CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA:	21951
Drug Name:	CIP-Isotretinoin Capsules
Indication(s):	Severe Recalcitrant Nodular Acne
Applicant:	Cipher Pharmaceuticals Inc.
Date(s):	Stamp date: 11/28/2011
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Keywords: 505(b)2, non-inferiority trial, Acne

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Cipher Pharmaceuticals Inc. is seeking approval for CIP-Isotretinoin 10, 20, 30, and 40 mg Capsules through 505(b)2 application for the treatment of severe recalcitrant nodular acne. This is the second resubmission of the original NDA (originally submitted on 7/1/2005 and resubmitted on 10/26/2006) in which no clinical study was included. The sponsor intended to rely on the safety and efficacy findings of the reference listed drug, Accutane®, to obtain approval of CIP-Isotretinoin using findings from bioavailability data. As there was inadequate information to establish the safety bridge upon completion of the original review, the Agency requested a clinical safety and efficacy trial to compare CIP-Isotretinoin (CIP) to Accutane®. In the current submission, the sponsor submitted the findings of a Phase 3 pivotal study, Study ISOCT.08.01, to address the Agency's concern in safety.

The protocol specified the co-primary endpoints as the noninferiority of CIP compared to the Reference Product (RP), a generic version of Accutane®, in (i) change from baseline to Week 20 in the total nodular lesion count with a margin of 4 and (ii) proportion of subjects achieving at least 90% clearance in the total number of nodular lesions with a margin of -10%. For both co-primary endpoints, noninferiority has been established based on per protocol (PP) population. For the ITT population with missing data imputed using last observation carried forward (LOCF), the noninferiority criterion for the absolute change in total nodular lesion count was met, however, the study missed the noninferiority criterion (b) (4) for proportion of subjects with at least 90% clearance (95% CI = (b) (4), 0.97%). The summary of the co-primary endpoint results is presented in Table 1.

Table 1 – Summary of the Efficacy Results (ITT – Reviewer's Analysis)

	CIP-Isotretinoin	Reference Product	95% CI of Difference
Baseline lesion count. Mean (SD)	18.4 (14.7)	17.7 (10.8)	N/A
Change in lesion count. Mean (SD)			
ITT (LOCF)	-15.68 (14.02)	-15.62 (10.59)	(-0.233, 1.205)
PP	-17.01 (14.26)	-16.52 (10.57)	(-0.271, 0.548)
Success Rate [a]			
ITT (LOCF)	324/464 (69.8%)	344/461(74.6%)	((b) (4), 0.97%)
PP	286/363 (78.8%)	292/361 (80.9%)	(-7.94%, 3.74%)

[a] Success is defined as at least 90% reduction from Baseline to Week 20 in the total number of nodular lesions.

1.2 Brief Overview of Clinical Studies

This NDA resubmission provides findings from one Phase 3 pivotal clinical study, Study ISOCT.08.01, per the request of the Agency (action letter dated 5/1/2006 and 4/25/2007). This

study was conducted between 9/23/2009 and 4/20/2011. The objective of this study is to evaluate the safety of CIP and to establish the noninferiority in efficacy compared to RP. A total of 925 subjects aged between 12 to 54 years old were recruited from 49 sites, 38 in the US and 11 in Canada. Enrolled subjects were randomized in a ratio of 1:1 to receive either CIP or RP. Specifically, 464 subjects were randomized to the CIP arm and 461 subjects were randomized to the RP arm. For enrollment, subjects had a weight of 40 to 110kg with 10 or more severe recalcitrant nodular acne. Subjects were treated 0.5 mg/kg/day divided into 2 doses with meals for the first 4 weeks and then 1 mg/kg/day divided into 2 doses with meals for next 16 weeks. Efficacy and safety evaluations were assessed at baseline, Week 2, Week 4, Week 8, Week 12, Week 16, and Week 20 with a follow up visit at Week 24.

1.3 Statistical Issues and Findings

The sponsor's goal of this submission is to address the safety concerns to meet the requirements for the 505(b)2 application. Findings from the Phase 3 pivotal study, Study ISOCT.08.01, were submitted for establishing a safety and efficacy bridge to the reference product.

The co-primary endpoints are defined as (i) change from Baseline to Week 20 in the total nodular lesion count, and (ii) success rate with success defined as at least 90% clearance in the total number of nodular lesions. CIP would be considered non-inferior to the reference product if both of the following criteria are met: 1) the upper bound of the 2-sided 95% confidence interval of mean difference was less than or equal to 4 for change in total nodular lesion count; 2) the lower bound of the 2-sided 95% confidence interval of difference in success rate was greater than or equal to -10%. The 95% confidence limit of the mean difference in the total nodular lesion counts (CIP minus RP) was estimated by the analysis of covariance (ANCOVA) model with treatment, analysis site, gender and baseline lesion counts as covariates. The 95% confidence limit of difference (CIP minus RP) in proportions of subjects who achieved at least a 90% reduction in the total nodular lesion count was estimated under the normal approximation.

