

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **20-583**

STATISTICAL REVIEW(S)

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Statistical Review and Evaluation

NDA#: 20-583

Applicant: Pharmos Corporation

Name of Drug: Loteprednol etabonate ophthalmic suspension
(LOTEMAX[®]), 0.5%

Drug Class: 1S

Documents Reviewed: Volumes 1 and 41-62, stamp dated March 29, 1995, and data on disk.

Indications: (1) Treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye (such as seasonal allergic conjunctivitis and acute anterior uveitis). (2) Also for use in the treatment of giant papillary conjunctivitis.

Medical Officer: Wiley Chambers, M.D., HFD-540

I. INTRODUCTION

The applicant has submitted four primary controlled clinical studies (107, 108, 121, and 122) as pivotal evidence to support the claim that lotemax is safe and effective in the treatment of external and intraocular ophthalmic inflammation and allergic conditions.

As agreed upon with the FDA during the "End of Phase II" meeting held on July 15, 1992, two of the studies (107, 108) evaluated patients with giant papillary conjunctivitis (an external ophthalmic inflammation), one (121) evaluated patients with seasonal allergic conjunctivitis, and one (122) evaluated patients with acute anterior uveitis (an intraocular ophthalmic inflammation).

Each of the four studies were six-week, multi-center, randomized, parallel, double-blind, controlled studies of lotemax 0.5%. Studies 107, 108, and 121 used a placebo control (lotemax vehicle), and study 122 used an active control (Prednisolone acetate, 1%). Studies 107 and 108 should be independent, since they evaluate the same indication (giant papillary conjunctivitis). There are 2 investigators who enrolled patients in both studies, which causes one to question whether the independence assumption is reasonable. However, after removing the patients in question and redoing the analysis, this reviewer finds that there is no difference in the substantive conclusions (i.e., lotemax is still more effective than placebo for treating the signs and symptoms of giant papillary conjunctivitis). The details of this analysis are given below.

Most of the primary efficacy variables in the 4 studies are

measured on 4 or 5 point scales. Since patients' ratings tend to concentrate in only 2 or 3 categories, rather than treat the variables as continuous the sponsor uses non-parametric tests such as the Cochran-Mantel-Haenszel (CMH) procedure to test for differences between treatment groups. Each of the studies is multi-center and often investigator differences appear. To deal with this, the CMH tests that are performed control for investigator differences. Analyses for studies 107, 108, and 122 were performed on the worse eye. In the case of a tie, the right eye was selected. The analyses for study 121 (seasonal allergic conjunctivitis) were performed on the mean score for both eyes, as both eyes were assumed to be equally involved. For all analyses, investigators with fewer than 10 patients per treatment group were pooled as a single investigator (there were 4 for study 107, 3 for 108, 3 for 121 -- 3 additional 121 investigators who had at least 7 patients per treatment arm were analyzed as single investigators, and 4 for 122). All p-values are two-sided, and values less than 0.05 were considered significant by the sponsor.

The main safety variable evaluated in each study was intraocular pressure (IOP). IOP is elevated by topical steroids and is considered the major adverse effect caused by this class of drug. Several criteria for evaluating IOP were used: (1) increases of 6 mm Hg or more, (2) increases of 10 mm Hg or more, (3) absolute values of 20 mm Hg or more, and (4) mean change from baseline. Lotemax was developed specifically by the sponsor to provide the efficacy of other topical steroids with less elevation in IOP. Other safety variables included visual acuity and funduscopy examination.

For the safety variables, the CMH procedure is used to test for differences between treatment groups, so that investigator differences may be statistically controlled for. For the subgroup analysis of IOP, however, Fisher's exact test is used to determine whether various demographics (age, etc.) affect IOP increase. In study 122, which compares lotemax to an active control, survival analysis is used to show that patients on lotemax are treated longer before they experience an increase in IOP. Safety analyses for studies 107, 108, and 121 were performed on both eyes. The proportion responding in "one or both eyes" was given for various criteria. Safety analyses for study 122 were performed only for the treated eye. No explanation for this difference was given. However, the overall conclusions should not be affected.

