U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW

NDA #:	22,221
Drug Name:	Akten (lidocaine hydrochloride) Ophthalmic Gel, 3.5%
Indication(s):	Topical Ocular Anesthesia
Applicant:	Akorn, Inc.
Date of Receipt:	July 2, 2007
User Fee Goal Date:	June 2, 2008
Review Priority:	Standard
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Christopher Kadoorie, Ph.D.
Concurring Reviewer:	Thamban Valappil, Ph.D.
Medical Division:	Division of Anti-Infective and Ophthalmology Drug Products
Clinical Reviewer:	Sonal Wadhwa, M.D.
Project Manager:	Jane Dean, RN, MSN

1. EXECUTIVE SUMMARY

1.1 Introduction

Akorn Inc. has submitted NDA 22-221 application to support approval of Akten™ (lidocaine hydrochloride) Ophthalmic Topical Gel (AK105) as a local anesthetic for ocular surface anesthesia during ophthalmic procedures. This is 505 (b) (2) NDA application which relies on evidence of safety and efficacy of lidocaine hydrochloride referenced in NDA 6-488 and 8-816. In this NDA submission, Akorn has included a single, multi-center, randomized, four arm, sham controlled double-blind study comparing the sham, Akten™ 1.5%, Akten™ 2.5%, and Akten™ 3.5% groups. This statistical review primarily focuses on this double-blind study and the strength and validity of its reported results.

1.2 Conclusions and Recommendations

There were no major statistical issues associated with Study 06AKO001 which was considered to be an adequate and well-controlled study. Study 06AKO001 provided evidence of an improvement in efficacy of Akten™ 3.5% versus sham treatment (placebo) with respect to the percentage of patients achieving anesthesia within 5 minutes of dosing and the duration of anesthesia. Based on results of this study and other supportive information, there appears to be adequate evidence presented to support the safety and efficacy of Akten™ 3.5% as a local anesthetic indicated for ocular surface anesthesia during ophthalmologic procedures.

2. INTRODUCTION

2.1 Overview

Lidocaine hydrochloride is a local anesthetic agent that stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses. The only ocular anesthetic currently approved by the FDA is proparacaine. The current proposed product is a preservative-free gel solution of lidocaine 3.5% developed for topical ocular anesthesia. The proposed dose is 2 drops applied to the ocular surface in the area of the planned ophthalmic procedure.

2.1.1 Class and Indication

Drug Class: Amino amide; local anesthetic

Indication: To be used as the sole anesthetic agent for ocular surface anesthesia during ophthalmologic procedures

Route of Administration: Topical

2.1.2 Rationale for Drug Product Development

The proposed gel formulation contains hypromellose to allow extended contact with the cornea, which is theorized to result in extended anesthesia at lower concentrations. The gel formulation is also theorized to result in significantly reduced or eliminated passage of anesthetic through the nasolacrimal system, thereby resulting in undetectable or negligible systemic exposure of lidocaine.

2.2 Data Sources

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

The effect of Akten™ on ocular anesthesia was studied in a multi-center, randomized, sham controlled, double-blind study. A total of 209 subjects were enrolled, with 54, 51, 53, and 51 subjects randomized to the sham, Akten™ 1.5%, Akten™ 2.5%, and Akten™ 3.5% groups, respectively. Inclusion/Exlusion Criteria for enrolled subjects were as follows:

Inclusion Criteria
Subjects meeting all of the following criteria were to be considered for enrollment into the study.
1. Ability to provide informed consent for mode of topical anesthesia delivery
2. Ability to verbally respond to pain
3. Ability to return within 36 hours following application of study article
4. At least 18 years of age
5. Condition that requires ocular anesthesia

Exclusion Criteria
Subjects meeting any of the following criteria were not to be included in the study.
1. Intravitreal injection within the past 14 days
2. Recent ocular surgery requiring retrobulbar anesthesia within past 4 weeks
3. Prior vitreous or retinal surgery within past 4 weeks
4. Preexisting diagnosis of ocular surface disease requiring punctal plug placement
5. Evidence of any current ocular inflammation
6. Any previous ocular condition (i.e. herpetic eye disease, presence of a corneal graft, etc.) that has permanently altered the native sensation of the ocular surface
7. Use of exclusionary medications:
a. Topical Steroid Drops
b. Non-Steroid Drops
c. Any Anti-viral medications uses for herpes

The goal of this multi-centered, randomized study was to evaluate the achievement of ocular anesthesia using Akten 1.5%, 2.5%, and 3.5% applied to the conjunctiva. Presence or absence of ocular anesthesia was determined by using a 0.3 forceps to pinch the conjunctiva at specified time intervals. The primary outcome variable was the percentage of subjects who achieved ocular surface anesthesia within 5 minutes post-application of the anesthetic gel. The secondary outcome variable was the determination of the time of onset and the duration of ocular surface anesthesia.