The analysis for the co-primary endpoints was based on both ITT population and PP population. The intent-to-treat (ITT) population is defined as all subjects who were randomized and received the study medication. The per-protocol (PP) population is defined as all randomized subjects who were at least 80% compliant with their assigned treatment with no major protocol violations. Last observation carried forward (LOCF) was used as primary method for imputing missing data. The specification of the co-primary endpoints, analysis population, statistical analysis methods and primary method of handling missing data were in agreement with the Agency's comments per the agreement letter dated 4/8/2009.

For the ITT population with missing data imputed using last observation carried forward (LOCF), the noninferiority criterion for the absolute change in total nodular lesion count was met, however, the study missed the noninferiority criterion (b) (4) for proportion of subjects with at least 90% clearance (95% CI = (b) (4), 0.97%). The noninferiority criteria for both co-primary endpoints were met based on the PP population.

2. INTRODUCTION

2.1 Overview

This is the second resubmission of the original NDA (dated 7/1/2005 and resubmitted on 10/26/2006), which included only bioavailability studies. The sponsor intended to rely on the safety and efficacy findings of the referenced listed drug, Accutane®, to obtain approval of CIP-Isotretinoin using findings from bioavailability data. Upon completion of the review for the original NDA submission, the division determined that CIP-Isotretinoin is more bioavailable compared to the listed drug under fasted condition and hence there was insufficient information to establish a safety bridge. The Division issued an action letter on 5/1/2006 and recommended a clinical safety and efficacy trial to compare CIP-Isotretinoin to Accutane®.

In response to the Agency's action letter on 5/1/2006, the sponsor resubmitted the application on 10/26/2006. As indicated by the clinical reviewer, this resubmission did not address the pivotal issue of establishing an adequate safety bridge to Accutane®. The Division issued another action letter on 4/25/2007 and recommended a clinical safety and efficacy study for the second time.

Following the action letter on 4/25/2007, the sponsor requested a formal dispute resolution on 5/29/2007. The response (Letter date: 8/10/2007) from the director of Office of Drug Evaluation III concurred with the decision made by the Division. Four additional meetings were held where the Agency reaffirmed the need for an additional clinical study to address safety concerns (6/27/2007, 7/11/2007, 10/1/2007, and 1/28/2008). A protocol for special protocol assessment (SPA) was submitted on 7/4/2008 and was discussed with the sponsor in meetings or teleconferences on 8/6/2008, 9/24/2008, 9/29/2008, and 1/7/2009.

In the letter issued on 4/8/2009, the Agency listed a set of agreements on the SPA. Most of the agreements were related to the safety assessments. The letter also included the following statement regarding the expectations for the trial.

> "We have communicated previously that, based on pharmacokinetic data provided to date, it is anticipated that the systemic exposure of CIP-Isotretinoin will equal or exceed that of marketed Accutane®. Because of this, it is important that any trial adequately assess the safety of your drug product. We do not expect that equal or greater exposure to isotretinoin would result in reduced efficacy. Hence, the primary focus of the FDA is on obtainment of adequate safety information."

The agreements that related to the overall study design and efficacy endpoints are listed in the following:

Agreements:

> "1. The general design of your study entitled "A Double-Blind, Randomized, Phase III, Parallel Group Study Comparing the Efficacy and Safety of CIP-ISOTRETINOIN to the marketed formulation of Isotretinoin in Patients with Severe Recalcitrant Nodular Acne" is acceptable.

2. Use of Accutane® (at dosages, using body weight ranges, consistent with those specified in the Accutane® package insert) as the only active control arm in clinical trials is acceptable.

3. Your proposed co-primary efficacy endpoints, the change in total nodular lesions (facial and truncal) at week 20 compared to baseline, and the proportion of subjects who achieve at least 90% reduction in the total number of nodules from baseline to week 20, are acceptable.

4. Your proposed secondary endpoints: the proportion of subjects with a Week 20 score of clear or almost clear on the Physician's Global Assessment and the change from baseline to Week 20 in the total number of facial inflammatory lesions (papules and pustules), are acceptable.

5. Your proposal to construct a confidence interval using estimates from an Analysis of Covariance (ANCOVA) of the Week 20 nodular lesion count with baseline as a covariate is acceptable.

6. Your proposal to construct a confidence interval using the normal approximation for the difference in proportion of subjects with at least a 90% reduction in nodular lesions at Week 20 is acceptable.

7. Your definitions of the Intent-To-Treat (ITT) and per protocol populations are acceptable, if in the ITT population 'receiving medication' means that the subject was dispensed medication. Note that in non-inferiority trials, both the ITT and per protocol analyses are considered together for establishing efficacy."