II. EVALUATION

A. Giant Papillary Conjunctivitis (GPC)

1. Methods

Studies 107 and 108 were both conducted to assess the safety and efficacy of lotemax 0.5% in treating contact lens-associated giant papillary conjunctivitis, an external ophthalmic inflammation. Patients were randomized to either lotemax 0.5% q.i.d. or placebo (the lotemax vehicle) q.i.d. for six weeks. Follow-up examinations occurred on days 2 or 3, 7, 14, 21, 28, 35, and 42. An off-therapy safety follow-up examination was conducted on Day 49.

To be enrolled in either study, patients had to meet the following criteria: (1) currently wearing contact lenses or discontinued wear within the previous 48 hours; and (2) active ocular signs and symptoms of GPC (i.e., papillae, itching, and lens intolerance of at least grade 2). For other inclusion/exclusion criteria, please refer to the medical officer's review.

By protocol, the primary efficacy variables selected by the sponsor were reduction in the severity of the papillae, itching, and lens intolerance. Secondary efficacy variables included palpebral and bulbar conjunctival injection, discharge, foreign body sensation, photophobia, physicians' clinical judgement, and patient opinion of treatment. Most variables were rated using a 4 point scale where the response 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. Itching was rated using a 5 point scale (0 = absent, 1 = trace, 2 = mild, 3 = moderate, and 4 = severe), as were physicians' clinical judgement and patient opinion of treatment (0 = fully controlled, . . . , 4 = worse).

The primary outcome of the study was the patient's condition at the final visit (Day 42). For any sign or symptom variable, a positive response (defined by the sponsor as the primary efficacy criterion) was defined as an improvement of at least 1 unit over baseline. Differences in response rates between treatment groups were analyzed using Cochran-Mantel-Haenszel statistics controlling for investigator. Since the sponsor's definition of efficacy given above is not totally satisfactory to the medical reviewer, this reviewer will also consider the mean change from baseline and the proportion of patients whose scores are "0" by the final visit (i.e., no symptoms) for each of the primary efficacy variables. Since the number of patients in each treatment group is large ($n > 100$) for both studies, the Z-test will be used to test for treatment differences. This analysis will not control for investigator differences.

The primary safety variable was IOP as described above.

2. Results

Study 107:

Two hundred twenty-three patients were randomized to treatment at 14 investigative sites (all in the US); 110 to lotemax and 113 to placebo. Of those, 203 (91%) completed treatment; 100 (91%) on lotemax and 103 (91%) on placebo. 12 patients discontinued treatment for reasons unrelated to treatment (5 on lotemax, 7 on placebo), 3 patients discontinued for lack of efficacy (1 on lotemax, 2 on placebo), and 5 discontinued due to adverse events (4 on lotemax, 1 on placebo).

ITT-LOCF analysis was planned for all patients with at least one follow-up visit. Four patients (1 on lotemax, 3 on placebo) were lost to follow-up entirely. Thus, the sponsor performed ITT analysis on 219 patients. As less than 2% of the remaining patients had major protocol deviations, no PP analysis was performed.

Prestudy characteristics were the same for both treatment groups, and no treatment*investigator interactions were discovered. However, differences between investigators were observed. As a result, the statistical analysis presented by the sponsor adjusts for investigator differences.

The sponsor's analysis of "positive response" concludes that patients treated with lotemax demonstrate a statistically significant reduction in 2 of the 3 primary efficacy variables compared to placebo, and a marginally statistically significant reduction in the third primary efficacy variable. More specifically, the 95% confidence intervals for the difference in the proportion of patients showing a positive response are as follows: (1) papillae $_{109,110} (0.15, 0.39)_{0.78,0.51}$, $p < 0.001$; (2) itching $_{109,110} (0.06, 0.22)_{0.95,0.81}$, $p = 0.001$, and (3) lens intolerance $_{109,110} (0.02, 0.18)_{0.87,0.77}$, $p = 0.053$.