Subject safety was assessed through the monitoring and reporting of any adverse events (AEs) that occur during the study. The frequency and severity of the AE profiles for each treatment group were evaluated to show their comparability.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition for Study 06AKO001 is shown below. One subject in the 2.5% Akten group was excluded from the per protocol (PP) population as the 5 minute pain assessment was actually conducted at 360 seconds. A second subject with an anesthesia duration value of 7192 seconds was deemed by the Sponsor to be an outlier and removed from the efficacy analyses performed on the ITT population. Anesthesia duration was defined by the Sponsor as a secondary endpoint.

Table 1: Patient Disposition

	Treatment Group				
	Sham Gel (N=54)	1.5% Gel (N=51)	2.5% Gel (N=53)	3.5% Gel (N=51)	Total (N=209)
Safety Population	54 (100%)	51 (100%)	53 (100%)	51 (100%)	209 (100%)
ITT Population	54 (100%)	51 (100%)	53 (100%)	51 (100%)	209 (100%)
Per Protocol (PP)	54 (100%)	51 (100%)	52 (98%)	51 (100%)	208 (100%)
Discontinued Study	0	0	0	0	0

Source: Sponsor's Table

Statistical Comments: *The primary efficacy analysis should be based on all 209 subjects who were included in the ITT population. The Sponsor includes analyses and reports based on 208 subjects where one subject was deemed an outlier with respect to anesthesia duration and excluded. The FDA analyses of the primary endpoint include this subject for all primary and secondary efficacy analyses as well as subgroup analyses by age, gender and race. Note that the inclusion of this additional subject did not affect primary or secondary analysis findings.*

Table 2: Demographic and Other Baseline Characteristics (ITT Population)

	Sham (N=54)	**Akten 1.5% (N=51)**	**Akten 2.5% (N=53)**	**Akten 3.5% (N=51)**	**Overall (N=209)**	**P-value[a]**
Age (yrs)						

n	54	51	53	51	209	0.771
Mean	40.3	38.9	40.5	37.4	39.3	
S.D.	13.66	14.10	14.98	14.68	14.31	
Median	36.5	35.0	41.0	34.0	36.0	
Min, Max	19, 71	19, 71	19, 69	20, 86	19, 86	
Gender						
Male	15 (28%)	15 (29%)	18 (34%)	17 (33%)	65 (31%)	0.873
Female	39 (72%)	36 (71%)	35 (66%)	34 (67%)	144 (69%)	
Race						
Asian	1 (2%)	2 (4%)	0	0	3 (1%)	0.304
Black or African American	7 (13%)	8 (16%)	4 (8%)	9 (18%)	28 (13%)	
White	46 (85%)	41 (80%)	49 (92%)	42 (82%)	178 (85%)	
Ethnicity						
Hispanic or Latino	19 (35%)	13 (25%)	17 (32%)	13 (25%)	62 (30%)	0.239
Not Hispanic or Latino	35 (65%)	38 (75%)	36 (68%)	38 (75%)	147 (70%)	

Note: Percentages are based on non-missing values.
S.D.=standard deviation; Min=minimum; Max=maximum
[a] p-value is for overall treatment comparison. Continuous variables are analyzed with a two-way ANOVA including treatment and center. Categorical variables are analyzed with Cochran-Mantel-Haenszel test controlling for center.
Source: Sponsor's Table

3.1.3 Statistical Methodologies

The primary efficacy variable (percent achieving anesthesia within 5 minutes) was analyzed using the normal approximation to the odds ratio of each level of treatment with sham. The significance associated with the test H: odds ratio = 1 will be rejected when the comparison exceeds the critical value for Dunnett's test for alpha=0.05. In performing Dunnett's test, let the following table represent the data collected on Pain less than or equal to 5 minutes:

Anesthetized <= 5 minutes?	Sham Gel	1.5% Lidocaine Gel	2.5% Lidocaine Gel	3.5% Lidocaine Gel
Yes	N11	N12	N13	N14

No	N21	N22	N23	N24

For any contrast of treatment group k with Sham group 1, Log(odds) = Log(n11/n21) – Log(n1k/n2k)

Log(0) and Log(1/0) are undefined, so to stabilize the Log odds, add ½ to each cell.