Additional Comments:

"1. We recommend selecting non-inferiority margins to ensure that the new therapy retains a sufficient proportion of the reference therapy's effect over placebo and that any difference in effect between the new and reference therapy is not clinically significant. The protocol should use margins for the co-primary endpoints that satisfy both of these criteria and should include justification for how the proposed margins satisfy these conditions. Note that for success rate endpoints the Division generally recommends noninferiority margins of (b) (4) or smaller.

2. All information needed for estimating sample sizes should be included in the protocol, because if unreliable estimates are used, the study could be underpowered. The rationale for the estimates used in the calculations should also be provided. For example, it is not clear from the protocol what information was used to calculate the power for the 90% reduction in nodules endpoint (i.e. no proportion estimates were provided).

3. Because the randomization is stratified by investigator, we recommend that the efficacy analyses include a term for the investigator. For the secondary endpoint of the change in facial inflammatory lesions, the protocol should provide a full description of the proposed analysis, including the specification of the non-inferiority margin.

4. We recommend implementing a strategy for imposing strong error control over the set of secondary efficacy endpoints.

5. The use of Last Observation Carried Forward (LOCF) in the analyses of the primary endpoints for missing data is acceptable; however, sensitivity analyses to evaluate the impact of the missing data on the conclusions should be proposed in the protocol, rather than deferred to the statistical analysis plan. The sensitivity analyses should also address subjects who discontinued treatment but remained in the trial for evaluation."

2.2 Data Sources

The sponsor provided the electronic datasets for the Phase 3 efficacy and safety study, Study ISOCT.08.01, used in this review:

Electronic submission for Study ISOCT.08.01: \\Cdsesub1\evsprod\NDA021951\0000

Datasets for Study ISOCT.08.01:
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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Per the Agency's requests (action letter dated 5/1/2006 and 4/25/2007) of a pivotal clinical safety and efficacy study, the sponsor provides findings from their Phase 3 study, Study ISOCT.08.01, in support of their NDA resubmission.

3.1.1 Study design

Study ISOCT.08.01 is a Phase III randomized, multi-center, double-blind, active controlled study, evaluating the safety and efficacy of CIP-Isotretinoin (CIP) Capsules compared to Reference Product (RP), a generic version of Accutane®. This study was conducted in 49 centers: 38 centers in the US and 11 centers in Canada. Subjects enrolled in the studies were male or females aged between 12 to 54 years old weighing 40kg to 110kg, having severe recalcitrant nodular acne with 10 or more nodular lesions. Female subjects were excluded from the trial if they were pregnant or at high risk for becoming pregnant during the trial. Enrolled

subjects were randomized in a ratio of 1:1 to CIP or RP. The randomization was stratified by gender and study center. A total of 925 subjects were enrolled: 464 in CIP arm and 461 in RP arm. Subjects were instructed to take the study medication with meals twice daily at breakfast and dinner. The study medication was at an initial titration dose of approximately 0.5 mg/kg/day divided into two doses for the first 4 weeks, followed by approximately 1 mg/kg/day divided into 2 doses for 16 weeks. Subjects were scheduled to have 9 visits: Screening, Baseline, Week 2, Week 4, Week 8, Week 12, Week 16 and Week 20 (Final treatment visit) with a post treatment follow-up at Week 24. The number of total nodular lesion (facial and truncal) count was collected at each visit.

The protocol defined the co-primary endpoints as:

- Change from Baseline to Week 20 in the total nodular lesion count, noninferiority with a margin of 4;
- Proportion of subjects with at least a 90% reduction from Baseline to Week 20 in the total number of nodular lesions, noninferiority with a margin of (b) (4)

The protocol defined the secondary endpoint as:

- The proportion of subjects rated as "Clear" or "Almost Clear" at Week 20 based on the 6-point Physicians' Global Severity Assessment (PGSA, presented in Table 2), noninferiority with a margin of (b) (4);

Table 2: Physicians' Global Severity Assessment

Description	Grade	Acne Disease Status
Clear	0	No nodules, pustules or papules visible.
Almost clear	1	Hardly visible. A few scattered comedones, few small papules, and very few pustules.
Mild	2	Easily recognizable, less than ½ face involved. Many comedones, papules, and pustules.
Moderate	3	More than ½ face involved. Numerous comedones, papules, and pustules.
Severe	4	Entire face involved. Covered with comedones, numerous papules and pustules and many nodules and cysts.
Very severe	5	Highly inflammatory acne covering the affected area; with many nodules and cysts present.

3.1.2 Disposition of Subjects

Study ISOCT.08.01 enrolled 925 subjects from 49 centers. This study was conducted from September 23rd, 2009 to April 20th, 2011. The discontinuation rate of subjects in CIP arm is similar to that of subjects in RP arm. Reasons for study discontinuations are presented in Table 3. The most common reason for discontinuation was lost to follow up.