This reviewer's analysis of the mean change from baseline for the actual score and the proportion of patients whose scores are "0" by the final visit provides further support for the effectiveness of lotemax in treating GPC. For each of the 3 variables, patients treated with lotemax demonstrate a statistically significantly lower reduction in score, and a statistically significantly higher proportion of patients whose scores are "0" by the final visit. More specifically, the 95% confidence intervals for the difference in mean change from baseline are as follows: (1) papillae $_{109,110} (-0.72, -0.26)_{-1.16,-0.67}$, $p < 0.0001$; (2) itching $_{109,110} (-0.94, -0.38)_{-2.20,-1.54}$, $p < 0.0001$, and (3) lens intolerance $_{109,110} (-0.69, -0.19)_{-1.64,-1.20}$, $p = 0.0006$. The 95% confidence intervals for the difference in the proportion of patients whose scores are "0" by the final visit are: (1)

papillae 109,110 (0.02, 0.20) $^{0.19,0.08}$, $p = 0.017$; (2) itching
 109,110 (0.13, 0.39) $^{0.70,0.44}$, $p < 0.0001$, and (3) lens intolerance
 109,110 (0.10, 0.36) $^{0.60,0.36}$, $p = 0.0006$.

Recall that there are two investigators (Kenneth Fox and Mitchell Friedlaender) who enrolled patients in both study 107 and study 108 (note: no patients were enrolled in more than 1 study), causing one to question the assumption that these studies are independent. This reviewer considered the results for study 107 after removing 12 patients (6 on lotemax, 6 on placebo) of investigator #151 (Kenneth Fox) and 23 patients (12 lotemax, 11 placebo) of investigator #124 (Mitchell Friedlaender). While the individual numbers vary somewhat, all substantive conclusions remain the same (i.e., treatment differences are statistically significant for all 3 primary efficacy variables both when mean change from baseline and the proportion of patients whose scores are 0 by the final visit are considered). After removing the above patients, the 95% confidence intervals for the difference in mean change from baseline are as follows: (1) papillae

91,93 (-0.74, -0.24) $^{-1.25,-0.76}$, $p = 0.0002$; (2) itching
 91,93 (-1.05, -0.47) $^{-2.27,-1.51}$, $p < 0.0001$, and (3) lens intolerance
 91,93 (-0.77, -0.23) $^{-1.47,-1.17}$, $p = 0.0004$. The 95% confidence intervals for the difference in the proportion of patients whose scores are "0" by the final visit are: (1) papillae
 91,93 (0.03, 0.24) $^{0.23,0.10}$, $p = 0.014$; (2) itching
 91,93 (0.15, 0.42) $^{0.71,0.43}$, $p < 0.0001$, and (3) lens intolerance
 91,93 (0.10, 0.38) $^{0.60,0.37}$, $p = 0.0012$.

Change from baseline data were also considered for each of the seven individual follow-up visits, without correcting significance levels for multiple comparisons. The individual visit analyses were to be considered merely "supportive" of the primary analyses. In general, they agreed with the overall conclusions from the previous paragraph. If we use the Bonferroni correction for each variable, the cutoff for significance at each visit becomes $0.05/7 = 0.007$ (there are 8 visits excluding the safety follow-up, and visit 1 is baseline). Six of the seven visits showed a significant improvement in papillae for lotemax versus placebo patients, none of the visits was significant for itching, and 4 of the 7 visits were significant for lens intolerance.

Subgroup analyses were performed for the main primary efficacy variable papillae. When patients were stratified with respect to age (<30 years, ≥30 years) and eye color (light, dark) no significant differences were found ($p = 1.000$; $p = 1.000$). Females fare somewhat better on lotemax than males (83% versus 61% positive responders, $p = 0.044$). Caucasians also fare marginally better on lotemax than other races (81% versus 55%, $p = 0.062$).

The main safety variable is elevation in IOP. Patients on

lotemax fared somewhat worse than those on placebo; 7% of the lotemax patients experienced an increase in IOP of 10 mm Hg or more, compared to 0% on placebo. However, the sponsor states that this incidence is lower than would be expected by a mild to high potency corticosteroid. Three lotemax patients discontinued treatment as a result of elevated IOP, and all returned to normal IOP ranges within one week. Subgroup analyses of IOP showed no significant differences for age, gender, race, or eye color ($p = 0.378$, $p = 0.276$, $p = 0.286$, and $p = 0.182$, respectively).

Study 108:

Two hundred twenty patients were randomized to treatment at 12 investigative sites (all in the US); 111 to lotemax and 109 to placebo. Of those, 192 (87%) completed treatment; 101 (91%) on lotemax and 91 (83%) on placebo. The proportion of patients completing each treatment was somewhat different ($p = 0.108$). Nine patients discontinued treatment for reasons unrelated to treatment (5 on lotemax, 4 on placebo), 12 discontinued for lack of efficacy (1 on lotemax, 11 on placebo), and 7 discontinued due to adverse events (4 on lotemax, 3 on placebo).