Let L= Log(n11+.5 /n21+.5) – Log(n1k+ .5 /n2k+.5).

s= Sqrt(1/(n11+.5)+ 1/(n12+.5) + 1/(nk1+.5) + 1/(nk2+.5))

L/s approximates a normal (0,1) deviate and test H0: the odds ratio = 1, placebo vs. treatment k. The critical value for L/s is 2.35.

An exploratory logistic regression of Pain/No Pain on treatment and center will be conducted to look for possible center effects or center-by-treatment interaction in predicting the outcome.

Statistical Comments: *The Sponsor defines the primary hypothesis in terms of an odds ratio. However, in prospective cohort studies, relative risks or risk differences are generally recommended over odds ratios since they provide more stable and interpretable estimates. Note however that in study 06AKO001, overall results as reported by the Sponsor were found to be robust regardless of whether odds ratios, relative risks or risk differences are assumed in the primary analysis. Overall results were also found to be robust using a conservative Bonferroni methodology to correct for multiple comparisons.*

3.1.4 Results and Conclusions

In Table 3, ocular anesthesia was achieved within 5 minutes of anesthetic application by 47 of 51 subjects (92%) in the Akten™ 3.5% group versus 12 of the 54 subjects (22%) in the sham group. In comparison with the 92% rate in the Akten™ 3.5% group, slightly lower rates (88%) were observed in the Akten™ 1.5% and Akten™ 2.5% groups. Comparisons in rates of ocular anesthesia achievement within 5 minutes between Akten™ 1.5%, Akten™ 2.5%, Akten™ 3.5%, were statistically significant in comparison to the sham group (adjusted p-values < 0.001).

The duration of anesthesia generally ranged from approximately 5 minutes to 30 minutes, with mean anesthesia durations of approximately 802 seconds (13.3 minutes) for the Akten™ 3.5% and 823 seconds and 614 seconds, respectively, in the Akten™2.5% and Akten™1.5% groups. Comparisons in durations of ocular anesthesia between Akten™ 1.5%, Akten™ 2.5%, Akten™ 3.5%, were statistically significant in comparison to the sham group (adjusted p-values < 0.001). According to the Sponsor, these results show a pattern of increasing anesthesia duration with increasing doses of Akten™ once a subject in the Akten™ 2.5% group deemed an outlier is removed. Note that approximately 84% of the subjects in the Akten™ 3.5% group experienced anesthesia for at least 5 minutes, approximately 55% of subjects experienced anesthesia for 10 minutes or longer and 27% experienced anesthesia for 15 minutes or longer.

Statistical Reviewer Comments: *The Sponsor does not provide statistical evidence of a trend of increasing anesthesia duration with increasing doses of Akten™. Such testing had not been pre-specified by the Sponsor.*

The mean time to anesthesia onset ranged from 20 seconds to 5 minutes was not affected by Akten™ dose. The mean time to anesthesia onset was approximately 60 seconds, with a median onset time of 40 seconds for the Akten™ 3.5% group. Among the subjects in the Akten™ groups who achieved anesthesia within 5 minutes, approximately 90% had achieved anesthesia within 60 seconds of application.