Table 3: Reasons for Discontinuation (ITT - Sponsor's Analysis*)

	CIP-Isotretinoin N=464	Reference Product N=461
Completed	394 (84.9%)	401 (87%)
Reason for Discontinuation	70 (15.1%)	60 (13%)
Adverse Event	19 (4.1%)	15 (3.3%)
Patient Withdrew Consent	15 (3.2%)	15 (3.3%)
Investigator's Discretion	1 (0.2%)	2 (0.4%)
Lost to Follow-up	20 (4.3%)	16 (3.5%)
Noncompliance	5 (1.1%)	8 (1.7%)
Other	10 (2.2%)	4 (0.9%)

*** Source: Table 14.1.1.1 in sponsor's clinical study report**

3.1.3 Baseline and Demographic Data

More males (60%) than females (40%) were enrolled in this study. Approximately 87% of the subjects were white. The average age was about 21 years and ranged from 12 to 52 years. The baseline demographic characteristics are comparable across the two treatment arms. A summary of baseline demographic data is presented in Table 4.

Table 4: Baseline Demographic Data (ITT – Reviewer's Analysis)

		CIP-Isotretinoin N=464	Reference Product N=461	Overall N=925
Gender	**Male**	277 (60%)	283 (61%)	560 (60%)
	Female	187 (40%)	178 (39%)	365 (40%)
Race	**White**	399 (86%)	404 (88%)	803 (87%)
	Black	28 (6%)	14 (3%)	42 (5%)
	Asian	27 (6%)	26 (6%)	53 (6%)
	Other [a]	10 (2%)	17 (4%)	27 (3%)
Age (Years)	**Mean (SD)**	20.8 (7.5)	20.7 (6.8)	20.8 (7.2)
	Range	12 – 50	12 – 52	12 – 52
	<18 yrs	205 (44%)	192 (42%)	397 (43%)
	18 - 52 yrs	259 (56%)	269 (58%)	528 (57%)

[a] Other includes Native Hawaiian, pacific islander, North American Indian and Alaska Native;

The baseline nodular lesion counts and PGSA scores are balanced across the two treatment arms. The baseline disease severity is presented in Table 5.

Most subjects were enrolled with baseline PSGA score of at least 3.

Table 5: Baseline Severity by Treatment Arm (ITT- Reviewer's Analysis)

		CIP-Isotretinoin N=464	Reference Product N=461	Overall N=925
Baseline lesion Mean (SD)		18.4 (14.7)	17.7 (10.8)	18.0 (12.9)
PGSA	**Missing**	8 (1.7%)	4 (0.9%)	12 (1.3%)
	0 (Clear)	0 (0%)	0 (0%)	0 (0%)
	1 (Almost Clear)	3 (0.6%)	2 (0.4%)	5 (0.5%)
	2 (Mild)	11 (2.4%)	10 (2.2%)	21 (2.3%)
	3 (Moderate)	49 (10.6%)	60 (13%)	109 (11.8%)
	4 (Severe)	329 (70.9%)	322 (69.8%)	651 (70.4%)
	5 (Very Severe)	64 (13.8%)	63 (13.7%)	127 (13.7%)

3.1.4 Primary Endpoints Analysis

The protocol defined the co-primary efficacy endpoints as the following:

- Change from Baseline to Week 20 in the total nodular lesion count, noninferiority with a margin of 4;
- Proportion of subjects with at least a 90% reduction from Baseline to Week 20 in the total number of nodular lesions, noninferiority with a margin of (b) (4);

The non-inferiority of CIP compared to RP can be claimed if non-inferiority can be established for both co-primary endpoints.

3.1.4.1 Analysis results for the Primary Endpoint

The analysis for primary endpoints was based on both ITT population and PP population. The protocol defined the intent-to-treat (ITT) population as all subjects who were randomized and received the study medication. The per-protocol (PP) population is defined as all randomized subjects who were at least 80% compliant with their assigned treatment with no major protocol violations. As indicated in the protocol, last observation carried forward (LOCF) was used as primary method for imputing missing data. CIP would be considered non-inferior to the reference product if both of the following criteria are met: 1) the upper bound of the 2-sided 95% confidence interval of mean difference was less than or equal to 4 for change in total nodular lesion count; 2) the lower bound of the 2-sided 95% confidence interval of difference in success rate was greater than or equal to (b) (4) for subjects with at least 90% reduction in the total number of nodular lesions.

The sponsor estimated the 95% confidence limit of the mean difference in the total nodular lesion counts (CIP minus RP) by the analysis of covariance (ANCOVA) model with treatment,

analysis site, gender and baseline lesion counts as covariates. CIP would be considered noninferior to RP if the upper bound of the 95% confidence interval of the adjusted least squared mean difference (CIP minus RP) was less than or equal to 4. The 95% confidence limit of difference (CIP minus RP) in proportions of subjects who achieved at least a 90% reduction in the total nodular lesion count was estimated under the normal approximation. CIP would be considered noninferior to RP if the lower bound of the 2-sided 95% CI of difference (CIP minus RP) was greater than or equal to -10%. The proposed analysis method was in agreement with the Division.

