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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Biometrics Division: DBIV

Statistical Reviewer: Yunfan Deng, Ph.D.

Concurring Reviewer: Thamban Valappil, Ph.D.

Medical Division: Division of Anti-Infective and Ophthalmologic Drug Products
(HFD-520)

Clinical Team: Wiley Chambers, M.D, Deputy Director

Project Manager: Raphael R Rodriguez

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This review focused on the efficacy of AzaSite™ (Azithromycin ophthalmic solution) for the treatment of bacterial conjunctivitis. For this submission, the sponsor submitted two pivotal studies: study C-01-401-003 and study C-01-401-004. Study C-01-401-003 is a randomized, double blind, multi-center, and vehicle-controlled superiority trial; study C-01-401-004 is a randomized, double-blind, multi-center, and active controlled non-inferiority trial with 0.03% Tobramycin topical eye drops as the active comparator.

There are several statistical issues in this submission. The one major statistical issue is the choice of non-inferiority margin of 20% used in study C-01-401-004.

a) Choice of Non-inferiority Margin of 20% (Study C-01-401-004)

Based on the ICH E-10 guideline, it states:

“The non-inferiority trial design is appropriate and reliable only when the historical estimate of drug effect size can be well supported by reference to the results of previous studies of the control drug.”

“The margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of the planned trial. If a difference between active control and the new drug favors the control by as much as or more than this margin, the new drug might have no effect at all. Identification of the smallest effect size that the active drug would be reliably expected to have is only possible when there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence.”

“The determination of the margin in a non-inferiority trial is based on both statistical reasoning and clinical judgment, should reflect uncertainties in the evidence on which the choice is based, and should be suitably conservative.”

“There are many conditions, however, in which drugs considered effective cannot regularly be shown superior to placebo in well-controlled trials; and one therefore cannot reliably determine a minimum effect the drug will have in the setting of a specific trial. Such conditions tend to include those in which there is substantial improvement and variability in placebo groups, and/or in which the effects of therapy are small or variable....”

For this submission, there is no sufficient scientific justification for the 20% margin. The original approval for Tobramycin (Tobrex) was based on an equivalence study compared with an active drug, gentamicin, and not based on a superiority study compared with a placebo control. And according to the sponsor, subsequent literature search did not reveal any superiority trials of Tobramycin against placebo. Thus there is lack of scientific basis for choosing a non-inferiority margin of 20% in a non-inferiority trial using Tobramycin as the active comparator for the

treatment of bacterial conjunctivitis. Consequently, the evidence of efficacy of Azithromycin in study C-01-401-004 compared to Tobramycin 0.03% cannot be meaningfully evaluated.

b) The Primary Analyses Populations (Studies C-01-401-003)

For the superiority study C-01-401-003, the sponsor considered per-protocol (PP) analysis as the primary analysis population. Per study protocol, the PP subset includes all randomized subjects who received at least one drop of the study medication, had baseline cultures indicating pathogenic bacteria levels and had at least one post-first-dose efficacy measurement. According to ICH E9, in superiority trials, the intent-to-treat is generally used in the primary analysis because it tends to avoid over-optimistic estimates of efficacy resulting from a per protocol subgroup analysis. Because PP population is only a subset of mITT population, which includes all randomized subjects who received at least one drop of the study medication, had baseline cultures indicating pathogenic bacteria levels, we looked at the consistency of the results in ITT, and mITT populations in this review.

Based on the review of the data, for the superiority study C-01-401-003, the treatment difference was statistically significant (although marginal) between Azithromycin and Vehicle group in all three analysis populations (mITT, PP, and ITT). For the non-inferiority study C-01-401-004, there is lack of scientific basis for choosing a non-inferiority margin of 20% in which Tobramycin was the active comparator for the treatment of bacterial conjunctivitis. Consequently, the evidence of efficacy of Azithromycin in study C-01-401-004 compared to Tobramycin 0.03% cannot be meaningfully evaluated.

1.2 Brief Overview of Clinical Studies

This submission contains two efficacy/safety studies.

Study C-01-401-003 is a prospective, multicenter, double-masked, randomized, vehicle-controlled study to evaluate the safety and efficacy of Azithromycin ophthalmic solution twice-daily (b.i.d.) on Days 1 and 2 and once-daily (q.d.) on Days 3, 4, 5 vs. its vehicle for the treatment of bacterial conjunctivitis. The primary efficacy endpoint was clinical resolution at Visit 3 (Days 6-7) in a per protocol subset based on all randomized subjects who received at least one drop of the study medication, had baseline cultures indicating pathogenic bacteria levels and had at least one post-first-dose efficacy measurement. Clinical resolution was defined as the absence of the following three clinical signs: conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection.

Study C-01-401-004 is a prospective, multicenter, double-blind, randomized, active-controlled study to evaluate the safety and efficacy of 1% Azithromycin ophthalmic solution twice-daily (b.i.d.) on Days 1 and 2 and once-daily (q.d.) on Days 3, 4, 5 vs. 0.3% Tobramycin ophthalmic solution four times per day (q.i.d.) for the treatment of bacterial conjunctivitis. In order to make this a double-masked study, dosing was as follows:

Table 1: Identity of Administered Dosages

Days 1 and 2:	Azithromycin group	Tobramycin group
Dose 1	Azithromycin	Tobramycin
Dose 2	Vehicle	Tobramycin
Dose 3	Vehicle	Tobramycin
Dose 4	Azithromycin	Tobramycin

Days 3 – 5:	Azithromycin group	Tobramycin group
Dose 1	Azithromycin	Tobramycin
Dose 2	Vehicle	Tobramycin
Dose 3	Vehicle	Tobramycin
Dose 4	Vehicle	Tobramycin

The primary efficacy endpoint was the clinical resolution, measured at Visit 3 (Day 6-7), in a per protocol subset based on all randomized subjects who had administered at least one drop of the appropriate study drug, demonstrated evidence of pathogenic bacteria levels, presented clinical signs of conjunctivitis at Visit 1, and returned for at least one post first dose clinical assessment. Clinical resolution was defined as the absence of the following three clinical signs: conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection.