ITT-LOCF analysis was performed on all 220 patients. Two patients were lost to follow-up entirely, but included in the analysis by the sponsor as unchanged. Four additional patients were identified as not evaluable, but included in the analysis as any bias should favor the placebo group (1 lotemax patient failed to take medication for about three weeks, 1 placebo patient used topical fluorometholone acetate, and 2 placebo patients failed to meet the inclusion criteria of minimum papillae and itching scores of 2). Since less than 2% of patients had major protocol deviations, the sponsor felt that a PP analysis was not needed.

Prestudy characteristics were the same for both treatment groups, and no treatment*investigator interactions were discovered. However, differences between investigators were observed. As a result, the statistical analysis presented by the sponsor adjusts for investigator differences.

Patients treated with lotemax demonstrated a statistically significant reduction compared to placebo in all 3 primary efficacy variables. More specifically, the 95% confidence intervals for the difference in the proportion of patients showing a positive response are as follows: (1) papillae $^{111,109}(0.13, 0.37)$ $^{0.75,0.50}$, $p < 0.001$; (2) itching $^{111,109}(0.07, 0.25)$ $^{0.92,0.76}$, $p = 0.001$; and (3) lens intolerance $^{111,109}(0.07, 0.29)$ $^{0.84,0.66}$, $p = 0.002$.

This reviewer's analysis of the mean change from baseline for the actual score and the proportion of patients whose scores are "0" by the final visit provides further support for the effectiveness

of lotemax in treating GPC. For each of the 3 variables, patients treated with lotemax demonstrate a statistically significantly lower-reduction in score, and a statistically significantly higher proportion of patients whose scores are "0" by the final visit. More specifically, the 95% confidence intervals for the difference in mean change from baseline are as follows: (1) papillae $_{111,109}(-0.81, -0.33)$ $_{111,109}(-1.17, -0.60)$, $p < 0.0001$; (2) itching $_{111,109}(-1.08, -0.50)$ $_{111,109}(-2.09, -1.30)$, $p < 0.0001$, and (3) lens intolerance $_{111,109}(-0.68, -0.18)$ $_{111,109}(-1.56, -1.13)$, $p = 0.0006$. The 95% confidence intervals for the difference in the proportion of patients whose scores are "0" by the final visit are: (1) papillae $_{111,109}(0.11, 0.30)$ $_{111,109}(0.29, 0.08)$, $p < 0.0001$; (2) itching $_{111,109}(0.22, 0.47)$ $_{111,109}(0.66, 0.31)$, $p < 0.0001$, and (3) lens intolerance $_{111,109}(0.03, 0.28)$ $_{111,109}(0.50, 0.34)$, $p = 0.019$.

Recall that there are two investigators who enrolled patients in both study 107 and study 108, causing one to question the assumption that these studies are independent. The results for study 108 after removing 31 patients (14 on lotemax, 17 on placebo) of investigator #151 (Kenneth Fox) and 26 patients (13 lotemax, 13 placebo) of investigator #124 (Mitchell Friedlaender) are given below. While the individual numbers vary somewhat, all substantive conclusions remain the same (i.e., treatment differences are statistically significant for all 3 primary efficacy variables both when mean change from baseline and the proportion of patients whose scores are 0 by the final visit are considered). The 95% confidence intervals for the difference in mean change from baseline are as follows: (1) papillae $_{84,79}(-0.91, -0.31)$ $_{84,79}(-1.27, -0.66)$, $p < 0.0001$; (2) itching $_{84,79}(-1.17, -0.47)$ $_{84,79}(2.05, -1.23)$, $p < 0.0001$, and (3) lens intolerance $_{84,79}(-0.83, -0.23)$ $_{84,79}(1.54, -1.01)$, $p = 0.0006$. The 95% confidence intervals for the difference in the proportion of patients whose scores are "0" by the final visit are: (1) papillae $_{84,79}(0.11, 0.35)$ $_{84,79}(0.35, 0.11)$, $p = 0.0004$; (2) itching $_{84,79}(0.23, 0.52)$ $_{84,79}(0.65, 0.28)$, $p < 0.0001$, and (3) lens intolerance $_{84,79}(0.03, 0.32)$ $_{84,79}(0.46, 0.29)$, $p = 0.0228$.