The results for both co-primary endpoints along with the baseline disease severity are presented in Table 6. The reviewer analysis results are the same as the results provided by the sponsor.

Table 6: Analysis Results for Co-Primary Endpoints (Reviewer's Analysis)

	CIP-Isotretinoin	Reference Product	95% CI of Difference
Baseline lesion count. Mean (SD)	18.4 (14.7)	17.7 (10.8)	N/A
Change in lesion count. Mean (SD)			
ITT (LOCF)	-15.68 (14.02)	-15.62 (10.59)	(-0.233, 1.205)
PP	-17.01 (14.26)	-16.52 (10.57)	(-0.271, 0.548)
Success Rate [a]			
ITT (LOCF)	324/464 (69.8%)	344/461(74.6%)	((b) (4), 0.97%)
PP	286/363 (78.8%)	292/361 (80.9%)	(-7.94%, 3.74%)

[a] Success is defined as at least 90% reduction from Baseline to Week 20 in the total number of nodular lesions.

For the ITT population with missing data imputed using LOCF, the noninferiority criterion for absolute change in total nodular lesion count was met. The study missed the noninferiority criterion (b) (4) for proportion of subjects with at least 90% clearance (95% CI = (b) (4) 0.97%). The noninferiority criteria for both co-primary endpoints were met for the PP population.

3.1.4.2 Missing Data Sensitivity Analysis

In addition to the primary imputation method of LOCF, two sensitivity analysis for handling missing data were planned in the protocol: 1) the baseline observation carried forward (BOCF) and 2) impute the missing data in CIP arm by the upper bound and impute the missing data in RP arm by the lower bound of the 95% confidence intervals based on the observed value at Week 20. The results using these two approaches are presented in Table 7.

Table 7: Sensitivity Analysis Results for Co-primary Endpoints (Sponsor's Analysis)

	CIP-Isotretinoin N=464	Reference Product N=461	95% CI of Difference
Change in lesion count. Mean (SD)			
ITT (BOCF)	-14.6 (14.35)	-14.53 (11.04)	(-0.533, 1.384)
ITT (missing imputed by the upper/lower CI)	-16.75 (14.20)	-16.43 (10.52)	(-0.082, 0.678)
Success Rate [a]			
ITT (BOCF)	310/464 (66.8%)	332/461(72%)	(-11.14%, 0.72%)
ITT (missing imputed by the upper/lower CI)	324/464 (69.8%)	383/461 (83.1%)	(-18.65%, -7.85%)

[a] Success is defined as at least 90% reduction from Baseline to Week 20 in the total number of nodular lesions.

It is shown that the noninferiority criteria were met for change in total nodular lesion counts based on both sensitivity analysis. However, the noninferiority criterion was not met for success rate of at least 90% reduction from either sensitivity analysis.

3.1.4.3 Efficacy Results by Center and by Study Visits

This study was conducted in 49 centers: 38 sites in the US and 11 sites in Canada. Small centers were pooled to have a total of 39 analysis centers. The plots showing the by analysis-center results for mean change in total nodular lesion counts and 90% clearance rate are presented in Figure 1 and Figure 2 of Appendix A, respectively. Based on the plots, the number of centers favoring CIP is approximately the same as the number of center favoring RP, which is expected for a non-inferiority trial.

The total nodular lesion counts by study visit are also investigated and presented graphically in Figure 3 of Appendix B. The plot shows that the number of nodular lesions decreases over time for both arms. The mean lesion count for subjects in CIP arm is larger than that for subjects in RP arm at baseline and each following study visit. The two lines in the plot are almost parallel indicating that the mean change in number of lesion count is similar for the two treatment arms.

3.1.5 Secondary Endpoints Analysis

The protocol defines the secondary efficacy endpoint as:

- The proportion of subjects rated as "Clear" or "Almost Clear" at Week 20 based on the 6-point Physicians' Global Severity Assessment (PGSA, presented in Table 2), noninferiority with a margin of (b) (4);

- The sponsor did not specify the PGSA score as one of the inclusion criteria. There are 3 subjects in CIP arm and 2 subjects in RP arm are enrolled with a PGA score of "Almost Clear". Therefore, it is difficult to interpret the results of proportion of subjects achieving "Clear" or "Almost Clear" at Week 20. Descriptively, there are 326 out of 464 (70%), 351 out of 461 (76%) subjects have a PGA score of "Clear" (0) or "Almost Clear" (1) at Week 20 based on ITT population.

3.2 Evaluation of Safety

Evaluation of safety was based on the safety population which included all subjects who were randomized and consumed at least one dose of the study medication. There were a total of 924 subjects evaluated for safety in this study.

3.2.1 Adverse Events

The sponsor reported that a total of 428 (92%) subjects in CIP arm and 413 (90%) subjects in RP arm who had experienced at least one adverse event (AE). The most common AE was lip dry, which occurred in approximately 45% of the total subjects. The AE rates are comparable across the two treatment arms and the results are presented in Table 8.