1.3 Statistical Issues and Findings

There are two statistical issues for this submission. The one major statistical issue for this submission is: the choice of non-inferiority margin for the non-inferiority study C-01-401-004.

Based on the ICH E-10 guideline, it states:

“The non-inferiority trial design is appropriate and reliable only when the historical estimate of drug effect size can be well supported by reference to the results of previous studies of the control drug.”

“The margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of the planned trial. If a difference between active control and the new drug favors the control by as much as or more than this margin, the new drug might have no effect at all. Identification of the smallest effect size that the active drug would be reliably expected to have is only possible when there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence.”

“The determination of the margin in a non-inferiority trial is based on both statistical reasoning and clinical judgment, should reflect uncertainties in the evidence on which the choice is based, and should be suitably conservative.”

“There are many conditions, however, in which drugs considered effective cannot regularly be shown superior to placebo in well-controlled trials; and one therefore cannot reliably determine a minimum effect the drug will have in the setting of a specific trial. Such conditions tend to include those in which there is substantial improvement and variability in placebo groups and/or in which the effects of therapy are small or variable....”

For study C-01-401-004, a non-inferiority margin of 20% was used. The sponsor's response to our request for justification of non-inferiority margin:

"We understand that according to ICH E9 and E10, the margin should be defined as 'the largest difference that can be judged as being clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator.' However, since Tobramycin is an old drug, the original approval (Tobrex) was based on an equivalence study compared with an active drug, gentamicin, and not based on a superiority study compared with a placebo control. Subsequent literature search did not reveal any superiority trials of Tobramycin against placebo. Therefore we cannot get an estimate of the effect size of Tobramycin to construct the equivalence margin and have to rely on the Agency's recommendation."

Therefore, for this submission, there is no sufficient scientific justification for the 20% margin. The original approval for Tobramycin (Tobrex) was based on an equivalence study compared with an active drug, gentamicin, and not based on a superiority study compared with a placebo control. And according to the sponsor, subsequent literature search did not reveal any superiority trials of Tobramycin against placebo. Thus there is lack of scientific basis for choosing a non-inferiority margin of 20% in a non-inferiority trial using Tobramycin as the active comparator for the treatment of bacterial conjunctivitis. Consequently, the evidence of efficacy of Azithromycin in study C-01-401-004 compared to Tobramycin 0.03% cannot be meaningfully evaluated.

Another important statistical issue: the primary analysis population for the superiority study C-01-401-003. For the superiority study C-01-401-003, the sponsor considered per-protocol (PP) analysis as the primary analysis population. Per study protocol, the PP subset includes all randomized subjects who received at least one drop of the study medication, had baseline cultures indicating pathogenic bacteria levels and had at least one post-first-dose efficacy measurement. According to ICH E9, in superiority trials, the intent-to-treat is generally used in the primary analysis because it tends to avoid over-optimistic estimates of efficacy resulting from a per protocol subgroup analysis. Because PP population is only a subset of mITT population, which includes all randomized subjects who received at least one drop of the study medication, had baseline cultures indicating pathogenic bacteria levels, we looked at the consistency of the results in ITT, and mITT populations in this review.

For the superiority study C-01-401-003, the treatment difference was statistically significant (although marginal) between Azithromycin and Vehicle group in all three analysis populations (mITT, ITT, and PP).

For the non-inferiority study C-01-401-004, there is lack of scientific basis for choosing a non-inferiority margin of 20% in which Tobramycin was the active comparator for the treatment of

bacterial conjunctivitis. Consequently, the evidence of efficacy of Azithromycin in study C-01-401-004 compared to Tobramycin 0.03% cannot be meaningfully evaluated.

2. INTRODUCTION

2.1 Overview

Azithromycin is an ophthalmic formulation of 1.0% azithromycin, a broad-spectrum antibiotic and is intended for the treatment of bacterial conjunctivitis. Azithromycin is an azalide, a subclass of macrolide antibiotics. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the 15-membered macrolide ring. The formulation for Azithromycin also contains the sponsor's patented delivery system, DuraSite®.

This submission contains two efficacy/safety studies. Study C-01-401-003 is a prospective, multicenter, double-masked, randomized, Vehicle-controlled study to evaluate the safety and efficacy of Azithromycin ophthalmic solution twice-daily (b.i.d.) on Days 1 and 2 and once-daily (q.d.) on Days 3, 4, 5 vs. its vehicle for the treatment of bacterial conjunctivitis. Study C-01-401-004 is a prospective, multicenter, double-blind, randomized, active-controlled study to evaluate the safety and efficacy of 1% Azithromycin ophthalmic solution twice-daily (b.i.d.) on Days 1 and 2 and once-daily (q.d.) on Days 3, 4, 5 vs. 0.3% Tobramycin ophthalmic solution four time per day (q.i.d.) for the treatment of bacterial conjunctivitis.