Change from baseline data were also considered for each of the individual visits, without correcting significance levels for multiple comparisons. As in study 107, the individual visit analyses were to be considered merely "supportive" of the primary analyses. In general, they agreed with the overall conclusions from the previous paragraph. If we use the Bonferroni correction for each variable, the cutoff for significance at each visit becomes $0.05/7 = 0.007$ (there are 8 visits excluding the safety follow-up, and visit 1 is baseline). Using this level, five of the seven visits showed a significant improvement in papillae for lotemax versus placebo patients, 1 of the 7 visits was significant for itching, and none of the visits were significant for lens intolerance.

Subgroup analyses were performed for the main primary efficacy

variable papillae. When patients were stratified with respect to age (<30 years, ≥30 years), gender, race (caucasian, other), and eye color (light, dark) no significant differences were found ($p = 1.000$, $p = 1.000$, $p = 0.392$, and $p = 0.270$, respectively).

The main safety variable is elevation in IOP. Patients on lotemax fared slightly worse than those on placebo; 3% of the lotemax patients experienced an increase in IOP of 10 mm Hg or more, compared to 0% on placebo. Only 1 lotemax patient discontinued treatment due to elevated IOP, and she returned to baseline levels within one week. Subgroup analyses of IOP showed no significant differences for age, gender, race, or eye color ($p = 0.183$, $p = 0.129$, $p = 0.486$, and $p = 0.426$, respectively).

B. Seasonal Allergic Conjunctivitis (SAC)

1. Methods

Study 121 was conducted to assess the safety and efficacy of lotemax 0.5% in preventing the ocular signs and symptoms accompanying seasonal allergic conjunctivitis during peak pollen levels. Approximately 3 weeks before the anticipated peak pollen season for each center, patients were randomized to either lotemax 0.5% q.i.d. or placebo (the lotemax vehicle) q.i.d.. Treatment lasted six weeks. Follow-up examinations occurred on days 7, 14, 21, 28, 35, and 42. An off-therapy safety follow-up examination was conducted on Day 49.

To be enrolled in the study, patients had to meet the following criteria: (1) a history of SAC for 2 years prior to the study to the allergen prevalent at the center; and (2) a positive test (skin or RAST) to that allergen. For other inclusion/exclusion criteria, please refer to the medical officer's review.

By protocol, the primary efficacy variables were bulbar conjunctival injection and itching, which were collapsed into a "primary composite" score equal to the sum of the individual scores (injection was measured on a 4 point scale: 0 = absent, ... , 3 = severe; itching was measured on a 5 point scale: 0 = absent, ... , 4 = severe). The secondary efficacy variables included control of overall signs and symptoms as assessed by the investigator.

The primary endpoint of the study was the peak score, defined to be the mean of the valid evaluations (up to 3) occurring within the predefined peak interval (i.e., maximum pollen count) for the center, usually 3 weeks. In this study, the primary composite was treated as a continuous variable. To test for differences, 2-way ANOVA was used (the factors being treatment, investigator, and their interaction). The rate of positive response, which required that no rating of moderate or above be recorded for

either bulbar conjunctival injection (a 2 or above) or itching (a 3 or above) during the peak period, was also considered. To test for differences in response rates controlling for investigator, the Cochran-Mantel-Haenszel procedure was used. All analyses were carried out on the mean rating of right and left eyes under the assumption that both eyes should be equally involved.

The primary safety variable was again IOP, which was evaluated using the 4 different standards described in Section I.

2. Results

Two hundred ninety-three patients were enrolled in 13 investigative sites (all in the US); 146 to lotemax and 147 to placebo. Of these, 137 (47%) reported they were allergic to ragweed pollen while 156 (53%) reported they were allergic to mountain cedar pollen. Two hundred forty-eight (85%) completed treatment; 126 (86%) on lotemax and 122 (83%) on placebo. Eight patients failed to complete the study due to lack of efficacy (3 on lotemax, 5 on placebo), 12 patients discontinued treatment due to adverse events (6 on lotemax, 6 on placebo), and 25 patients failed to complete the study for reasons unrelated to treatment (11 on lotemax, 14 on placebo). The proportion of patients completing treatment in each group was not significantly different.