Table 8: Adverse Events Occurring in at Least 1% of All Subjects Per Treatment Arm

Adverse Events (Preferred Term)	CIP N=464	RP N=460
Lip Dry	209 (45%)	210 (46%)
Dry Skin	205 (44%)	206 (45%)
Back Pain	96 (21%)	89 (19%)
Dry Eye	87 (19%)	78 (17%)
Arthralgia	64 (14%)	60 (13%)
Epistaxis	54 (12%)	42 (9%)
Nasopharyngitis	36 (8%)	48 (10%)
Headache	37 (8%)	36 (8%)
Chapped Lips	34 (7%)	32 (7%)
Blood creatine phosphokinase increased	26 (6%)	27 (6%)
Dermatitis	28 (6%)	23 (5%)
Visual acuity reduced	23 (5%)	25 (5%)
Cheilitis	26 (6%)	19 (4%)

* Source: Table 14.3.1.2 in sponsor's clinical study report

4. FINDINGS IN SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The two co-primary endpoints were investigated by gender, age group (12-17 or ≥18), and total baseline nodular lesion count (<14 or ≥14). As White subjects account for more than 86% and all other categories account for less than 6% of the total subjects enrolled, it did not allow for a meaningful analysis of subgroups defined by race. The results produced by the reviewer based on ITT population are the same as provided by the sponsor and are presented in Table 9 and Table 10.

Overall, the decrease in total nodular lesion count is similar in CIP arm and RP arm. However the proportion of subjects with at least 90% clearance was greater with RP in all subpopulations. Female subjects reported a notably larger success rate (75.9%) of 90% clearance compared to that (65.7%) of male subjects in CIP arm. Subjects who had more nodular lesions (>=14) had a significantly larger decrease in the total lesion counts than those had less nodular lesions (<14).

Table 9: Mean Change in Total Lesion Counts by Gender, Age and Baseline Severity (ITT – Reviewer's Analysis)

		CIP-Isotretinoin N=464	**Reference Product N=461**
Gender	Male	-17.0 (16.5)	-16.5 (11.6)
	Female	-13.8 (9.0)	-14.3 (8.6)
Age			
	<18 yrs	-17.4 (16.8)	-17.5 (12.6)
	>=18 yrs	-14.3 (11.2)	-14.3 (8.6)
Baseline Lesion Counts			
	<14	-9.5 (3.3)	-10.1 (2.8)
	>=14	-21.4 (17.4)	-21.0 (12.5)

Table 10: Success rate of 90% Clearance by Gender, Age and Baseline Severity (ITT – Reviewer's Analysis)

		CIP-Isotretinoin N=464	Reference Product N=461
Gender	Male	182/277 (65.7%)	208/283 (73.5%)
	Female	142/187 (75.9%)	136/178 (76.4%)
Age			
	<18 yrs	141/205 (68.8%)	145/192 (75.5%)
	>=18 yrs	183/259 (70.7%)	199/269 (74.0%)
Baseline Lesion Counts			
	<14	159/224 (71.0%)	175/227 (77.1%)
	>=14	165/240 (68.8%)	169/234 (72.2%)

4.2 Other Special/Subgroup Populations

No other subgroup was analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This is the second resubmission of the original NDA (originally submitted on 7/1/2005 and resubmitted on 10/26/2006) in which the sponsor intended to rely on the safety and efficacy findings of the reference listed drug, Accutane®, to obtain approval of CIP-Isotretinoin using findings from bioavailability data. No clinical study was included in their original submission. Upon completion of the review, the Agency determined that the information provided was inadequate to establish a safety bridge and requested a clinical safety and efficacy trial to compare CIP-Isotretinoin (CIP) to Accutane®. As the sponsor's first resubmission on 10/26/2006 did not address this issue, the Agency sent the action letter on 4/25/2007 reiterating previous requests. The sponsor initiated a dispute resolution then and the Agency reaffirmed the need for an additional clinical study to address safety concerns. Several meetings were scheduled afterwards to discuss the need and design of a pivotal clinical trial. In the current submission, the sponsor provided the safety and efficacy findings from one Phase 3 pivotal study in support of their NDA.

Per the agreement letter issued on 4/8/2009, the Agency is in agreement with the sponsor in 1) the general design of Study ISOCT.08.01; 2) the co-primary endpoints of non-inferiority in the change of total nodular lesion counts and success rate of achieving 90% clearance; 3) secondary endpoints of proportion of subjects with "Clear" or "Almost Clear" on a PGA scale; 4) the statistical analysis method to construct the confidence interval for both co-primary endpoints; 5) Definition of Intent-To-Treat (ITT) and per protocol (PP) populations. Although no agreements

were made regarding the non-inferiority margin, the Agency recommended a non-inferiority margin of 10% or smaller for the co-primary endpoint of success rate of achieving 90% clearance.