2.2 Data Sources

The Sponsor's study reports for studies C-01-401-003 and C-01-401-004 are available on the EDR at \\Cdsesub1\N50810\N_000.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The primary objective of study C-01-401-003 was to evaluate the clinical and microbial efficacy, and safety of 1.0% Azithromycin ophthalmic solution compared to Vehicle in the treatment of bacterial conjunctivitis. Study C-01-401-004 was designed to evaluate the safety and the equivalence of clinical and microbial efficacy of Azithromycin ophthalmic solution compared to 0.3% Tobramycin ophthalmic solution, USP in the treatment of bacterial conjunctivitis. Azithromycin was considered non-inferior to Tobramycin if the 95% (two-sided) CI for the difference in response rates between two treatment groups contained zero and the lower limit of the CI was greater than -20%.

3.1.1 Study Design and Endpoints

Study C-01-401-003 was a multi-center, randomized, double-masked, parallel-group, vehicle-controlled clinical trial. Subjects with a clinical diagnosis of bacterial conjunctivitis were randomly assigned to use either 1.0% Azithromycin, a topical ophthalmic azithromycin formulation, or its Vehicle for five days. Azithromycin or its Vehicle was to be dosed twice a day on Days 1 and 2 and once a day for the next three days. The study consisted of three visits: Visit 1 took place on the first treatment day (Day 1), Visit 2 on the third treatment day (Day 3 (+1 day)) and Visit 3 (Day 6 (+ 1 day)) at least 12 hours after the subject had last used his/her study medication.

Study C-01-401-004 was a multi-center randomized, double masked, parallel clinical trial. Subjects with a clinical diagnosis of bacterial conjunctivitis were randomly assigned to use either Azithromycin, a topical ophthalmic formulation of 1.0% azithromycin in DuraSite, or 0.3% Tobramycin for five days. Azithromycin was dosed b.i.d. on Days 1 and 2 and q.d. for the next three days. Tobramycin was dosed q.i.d. for five days. Subjects were given four identical bottles for each day's allotment of study medication. In the Azithromycin group, instillation was performed q.i.d. as well, but two or three of the bottles contained vehicle. In the comparison group, all four bottles contained Tobramycin. In this manner, the study drugs were effectively masked. The study consisted of three visits: Visit 1 occurred on the first treatment day (Day 1), Visit 2 took place on the third treatment day (Day 3 (+1 day)) and Visit 3 (Day 6 (+ 1 day)) was scheduled for at least 12 hours after the subject had used the last dose of study medication.

For both study C-01-401-003 and study C-01-401-004, the primary efficacy variable was clinical resolution, defined as a clinical severity rating of 0 for the following three clinical signs ocular (conjunctival) discharge, bulbar and palpebral conjunctival injection. Clinical efficacy was assessed at the beginning of each office visit.

Table 2: Investigator's severity rating of clinical signs
Ocular Discharge Bulbar Injection Palpebral Injection

0 = absent	0 = normal	0 = normal
1 = mild	1 = mild	1 = mild
2 = moderate	2 = moderate	2 = moderate
3 = severe	3 = severe	3 = severe

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

For study C-01-401-003, 685 subjects were enrolled at 69 study sites. The packed study drug for two subjects, 3037-0434 and 3037-0436 from one investigator were from the wrong lot of study drug. Thus only 683 of the 685 subjects (333 in the Azithromycin group and 350 in the Vehicle group) were considered as the safety population in this report. Of the 685 subjects, 630 (92%) successfully completed the study (93.4% 313/335 in the Azithromycin group and 90.6%, 317/350 in the Vehicle group). Fifty-five subjects (22 subjects in the Azithromycin group and 33 subjects in the Vehicle group) were terminated from the study before completion (Table 3).

Table 3: Study C-01-401-003 Disposition of all enrolled subjects

	Azithromycin (N=335)	Vehicle (N=350)	Total (N=685)
Total Number of Subjects			
Randomized	335 (100.0%)	350 (100.0%)	685 (100.0%)
Completed	313 (93.4%)	317 (90.6%)	630 (92.0%)
Discontinued	22 (6.6%)	33 (9.4%)	55 (8.0%)
Primary Reason for Discontinuation			
Adverse Event	2 (0.6%)	5 (1.4%)	7 (1.0%)
Protocol Violation	1 (0.3%)	4 (1.1%)	5 (0.7%)
Withdrew Consent	6 (1.8%)	6 (1.7%)	12 (1.8%)
Lost to Follow-up	5 (1.5%)	1 (0.3%)	6 (0.9%)
Lack of Efficacy	7 (2.1%)	15 (4.3%)	22 (3.2%)
Treatment Unmasked	1 (0.3%)	0 (0.0%)	1 (0.1%)
Other	0 (0.0%)	2 (0.6%)	2 (0.3%)

For study C-01-401-004, 747 subjects were enrolled in 47 study sites. The Case Report Forms for 4 subjects: 4004-0059 and 4004-0060 from Dr. Caldwell, 4011-0166 and 4011-0167 from Dr. Insler, were lost due to the Katrina hurricane in New Orleans. Thus only 743 of the 747 subjects (365 in the Azithromycin group and 378 in the Tobramycin group) have data to be considered as All Enrolled in this report. Of the 743 subjects, 710 (95.6%) successfully completed the study (94.0% 343/365 in the Azurite group and 97.1%, 367/378 in the Tobramycin group). Thirty-three subjects (22 subjects in the Azithromycin group and 11 subjects in the Tobramycin group) were terminated from the study before completion; 17 of which were due to AE dropouts, 9 subjects were in the Azithromycin group and 8 subjects in the Tobramycin group (Table 4).