There were 5 patients identified as not evaluable. Of these, 1 placebo patient never had drug dispensed, and 2 patients entered the study twice at 2 different sites and hence were counted as 4 patients (one was randomized to placebo twice, the other was randomized once to lotemax and once to placebo). ITT analysis was thus performed on 288 patients. PP analysis was performed on 258 patients (132 on lotemax, 126 on placebo). 30 patients were excluded from the PP analysis for the following reasons: 1 lotemax and 1 placebo patient had itching scores greater than 2, 2 placebo patients had tearing scores greater than 1, 1 placebo patient had GPC at baseline, 1 lotemax and 6 placebo patients used disallowed concomitant medications during the peak interval that were thought by the sponsor to affect the validity of the data (such as oral antihistamines), and 11 lotemax and 7 placebo patients had no valid visit during the peak interval. "Fully documented" (i.e., patients with full documentation as required in the protocol of SAC history for the 2 years prior to the study to the specific allergen, ragweed or mountain cedar pollen) PP analysis was performed on 173 patients (89 on lotemax, 84 on placebo).

Prestudy characteristics were the same for both treatment groups. Several tests were used to determine this, including the Cochran-Mantel-Haenszel procedure. Since investigator differences were found, tests used in the remainder of the analyses control for site.

ITT-LOCF analysis concluded that in the primary composite, secondary composite, and investigator global assessment scores, and in all the individual parameters except chemosis, lotemax was more effective than placebo. The PP analyses concurred. More specifically, the ITT 95% confidence interval for the difference between lotemax and placebo in peak primary composite score is $_{145,143}(-0.87, -0.47)_{0.88,1.50}$ (note: a negative difference implies that lotemax is more effective than placebo in preventing the signs and symptoms of SAC). In addition, 94% of the ITT lotemax patients displayed a positive response on the primary composite score compared to 78% of placebo patients ($p < .001$). Bulbar conjunctival injection and itching also show significant differences (favoring lotemax) when considered separately.

Subgroup analyses were performed for the primary composite score during the peak interval. No significant differences were found when patients were stratified by gender, race (caucasian versus other), or eye color (light versus dark); $p = 0.66$, $p = 0.51$, and $p = 0.94$, respectively. However, younger patients (<30 years old) have somewhat lower scores than older patients ($p = 0.047$), and patients who are allergic to ragweed have slightly lower scores than patients allergic to mountain cedar pollen ($p = 0.097$): When subgroup analyses are performed on the positive response rate, the only difference is in the type of pollen. Again, patients allergic to ragweed respond better than patients allergic to mountain cedar pollen ($p = 0.035$).

The main safety variable was IOP. None of the lotemax patients had an IOP elevation of 10 mm Hg or more, whereas 2 placebo patients did (1%). 17% of lotemax patients had an IOP elevation of 6 mm Hg or more compared to 12% of placebo patients ($p = 0.15$). Subgroup analyses of IOP response of 6 mm Hg or more show no difference when patients are stratified with respect to age (<30 versus ≥ 30 years), gender, race (caucasian versus other), or eye color (light versus dark) ($p = 0.368$, $p = 0.169$, $p = 0.253$, and $p = 1.0$, respectively). However, patients who are allergic to mountain cedar pollen had a higher incidence of increased IOP than patients allergic to ragweed ($p = 0.046$). The sponsor states that pollen type is confounded with investigator, region of country, and season (mountain cedar pollen peak season is December - February, while ragweed pollen peak season is August - October), and thus is hard to interpret.

C. Acute Anterior Uveitis (AAU)

1. Methods

Study 122 was conducted to assess the safety and efficacy of lotemax 0.5% in treating acute anterior uveitis, an intraocular ophthalmic inflammation. Patients were randomized to either lotemax 0.5% or prednisolone acetate (PA) 1.0% 8 times daily for

the first week, 6 times daily for the second week, and 4 times daily for the third week. Thereafter, the daily dose was reduced according to one of two schedules based upon the anterior chamber cell rating. Follow-up examinations occurred on Days 2, 7, 14, 21, 35, and 42. An off-therapy safety examination was carried out on Day 49 or on the 7th day after discontinuation of dosing.