This reviewer analyzed the data based on both intent-to-treat (ITT) and per protocol (PP) populations. The primary method for handling missing data was last observation carried forward (LOCF). For both co-primary endpoints, noninferiority has been established based on per protocol (PP) population. For the ITT population, the noninferiority criterion for the absolute change in total nodular lesion count was met, however, the study missed the noninferiority criterion (b) (4) for proportion of subjects with at least 90% clearance (95% CI = (b) (4) 0.97%). The efficacy analysis by study centers shows that the number of centers favoring CIP is approximately the same as the number of center favoring RP, which can be expected for a non-inferiority trial.

5.2 Conclusions and Recommendations

In Summary, this Phase 3 pivotal study, Study ISOCT.08.01, was conducted primarily to address Agency's concern of safety due to greater exposure than the reference listed drug Accutane® in the treatment of severe recalcitrant nodular acne. The co-primary efficacy endpoints are (i) change from Baseline at Week 20 in the total nodular lesion count and (ii) proportion of subjects with at least 90% clearance in the total number of nodular lesions. All enrolled subjects had severe recalcitrant nodular acne with 10 or more nodular lesions. For the ITT population with missing data imputed using LOCF, the noninferiority criterion for absolute change in total nodular lesion count was met. The study missed the noninferiority criterion for proportion of subjects with at least 90% clearance (95% CI = (b) (4), 0.97%). The noninferiority criteria for both co-primary endpoints were met for the PP population. The primary efficacy results for Study ISOCT.08.01 are presented in Table 11.

Table 11: Summary of the Efficacy Results (ITT – Reviewer's Analysis)

	CIP-Isotretinoin	Reference Product	95% CI of Difference
Baseline lesion count. Mean (SD)	18.4 (14.7)	17.7 (10.8)	N/A
Change in lesion count. Mean (SD)			
ITT (LOCF)	-15.68 (14.02)	-15.62 (10.59)	(-0.233, 1.205)
PP	-17.01 (14.26)	-16.52 (10.57)	(-0.271, 0.548)
Success Rate [a]			
ITT (LOCF)	324/464 (69.8%)	344/461(74.6%)	((b) (4), 0.97%)
PP	286/363 (78.8%)	292/361 (80.9%)	(-7.94%, 3.74%)

[a] Success is defined as at least 90% reduction from Baseline to Week 20 in the total number of nodular lesions.

APPENDICES
A. Center-by-Center Plot

Figure 1 – Mean Change in Total Nodular Lesion Counts by Center (ITT)