Table 4: Study C-01-401-004 Disposition of All Enrolled subjects

	Azithromycin (N=365)	Tobramycin (N=378)	Total (N=743)
Total Number of Subjects			
Randomized	365 (100.0%)	378 (100.0%)	743 (100.0%)
Completed	343 (94.0%)	367 (97.1%)	710 (95.6%)
Discontinued	22 (6.0%)	11 (2.9%)	33 (4.4%)
Primary Reason for Discontinuation			
Adverse Event	9 (2.5%)	8 (2.1%)	17 (2.3%)
Protocol Violation	4 (1.1%)	0	4 (0.5%)
Withdrew Consent	2 (0.5%)	3 (0.8%)	5 (0.7%)
Lost to Follow-up	1 (0.3%)	0	1 (0.1%)
Lack of Efficacy	2 (0.5%)	0	2 (0.3%)
Treatment Unmasked	0	0	0
Other	4 (1.1%)	0	4 (0.5%)

Summary of analysis population by study and by treatment arm are presented in the following table.

Table 5: Analysis Population by Treatment Arm

	ITT (All randomized)	Per Protocol	
	n	n	(%)
Study C-01-401-003			
Azithromycin	333	130	(39.0)
Vehicle	350	149	(42.6)
Total	683	279	(40.8)
Study C-01-401-004			
Azithromycin	365	159	(43.5)
Tobramycin	378	157	(41.5)
Total	743	316	(42.5)

Statistical Reviewer's Comments:

The percentage of the PP population is only around 40% of the ITT, all randomized population for both studies.

Table 6: Study C-01-401-003 Demographics (Intent-to-Treat Population)

		Azithromycin (N=333)		Vehicle (N=350)		Total (N=683)	
		n	(%)	n	(%)	n	(%)
Gender	Male	116	(34.8)	139	(39.7)	255	(37.3)
	Female	217	(65.2)	211	(60.3)	428	(62.7)
Age	0 to 11	90	(27.0)	94	(26.9)	184	(26.9)
	12 to 16	30	(9.0)	26	(7.4)	56	(8.2)
	17 to 64	176	(52.9)	190	(54.3)	366	(53.6)
	Over 64	37	(11.1)	40	(11.4)	77	(11.3)
	MEAN		31.0		31.0		31.0
	SD		23.13		23.94		23.53
	MEDIAN		28.0		29.0		28.0
	RANGE		1 to 84		1 to 96		1 to 96
Race	Caucasian	161	(48.4)	179	(51.1)	340	(49.8)
	African American	34	(10.2)	29	(8.3)	63	(9.2)
	Asian/Pacific Islander	4	(1.2)	9	(2.6)	13	(1.9)
	Hispanic	128	(38.4)	128	(36.6)	256	(37.5)
	Native American/Alaskan	1	(0.3)	2	(0.6)	3	(0.4)
	Other	5	(1.5)	3	(0.9)	8	(1.2)

Table 7: Study C-01-401-004 Demographics (Intent-to-Treat Population)

		Azithromycin (N=365)		Tobramycin (N=378)		Total (N=743)	
		n	(%)	n	(%)	n	(%)
Gender	Male	160	(43.8)	161	(42.6)	321	(43.2)
	Female	205	(56.2)	217	(57.4)	422	(56.8)
Age	0 to 11	134	(36.7)	126	(33.3)	260	(35.0)
	12 to 16	17	(4.7)	21	(5.6)	38	(5.1)
	17 to 64	194	(53.2)	205	(54.2)	399	(53.7)
	Over 64	20	(5.5)	26	(6.9)	46	(6.2)
	MEAN		26.1		27.8		27.0
	SD		21.62		21.70		21.66
	MEDIAN		22		25.5		24
	RANGE		1 to 87		1 to 93		1 to 93
Race	Caucasian	243	(66.6)	244	(64.6)	487	(65.5)
	African American	25	(6.9)	40	(10.6)	65	(8.7)
	Asian/Pacific Islander	19	(5.2)	13	(3.4)	32	(4.3)
	Hispanic	70	(19.2)	75	(19.8)	145	(19.5)
	Native American/Alaskan	3	(0.8)	1	(0.3)	4	(0.5)
	Other	5	(1.4)	5	(1.3)	10	(1.3)

3.1.3 Statistical Methodologies

3.1.3.1 Study C-01-401-003

Analysis of Primary Efficacy Endpoint

The primary study objective was to evaluate the clinical efficacy and safety of 1.0% Azithromycin compared to Vehicle in the treatment of bacterial conjunctivitis as measured by clinical resolution.

The primary efficacy variable was clinical resolution at Visit 3 (Days 6-7). Clinical resolution was defined as the absence of the following three clinical signs: conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection. The secondary efficacy variable was bacterial eradication as indicated by the absence of growth of baseline bacteria. The final primary analysis was the 95% confidence interval and the Fisher's Exact Test for the difference in resolution rates using normal approximation among per protocol subjects, as requested by FDA. Specifically, the primary hypothesis tested for the study was:

Ho: Subjects treated with Azithromycin and those treated with Vehicle have the same proportion of subjects with clinical resolution.

Ha: The proportion of subjects with clinical resolution differs between the Vehicle and Azithromycin groups.

Superiority was demonstrated by a $p < 0.05$ for the treatment differences.