To be enrolled in either study, patients had to meet the following criteria: (1) clinical diagnosis with the signs and symptoms of AAU (e.g., an anterior chamber cell reaction of at least 1.5); and (2) any previous episode of AAU must have been at least 6 weeks prior to study enrollment. For other inclusion/exclusion criteria, please refer to the medical officer's review.

By protocol, the primary efficacy variable was cell reaction in the anterior chamber; both the time until the cell rating reached 0, the proportion of patients whose cell rating reached 0 by the final visit, and the proportion of patients whose cell rating was reduced by at least 1 unit by the final visit were considered by the sponsor. The secondary efficacy variables included anterior chamber flare, photophobia, and ciliary flush ratings. Most of the secondary variables were rated on a 4 point scale (0-3), where 0 = absent and 3 = severe. The anterior chamber cell reaction was rated from 0 to 5 in steps of 0.5 (with the exception that there is no 4.5). A 0 rating meant less than or equal to 4 cells, a 4.0 meant greater than 50 cells, and a 5.0 meant hypopyon.

Survival analysis was used to test for differences between the treatment groups in the time required to return the cell count to 0 from a baseline score of at least 1.5. The CMH statistic, controlling for investigator, was used to test for differences between the treatment groups in the proportion of patients whose cell rating reached 0 and whose cell rating improved by at least 1 unit by the final visit.

The primary safety variable was IOP. The same 4 criteria as in the previous studies were used for evaluation. In addition, survival analysis was used to compare the time to increase in IOP of 6 mm Hg or more for the two treatment groups. Analyses were performed only on the treated eye.

2. Results

Eleven investigators (3 in U.K., 8 in U.S.) enrolled 162 patients (83 on lotemax, 79 on PA). Of these, 125 (77%) completed treatment; 57 (69%) on lotemax and 68 (86%) on PA. There was a statistically significant association between treatment and the proportion of patients completing treatment. When tested within U.S. sites alone, the association was not significant ($p =$

0.636). However, for U.K. sites the association was highly significant, with only 60% of lotemax patients completing treatment ($p = 0.004$). Of the 37 patients who failed to complete treatment, 22 discontinued due to lack of efficacy (18 on lotemax, 4 on PA), 10 were lost to follow-up (4 on lotemax, 6 on PA), 2 discontinued for reasons unrelated to treatment (1 on each), and 3 patients discontinued for other reasons (all on lotemax). No patients were discontinued for adverse events.

The sponsor notes that the sample of active patients who remained after Visit 2 (day 2 or 3 after starting medication) may be biased in favor of PA. This is due to the fact that investigators were allowed to discontinue treatment when sufficient relief was not observed. 11 of the 22 patients who discontinued prematurely for lack of efficacy did so at Visit 2, and 9 of these 11 were in the lotemax group (all were from U.K. investigators). All of these patients are carried forward as failures in the ITT-LOCF analysis.

Four patients did not return after the initial enrollment (1 lotemax, 3 PA), and two patients were entered a second time in the study after successfully completing the protocol once when their other eye became infected (1 on each treatment). For the latter two patients, the data on their second eye was excluded from the ITT analysis but included in the safety analysis. Thus, ITT-LOCF analysis was performed on 156 patients. A PP analysis was planned but not performed, as only 8 (5%) patients (5 on lotemax, 3 on PA) had major protocol deviations.

Since prestudy characteristics were significantly different across investigators (race, gender, and eye color were all significant, and the treatment*investigator interaction for age was significant), the remainder of the analyses controlled for investigator differences.

Survival analysis for the time until a "0" cell rating show that patients on PA reach "0" ratings faster. The median time to achieve a "0" cell rating was 23 days for lotemax and 20 days for PA ($p = 0.003$). In addition, a significantly lower proportion of lotemax patients reached a "0" cell score by final visit than PA patients ($_{81,75}(-0.39, -0.12)_{0.64, 0.89}$) and had an improvement of at least 1 unit ($_{81,75}(-0.37, -0.12)_{0.69, 0.93}$). However, clinically significant changes of a mean cell rating of more than 1 unit were observed in both groups (cell rating decreased an average of 1.6 in the lotemax group and 2.2 in the PA group). Thus, this data provide statistical support for the conclusion that, while lotemax is not better than PA, it is still considered clinically effective.