Table 1: Analysis and Summary of Treatment Effects (ITT Population)

			Sham Gel (N=54)	1.5% Gel (N=51)	2.5% Gel (N=53)	3.5% Gel (N=51)	Overall (N=209)
Primary Analysis:							
Percent Achieving Anesthesia within 5 Minutes of Dosing n/N(%)			12/54 (22%)	45/51 (88%)	47/53 (89%)	47/51 (92%)	150/209 (72%)
p-values[1]			<0.001	<0.001	<0.001	<0.001	<0.001
Secondary Analysis							
Duration of Anesthesia							
Mean			171.2	614.3	823.1	801.8	598.5
S.D.			433.48	458.54	1074.76	497.46	719.12
Median			0.0	561.0	580.0	620.0	560.0
Min			0	0	0	0	0
Max			2062	2360	7192	2080	7192
p-values				0.001	<0.001	<0.001	<0.001
Time to Anesthesia							
Mean			85.0	46.6	59.8	58.2	57.4
S.D.			101.67	57.18	89.34	75.99	77.67
Median			50.0	40.0	20.0	40.0	40.0
Min			20	15	20	20	15
Max			300	301	360	302	360

Source: FDA Table

1 P-values below treatment are Dunnett's adjusted comparison with Sham. P-value below overall is the test of homogeneity of all treatments.
NOTE: Duration and Time to Anesthesia are in seconds

Statistical Comments: *The Sponsor does provide statistical control of the overall type I error rate in the primary and secondary analyses through the use of Dunnett's test which allows multiple treatment arm comparisons against the sham treatment.*

3.2 Evaluation of Safety

Doses of Akten 1.5%, 2.5%, and 3.5% appeared to be tolerated by the subjects in this study, and the incidence of AEs was comparable across all groups. Across all treatment groups, the most frequently occurring AEs were conjunctival hyperemia (13 subjects [6%]) and conjunctival hemorrhage (7 subjects [3%]). Conjunctival hyperemia was reported by 4 subjects each (8%) in the Akten 1.5%, 2.5%, and 3.5% groups and by 1 subject (2%) in the sham group. Conjunctival hemorrhage was reported by 3 subjects (6%), 1 subject (2%), and 3 subjects (6%) in the Akten 1.5%, 2.5%, and 3.5% groups, respectively, and was most likely related to repeated pinching of the conjunctiva with forceps to determine whether anesthesia had been achieved and duration of anesthesia. Corneal staining was reported in 3 subjects (6%) in the Akten 3.5% group and 1 subject (2%) in the sham group. Headache was reported by 1 subject each (2%) in the Akten 1.5%, 2.5%, and 3.5% groups. All other AEs (eye pain, lacrimal disorder, and hyperhidrosis) were reported by 1 subject (<1.0%) each. The majority of AEs were mild or moderate and resolved.

For additional safety information, refer to the medical review by Dr. Sonal Wadhwa.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

There was no evidence that treatment group comparisons differed substantially based on age or race. For gender, however, achievement of anesthesia within 5 Minutes of dosing with Atken gel dosing appeared more pronounced in males than in females. However, these comparisons are post-hoc and greatly limited due to the small sample sizes in some categories.

			Sham Gel (N=54)	1.5% Gel (N=51)	2.5% Gel (N=53)	3.5% Gel (N=51)	Overall (N=209)
Percent Achieving Anesthesia within 5 Minutes of Dosing							
Age							
35 or lower			5/24 (21%)	22/26 (85%)	22/24 (92%)	24/28 (86%)	73/102 (72%)
Over 35			7/30 (23%)	23/25 (92%)	25/29 (86%)	23/23 (100%)	78/107 (73%)
Race							

White			10/46 (22%)	35/41 (85%)	45/49 (92%)	38/42 (90%)	128/178 (72%)
African American			1/7 (14%)	8/8 (100%)	2/4 (50.0%)	9/9 (100%)	20/28 (71%)
Asian			1/1 (100%)	2/2 (100%)	0	0	3/3 (100%)
Gender							
Male			1/15 (7%)	14/15 (93%)	18/18 (100%)	16/17 (94%)	49/65 (75%)
Female			11/39 (28%)	31/36 (86%)	29/35 (83%)	31/34 (91%)	102/144 (71%)

Source: FDA Table

5. CONCLUSIONS

There were no major statistical issues associated with Study 06AKO001 which was considered to be an adequate and well-controlled study. Study 06AKO001 provided evidence of an improvement in efficacy of Akten™ 3.5% versus sham treatment (placebo) with respect to the percentage of patients achieving anesthesia within 5 minutes of dosing and the duration of anesthesia. Based on results of this study and other supportive information, there appears to be adequate evidence presented to support the safety and efficacy of Akten™ 3.5% as a local anesthetic indicated for ocular surface anesthesia during ophthalmologic procedures.

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Date: 4/08/2008

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