Efficacy Analysis Population

According to the submission, the primary efficacy analysis population was a per protocol (PP) subset based on all randomized subjects who received at least one drop of the study medication, had baseline cultures indicating pathogenic bacteria levels and had at least one post-first-dose efficacy measurement. If data were missing for Visit 3, the test of cure visit, a last observation carried forward (LOCF) procedure was followed, using efficacy data from the last visit. Two intent-to-treat (ITT) analyses were used: ITT included all randomized subjects who received at least one dose of study drug and had at least one post-dose clinical evaluation and ITT2 included all randomized subjects. If any major protocol violations occurred, an additional per protocol (Efficacy Evaluable-EE) analysis was performed excluding subjects whose efficacy data might have been affected by a violation. For subjects in whom both eyes qualified for the study, data from the eye with the higher combined clinical severity score on Day 1 were analyzed. If the score was the same for both eyes, data from the right eye were analyzed for efficacy.

Statistical Reviewer's Comments:

According to ICH E9, in superiority trials, the intent-to-treat is generally used in the primary analysis because it tends to avoid over-optimistic estimates of efficacy resulting from a per protocol subgroup analysis. Because PP population is only a subset of mITT population, which includes all randomized subjects who received at least one drop of the study medication, had baseline cultures indicating pathogenic bacteria levels, we looked at the consistency of the results in ITT, and mITT populations in this review.

Determination of Sample Size

Two hundred twenty-four (224) subjects with bacteriologically confirmed acute bacterial conjunctivitis, 112 subjects in each treatment group, were planned to participate in the study. The sample size was calculated based on a power of 0.90, and $\alpha=0.05$ (two-sided, chi-square test) and a clinical resolution rate of 83% in the active treatment group (1.0% Azithromycin) and a 64% clinical resolution rate in the Vehicle group after 5 days of treatment. The Azithromycin clinical resolution rate estimate was based on a subgroup of subjects in a Phase 2 pilot study conducted by the sponsor, subjects who had symptoms for 3 days or less, an entry criterion for the current study. The Vehicle clinical resolution rate was from the same study. Since bacterial confirmation is usually 40% to 50% of the subjects with clinically diagnosed bacterial conjunctivitis, subjects were recruited until the target sample size of 224 subjects with bacteriologically confirmed acute bacterial conjunctivitis was achieved.

3.1.3.2 Study C-01-401-004

Analysis of Primary Efficacy Endpoint

The primary objective of this study was to determine if Azithromycin dosed b.i.d. on Days 1 and 2 and q.d. for the next three days cures bacterial conjunctivitis as effectively as 0.3% Tobramycin ophthalmic solution dosed q.i.d. as measured by clinical resolution. Specifically, the primary hypothesis tested for the study was:

H0: The limits of the 95% confidence intervals for the differences between the Azithromycin and Tobramycin treatment groups in the proportion of subjects with clinical resolution are outside the equivalence boundary $\pm 20\%$.

Ha: The limits of the 95% confidence intervals for the differences between the Azithromycin and Tobramycin treatment groups in the proportion of subjects with clinical resolution are within the equivalence boundary $\pm 20\%$

The primary efficacy variable was clinical resolution at Visit 3 Day 6 (+1 day). To compare treatments, the 95% 2-sided CI for the difference (Azithromycin - Tobramycin) in the proportion of success was presented. The equivalence limits governing the comparisons depended on the proportion of success in the Tobramycin group. If the Tobramycin success rate was 80% or greater, then the comparison was evaluated using $\pm(100 - \text{Tobramycin})\%$ equivalence limits. For example, if the Tobramycin success rate was 87%, then the equivalence limits would be $\pm 13\%$. If the Tobramycin success rate was 80% or less, then the equivalence limits would be $\pm 20\%$ for that comparison.

Statistical Reviewer's Comments:

A non-inferiority margin of 20% was used based on using the above stated criteria (step function). However, this method is no longer acceptable and it was discussed at the previous Advisory Committee meetings. The sponsor didn't provide a sufficient scientific justification for this margin. The original approval for Tobramycin (Tobrex) was based on an equivalence study compared with an active drug, gentamicin, and not based on a superiority study compared with a placebo control. And according to the sponsor, subsequent literature search did not reveal any superiority trials of Tobramycin against placebo. Thus there is lack of scientific basis for choosing a margin of 20% in a non-inferiority trial using Tobramycin as the active comparator for the treatment of bacterial conjunctivitis.

There were three efficacy data sets, which were Per Protocol (PP), Efficacy Evaluable (EE) and Intent-to-Treat (ITT2). The PP data set was the primary data set for efficacy analyses. This data set included all randomized subjects who had administered at least one drop of the appropriate study drug, demonstrated evidence of pathogenic bacteria levels, presented clinical signs of conjunctivitis at Visit 1, and returned for at least one post-first dose clinical assessment. If data were missing for Visit 3, the test of cure visit, a last observation carried forward (LOCF) procedure was followed, using efficacy data from the last visit. EE data set included all PP who had no significant protocol violations that might affect the efficacy data. Additional, limited analyses were performed on the ITT2 data set which included all randomized patients.