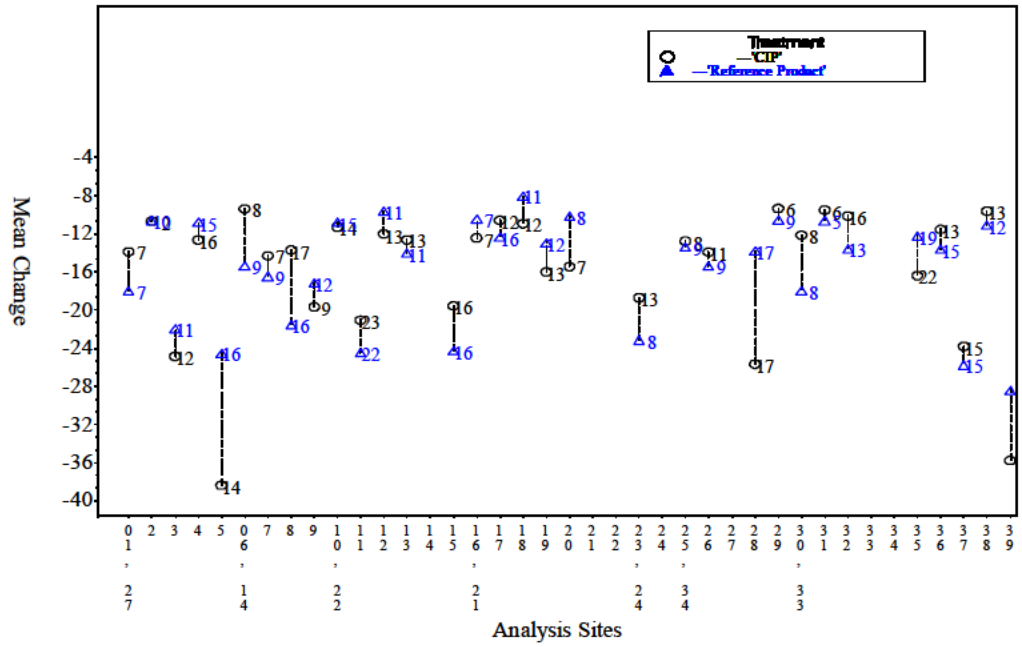
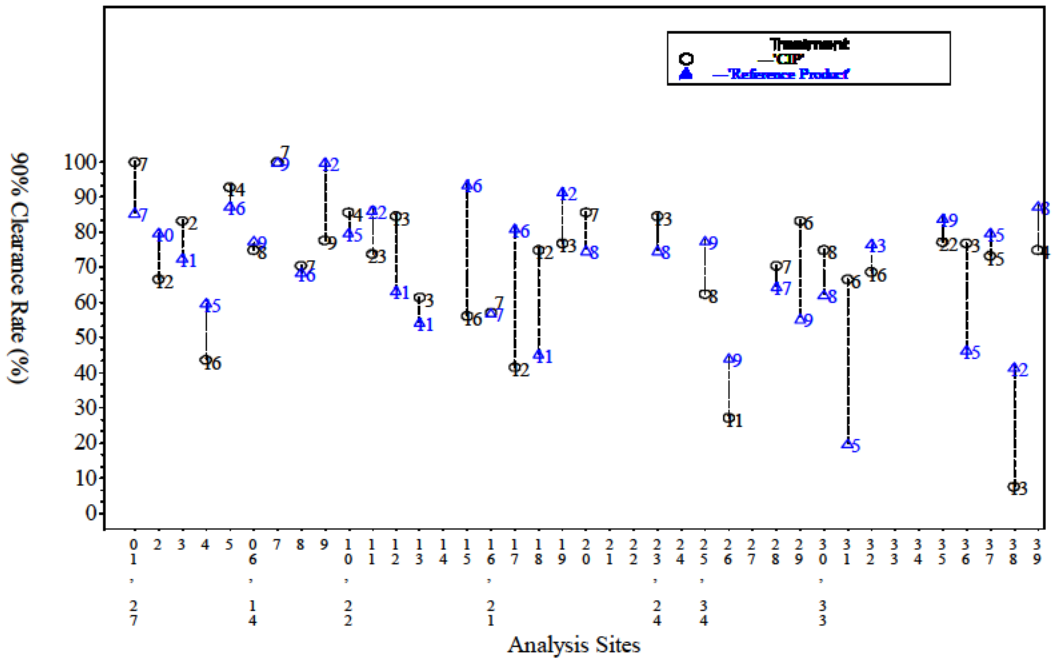
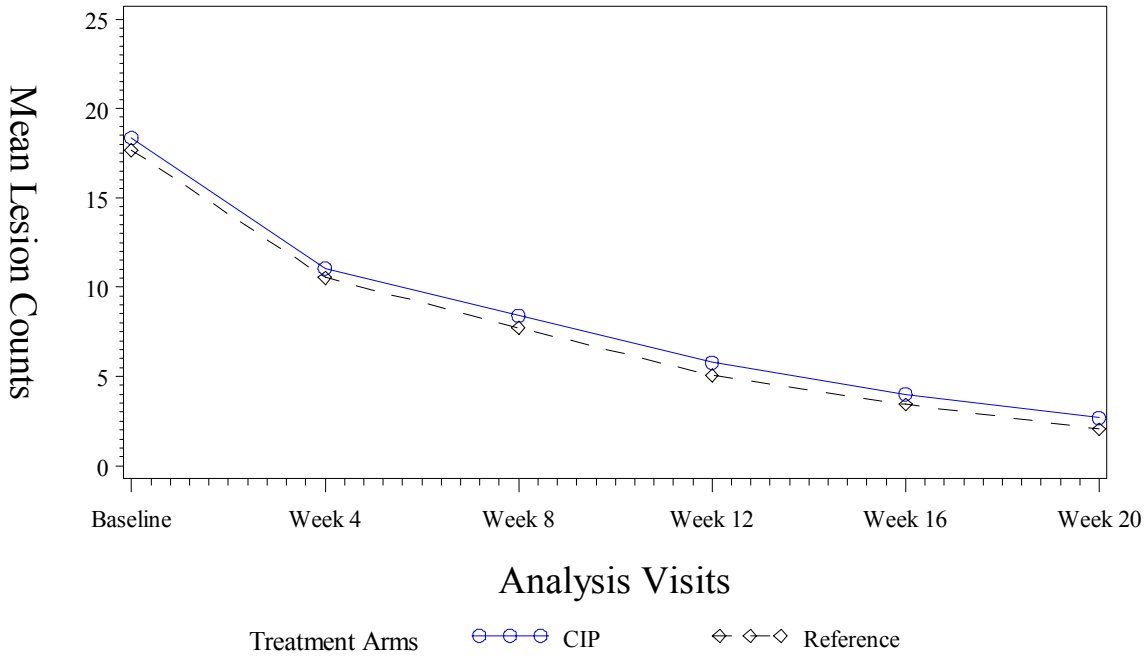


Figure 2 – Proportion of Subjects with 90% Clearance Rate by Center (ITT)



B. By Visit Plot

Figure 3 – Mean Total Nodular Lesion Counts by Study Visits (ITT)



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Concur with review