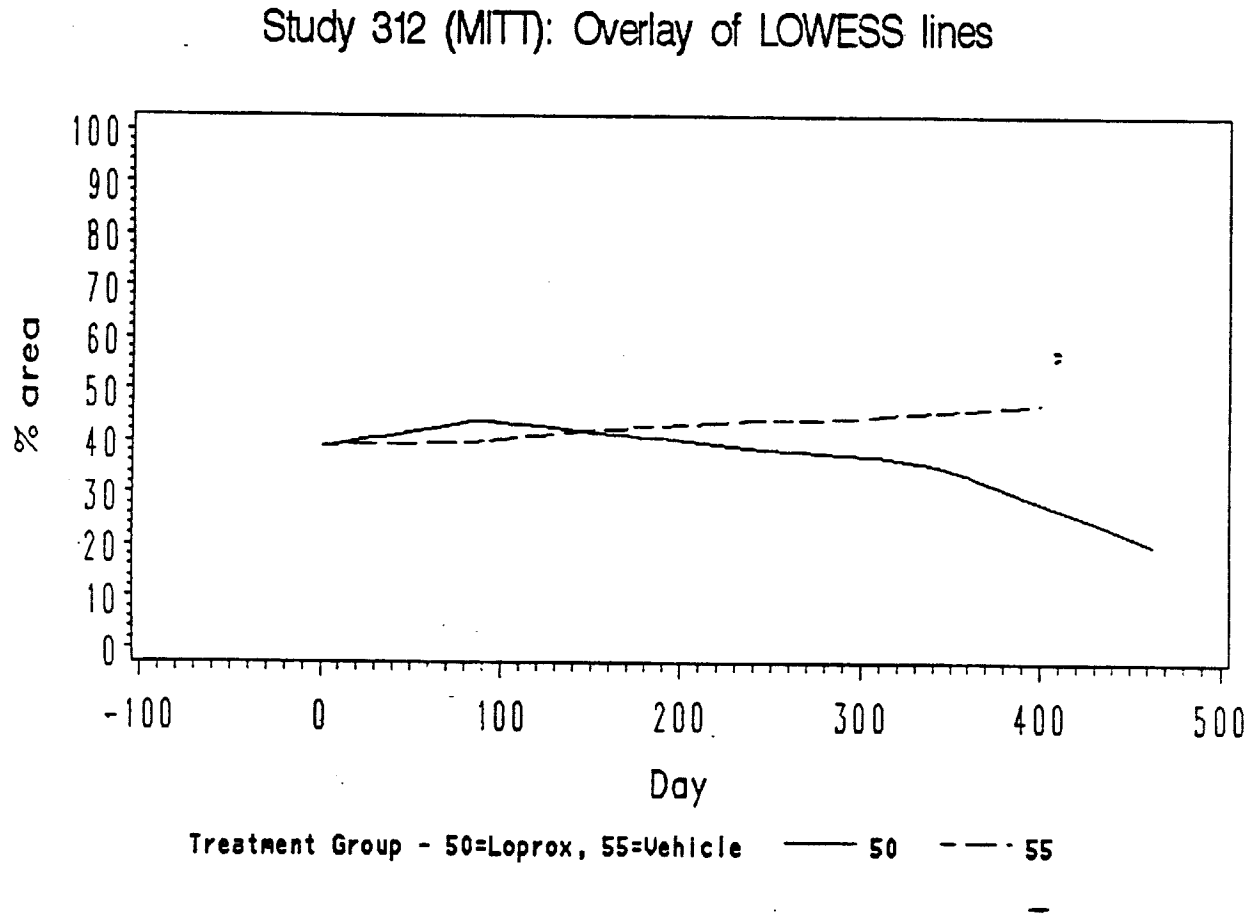
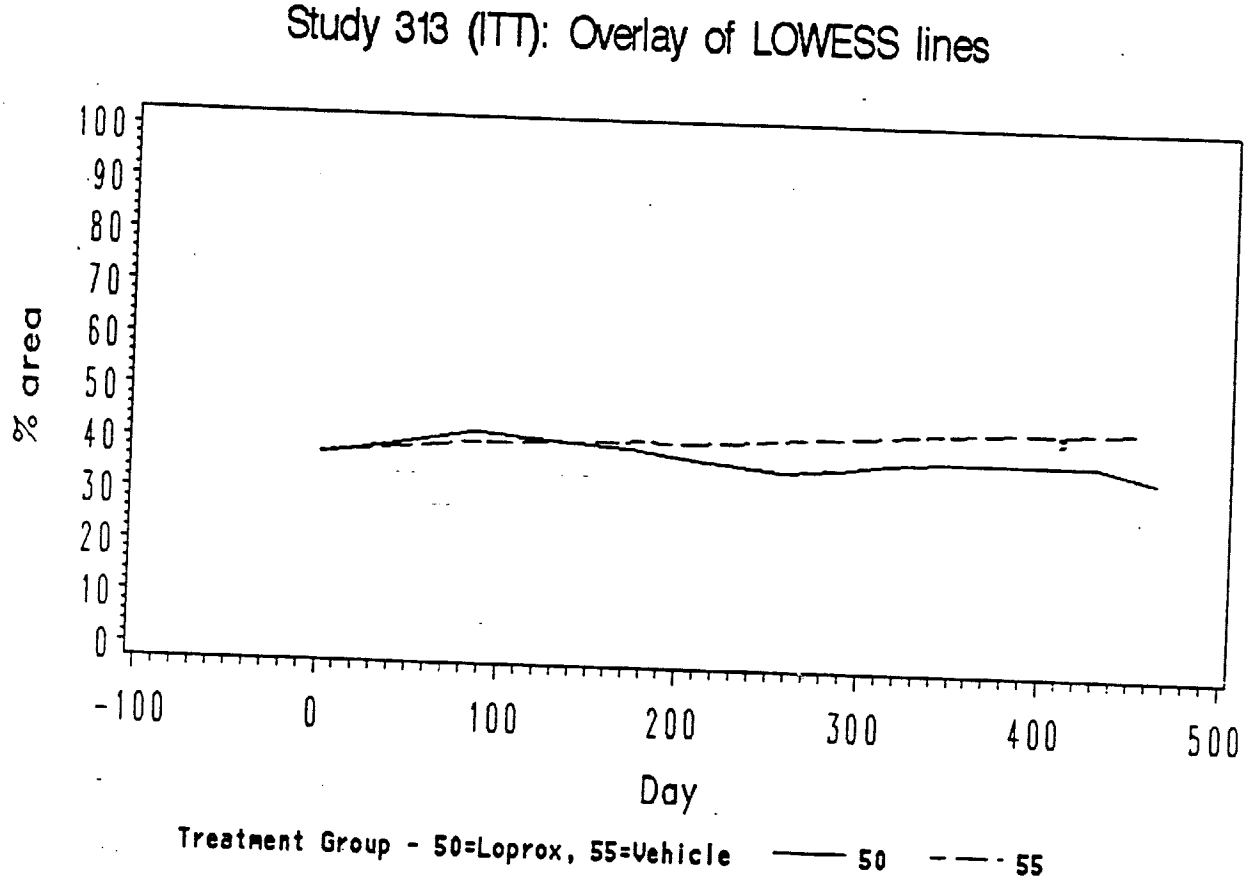


Figure 7.0 ITT population (313 Study):



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cc:
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Chron.

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