3.1.4 Results and Conclusions

The sponsor's efficacy results of clinical resolution at Visit 3 Day 6 (+1) are presents in the following table

Table 8: Efficacy Analysis Results for Study C-01-401-003 and Study C-01-401-004

Study C-01-401-003 (Superiority Trial)					
		Azithromycin n/N (%)	Vehicle n/N (%)	p-value	95% CI
Clin. Resolution (PP)	LOCF	82/130 (63.1)	74/149 (49.7)	0.03	(1.9, 25.0)
Clin. Resolution (ITT)	LOCF	203/333 (61.0)	184/350 (52.6)	0.03	(1.0, 15.8)
Study C-01-401-004 (Non-inferiority Trial)					
		Azithromycin n/N (%)	Tobramycin n/N (%)	p-value	95% CI
Study C-01-401-004 (non-inferiority trial)					
Clin. Resolution (PP)	LOCF	127/159 (79.9)	123/157 (78.3)		(-7.4, 10.5)
Clin. Resolution (ITT)	LOCF	257/365 (70.4)	260/378 (68.8)		(-5.0, 8.2)

Statistical Reviewer's Comments:

Additional sensitivity analysis using the mITT population for Study C-01-401-003 was also performed. The efficacy analysis result is listed in the following table.

Table 9: Efficacy Analysis Results for Study C-01-401-003 (mITT population)

Study C-01-401-003 (Superiority Trial)					
		Azithromycin n/N (%)	Vehicle n/N (%)	p-value	95% CI
Clin. Resolution (mITT)		82/133 (60.2)	74/150 (48.7)	0.04	(1.0, 23.8)

From these results, for study C-01-401-003, the treatment difference was statistically significant (although marginal) between Azithromycin and Vehicle group in all the analysis populations.

For study C-01-401-004, there is lack of scientific basis for choosing a margin of 20% in a non-inferiority trial using Tobramycin as the active comparator for the treatment of bacterial conjunctivitis. Thu, the efficacy results are not interpretable.

3.2 Evaluation of Safety

The following two tables summarized AEs for Study C-01-401-003 and C-01-401-004 respectively.

Table 10: Adverse events in >1% of subjects in either group for study C-01-401-003

Adverse Event	Azithromycin (n = 333)	Vehicle (n = 350)
Eye irritation	5 (1.5%)	1 (0.3%)
Worsening bacterial conjunctivitis	5 (1.5%)	3 (0.9%)
Headache	4 (1.2%)	8 (2.3%)
Pharyngolaryngeal pain	4 (1.2%)	2 (0.6%)
Conjunctival oedema	2 (0.6%)	5 (1.4%)

Source: Sponsor's study C-01-401-003 report Section 14.3.3.1 and Appendix 16.2.7.1

Table 11: Adverse events in >1% of subjects in either group for study C-01-401-004

Adverse Event	Azithromycin (n = 365)	Tobramycin (n = 378)
Eye irritation	7 (1.9%)	4 (1.1%)
Conjunctivital hyperaemia	4 (1.1%)	4 (1.1%)
Worsening bacterial conjunctivitis	4 (1.1%)	8 (2.1%)

Source: Sponsor's study C-01-401-003 report Section 14.3.3.1

In study C-01-401-003, two serious adverse events were noted (corneal ulcer and cerebrovascular accident), both in the Vehicle group which were judged by the Investigator not to be study medication related. In study C-01-401-004, there were no serious or significant adverse events reported. Please see the review of the medical officer for details of the safety evaluation.

APPEARS THIS WAY ON ORIGINAL

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Study C-01-401-003

The proportion of patients with clinical resolution using LOCF at Visit 3 (Days 6-7) in the PP and ITT populations by gender, age group, and race are listed in Table 12, and Table 13 respectively.

Table 12 Analyses of Outcomes by gender, age, and race (PP Population)

	Azithromycin (A)		Vehicle (B)		Observed Differences (A-B)
	(N=107)		(N=124)		
	Observed Response		Observed Response		
	n/m	%	n/m	%	%
Gender					
Male	29/41	70.7	34/59	57.6	13.1
Female	47/66	71.2	37/65	56.9	14.3
Age					
0-11	35/47	74.5	31/52	59.6	14.9
≥ 12	41/60	68.3	40/72	55.6	12.7
<65	68/95	71.6	55/99	55.6	16.0
≥ 65 years	8/12	66.7	16/25	64.0	3.7
Race					
Caucasian	32/45	71.1	37/54	68.5	2.6
African American	7/9	77.8	7/12	58.3	19.5
Hispanic	34/48	70.8	24/54	44.4	26.4
Other	3/5	60.0	3/4	75.0	-15.0
N = Number of PP patients in each treatment group. n/m = Number of PP patients with a favorable assessment / number of PP patients with assessment.					

APPEARS THIS WAY ON ORIGINAL

Table 13 Analyses of Outcomes by gender, age, and race (ITT Population)

	Azithromycin (A)		Vehicle (B)		Observed Differences (A-B)
	(N=333)		(N=350)		
	Observed Response		Observed Response		
	n/m	%	n/m	%	
Gender					
Male	71/116	61.2	65/139	46.8	14.4
Female	132/217	60.8	119/211	56.4	4.4
Age					
0-11	61/90	67.8	55/94	58.5	9.3
≥ 12	142/243	58.4	129/256	50.4	8.0
<65	181/296	61.1	161/310	51.9	9.2
≥ 65 years	22/37	59.5	23/40	57.5	2.0
Race					
Caucasian	97/161	60.2	101/179	56.4	3.8
African American	20/34	58.8	14/29	48.3	10.5
Hispanic	79/128	61.7	62/128	48.4	13.3
Other	7/10	70.0	7/14	50.0	20.0
N = Number of ITT patients in each treatment group. n/m = Number of ITT patients with a favorable assessment / number of ITT patients with assessment.					

Statistical Reviewer's Comments:

Overall, there were no major issues identified in the subgroups with respect to age, gender and race.

Study C-01-401-004

The proportion of patients with clinical resolution using LOCF at Visit 3 (Days 6-7) in the PP and ITT populations by gender, age group, and race are listed in Table 14, and Table 15 respectively.

APPEARS THIS WAY ON ORIGINAL

Table 14 Analyses of Outcomes by gender, age, and race (PP Population)

	Azithromycin (A)		Tobramycin (B)		Observed Differences (A-B)
	(N=159)		(N=157)		
	Observed Response		Observed Response		
	n/m	%	n/m	%	
Gender					
Male	58/78	74.4	53/67	79.1	-4.7
Female	69/81	85.2	70/90	77.8	7.4
Age					
0-11	79/93	84.9	65/77	84.4	0.5
≥ 12	48/66	72.7	58/80	72.5	0.2
<65	124/153	81.0	118/147	80.3	0.7
≥ 65 years	3/6	50.0	5/10	50.0	0.0
Race					
Caucasian	94/113	83.2	78/100	78.0	5.2
African American	10/10	100.0	11/15	73.3	26.7
Hispanic	18/29	62.1	30/37	81.1	-19.0
Other	5/7	71.4	4/5	80.0	-15.0

N = Number of PP patients in each treatment group.
n/m = Number of PP patients with a favorable assessment / number of PP patients with assessment.

Table 15 Analyses of Outcomes by gender, age, and race (ITT Population)

	Azithromycin (A)		Tobramycin (B)		Observed Differences (A-B)
	(N=365)		(N=378)		
	Observed Response		Observed Response		
	n/m	%	n/m	%	
Gender					
Male	102/160	63.8	107/161	66.5	-2.7
Female	155/205	75.6	153/217	70.5	5.1
Age					
0-11	106/134	79.1	104/126	82.5	-3.4
≥ 12	151/231	65.4	156/252	61.9	3.5
<65	245/345	71.0	246/352	69.9	1.1
≥ 65 years	12/20	60.0	14/26	53.8	6.2
Race					
Caucasian	177/243	72.8	179/244	73.4	-0.6
African American	21/25	84.0	24/40	60.0	24.0
Hispanic	45/70	64.3	49/75	65.3	-1.0
Other	14/27	51.9	8/19	42.1	9.8

N = Number of ITT patients in each treatment group.
n/m = Number of ITT patients with a favorable assessment / number of ITT patients with assessment.

Statistical Reviewer's Comments:

Overall, there were no major issues identified in the subgroups with respect to age, gender and race.

However, for study C-01-401-004, there is lack of scientific basis for choosing a non-inferiority margin of 20% in a non-inferiority trial using Tobramycin as the active comparator for the treatment of bacterial conjunctivitis. Thus the efficacy results are not interpretable.

4.2 Other Special/Subgroup Populations

Study C-01-401-003

The proportion of patients with clinical resolution using LOCF at Visit 3 (Days 6-7) in the PP and ITT populations by iris color are listed in Table 16.

Table 16 Analyses of Outcomes by iris color

PP Population	Azithromycin (A)		Vehicle (B)		Observed Differences (A-E)
	(N=107)		(N=124)		
	Observed Response		Observed Response		
	n/m	%	n/m	%	%
Dark	55/87	63.2	42/98	42.9	20.3
Hazel	9/13	69.2	4/8	50.0	19.2
Light	18/30	60.0	28/43	65.1	-5.1
ITT Population	(N=333)		(N=350)		Observed Differences (A-B)
	Observed Response		Observed Response		
	n/m	%	n/m	%	
Dark	138/220	62.7	99/204	48.5	14.2
Hazel	20/35	57.1	13/28	46.4	10.7
Light	45/78	57.7	72/118	61.0	-3.3

N = Number of PP or ITT patients in each treatment group.
n/m = Number of PP or ITT patients with a favorable assessment / number of PP or ITT patients with assessment.

Statistical Reviewer's Comments:

Overall, there was no major issue identified in the subgroups with respect to iris color.

Study C-01-401-004

The proportion of patients with clinical resolution using LOCF at Visit 3 (Days 6-7) in the PP and ITT populations by iris color are listed in Table 17.

Table 17 Analyses of Outcomes by IRIS color

PP Population	Azithromycin (A)		Vehicle (B)		Observed Differences (A-B)
	(N=159)		(N=157)		
	Observed Response		Observed Response		
	n/m	%	n/m	%	
Dark	65/84	77.4	66/83	79.5	-2.1
Hazel	9/12	75.0	14/21	66.7	8.3
Light	53/63	84.1	43/53	81.1	3.0
ITT Population	(N=365)		(N=378)		Observed Differences (A-B)
	Observed Response		Observed Response		
	n/m	%	n/m	%	
	Dark	139/196	70.9	140/205	
Hazel	24/39	61.5	29/45	64.4	-2.9
Light	94/130	72.3	91/128	71.1	1.2

N = Number of PP or ITT patients in each treatment group.
n/m = Number of PP or ITT patients with a favorable assessment / number of PP or ITT patients with assessment.

Statistical Reviewer’s Comments:

Overall, there was no major issue identified in the subgroups with respect to iris color.

However, for study C-01-401-004, there is lack of scientific basis for choosing a non-inferiority margin of 20% in a non-inferiority trial using Tobramycin as the active comparator for the treatment of bacterial conjunctivitis. Thus the efficacy results are not interpretable.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There are several statistical issues for this submission. The one major statistical issue for this submission is: the choice of non-inferiority margin for the non-inferiority study C-01-401-004.

Based on the ICH E-10 guideline, it states:

“The non-inferiority trial design is appropriate and reliable only when the historical estimate of drug effect size can be well supported by reference to the results of previous studies of the control drug.”

“The margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of the planned trial. If a difference between active control and the new drug favors the control by as much as or more than this margin, the new drug might have no effect at all. Identification of the smallest effect size that the active drug would be reliably expected to have is only possible when

there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence.”

“The determination of the margin in a non-inferiority trial is based on both statistical reasoning and clinical judgment, should reflect uncertainties in the evidence on which the choice is based, and should be suitably conservative.”

“There are many conditions, however, in which drugs considered effective cannot regularly be shown superior to placebo in well-controlled trials; and one therefore cannot reliably determine a minimum effect the drug will have in the setting of a specific trial. Such conditions tend to include those in which there is substantial improvement and variability in placebo groups, and/or in which the effects of therapy are small or variable....”

For this submission, there is not a sufficient scientific justification for the 20% margin. The original approval for Tobramycin (Tobrex) was based on an equivalence study compared with an active drug, gentamicin, and not based on a superiority study compared with a placebo control. And according to the sponsor, subsequent literature search did not reveal any superiority trials of Tobramycin against placebo. Thus there is lack of scientific basis for choosing a non-inferiority margin of 20% in a non-inferiority trial using Tobramycin as the active comparator for the treatment of bacterial conjunctivitis. Consequently, the evidence of efficacy of Azithromycin in study C-01-401-004 compared to Tobramycin 0.03% cannot be meaningfully evaluated.

Another important statistical issue: the primary analysis population for the superiority study C-01-401-003. For the superiority study C-01-401-003, the sponsor considered per-protocol (PP) analysis as the primary analysis population. Per study protocol, the PP subset includes all randomized subjects who received at least one drop of the study medication, had baseline cultures indicating pathogenic bacteria levels and had at least one post-first-dose efficacy measurement. According to ICH E9, in superiority trials, the intent-to-treat is generally used in the primary analysis because it tends to avoid over-optimistic estimates of efficacy resulting from a per protocol subgroup analysis. Because PP population is only a subset of mITT population, which includes all randomized subjects who received at least one drop of the study medication, had baseline cultures indicating pathogenic bacteria levels, we looked at the consistency of the results in ITT, and mITT populations in this review.

5.2 Conclusions and Recommendations

For the superiority study C-01-401-003, the treatment difference was statistically significant (although marginal) between Azithromycin and Vehicle group in all the analysis populations (mITT, ITT, and PP).

For the non-inferiority study C-01-401-004, there is lack of scientific basis for choosing a non-inferiority margin of 20% in which Tobramycin was the active comparator for the treatment of bacterial conjunctivitis. Consequently, the evidence of efficacy of Azithromycin in study C-01-401-004 compared to Tobramycin 0.03% cannot be meaningfully evaluated.

SIGNATURES/DISTRIBUTION LIST

Yunfan Deng, Ph.D.
Primary Statistical Reviewer

Concurring Reviewer:

Thamban Valappil, Ph.D
Statistical Team Leader:

cc:

HFD-520/Project Manager: Raphael R Rodriguez

HFD-520/ Deputy Director: Wiley Chambers, M.D

HFD-520/Medical Team Leader: William Boyd, M.D

HFD-725/Primary Statistical Reviewer: Yunfan Deng, Ph.D.

HFD-725/Statistical Team Leader: Thamban Valappil, Ph.D

HFD-725/Biometrics Deputy Division Director: Daphne Lin, Ph.D

HFD-725/Biometrics Division Director: Mohammad Huque, Ph.D

HFD-700/Office of Biostatistics: Lillian Patrician

HFD-700/Office of Biostatistics Deputy Director: Edward Nevious, Ph.D

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/s/

Yunfan Deng
2/27/2007 05:40:47 PM
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Thamban Valappil
3/1/2007 10:29:48 AM
BIOMETRICS

NDA 50810

Statistical Comments for AzaSite Label

Date: April 25, 2007

We have the following two comments regarding the proposed AzaSite label:

1. Reporting of the superiority study results in the clinical studies section without p-value or 95% CI.

We agree with the Sponsor's original proposed label that the p-value and the 95% CI should be reported for the superiority study. According to guidance for industry "Clinical studies section of labeling for prescription drug and biological products - content and format" III C: Summarizing Study Findings part 2. Treatment Effect,

"Uncertainty of Treatment Effect: A confidence interval and a p-value provide complementary information, and both should usually be provided when describing uncertainty of the treatment effect. A confidence interval provides a better numerical description of the uncertainty of the treatment effect and provides some information about its size. A p-value better conveys the strength of the finding (i.e., how likely it is that the observed treatment effect is a chance finding). However, it is generally better not to use a p-value alone."

2. The report of the non-inferiority study in the _____

We recommend that the efficacy results of the noninferiority study be _____ because of the difficulty in interpreting the efficacy results in the noninferiority setting as discussed in the statistical review for this NDA. In addition, there is also a concern about the difference in dosing for the active-control study from the actual proposed dosing.

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/s/

Yunfan Deng
4/25/2007 03:56:22 PM
BIOMETRICS

Scott Komo
4/25/2007 04:04:09 PM
BIOMETRICS
Signing for Thamban Valappil