Individual visit data were also considered, without correcting for multiple comparisons. Using the Bonferroni correction, the cutoff for significance becomes $.05/7 = .007$ (there are 7 visits

on medication). Only 1 of the 7 visits shows a significant difference in the proportion of patients with a cell rating of 0 and the proportion of patients whose cell rating improves by at least 1 unit. None of the visits show a significant difference in the change of cell score.

Subgroup analyses were performed for the main efficacy variables. For the median time to a cell rating of "0", no significant differences were observed when patients were stratified with respect to age, gender, race, or eye color, $p = 0.535$, $p = 0.159$, $p = 0.998$, and $p = 0.809$, respectively (note: in this study, the age groups looked at are <40 and ≥ 40 years; in the 3 previous studies age was split at 30 years; no explanation for this difference is given, but overall conclusions should not be much affected). When patients were stratified with respect to type of pathology, patients with a granulomatous anterior chamber reaction were found to perform significantly worse than patients in the nongranulomatous subgroup ($p = 0.032$). For the proportion of patients achieving a cell score of 0 by the final visit, age, gender, race, and eye color again were not significant ($p = 0.488$, $p = 0.492$, $p = 0.798$, and $p = 0.356$, respectively). Type of pathology was significant, with granulomatous patients performing worse ($p = 0.014$). For the proportion of patients achieving an improvement of at least 1 unit in cell score, there were no significant differences (although pathology was marginally significant in the same direction as before, $p = 0.085$).

The main safety variable is elevation in IOP. Only 1/81 (1%) lotemax patients experienced a treatment related increase in IOP of 10 mm Hg or more, compared to 5/75 (7%) of the PA patients. One PA patient discontinued treatment due to elevated IOP and one lotemax patient was discontinued for elevated IOP on presentation (visit 1, before medication). Survival analysis shows that lotemax patients "survive" a significantly longer time until their IOP increases by ≥ 6 mm Hg ($p = 0.012$). There is no significant difference between lotemax and PA in the time until IOP increases by ≥ 10 mm Hg. Subgroup analyses of the change in IOP from baseline show no significant differences for race or eye color ($p = 0.388$ and $p = 0.390$, respectively). However, younger patients (<40 years) have an average decrease in IOP of 0.6 while older patients have an average increase in IOP of 0.2 ($p = 0.031$), and females have an average decrease in IOP of 1.3 while males have an average increase in IOP of 0.9 ($p = 0.106$).

Recall that 8 investigators enrolled patients in the U.S., while 3 investigators enrolled patients in the U.K.. As differences were observed in patients' responses in the two countries, the sponsor performed several unplanned analyses. These differences are believed to be due to the fact that the U.K. investigators were more liberal in removing patients showing unsatisfactory improvement very early in the study (almost all of whom were

being treated with lotemax). The sponsor believes that with aggressive, early dosing there might be no difference in the effectiveness of lotemax and PA to treat AAU. To summarize the results, if only the U.S. data are considered, no statistically or clinically significant differences in either the time until cell rating goes to 0 or the proportion of patients whose cell rating goes to 0 are found between the effectiveness of lotemax and PA. In the U.K., performance of patients on PA is significantly better on both variables. As for safety, in the U.S. the time until IOP increases ≥ 6 mm Hg is significantly longer for lotemax compared to PA patients. In the U.K. there is no significant difference.

D. Integrated Safety Summary

The overall safety of lotemax appears acceptable. The main safety variable evaluated was intraocular pressure. IOP is elevated by topical steroids and is considered the major adverse effect caused by this class of drug. Of the 622 patients considered in the Phase I-III trials who were treated with lotemax (any dose, although 601 were treated with 0.5%), 11.1% experienced an increase in IOP of ≥ 6 mm Hg compared to 23.4% on PA and 5.3% on placebo. Of the other safety variables, the most frequent events in the lotemax group were foreign body sensation (3.1%), itching (3.1%), injection (2.9%), burning (2.3%), abnormal vision (2.1%), epiphora (1.9%), and increased IOP of ≥ 10 mm Hg (1.9%).

Due to the low incidence of adverse events in each study and overall, this reviewer felt that a formal meta-analysis of safety variables was unnecessary (the medical officer concurs).

III. CONCLUSIONS (Which May be Conveyed to the Sponsor)

Overall, lotemax appears safe and effective for the treatment of external and intraocular ophthalmic inflammation (such as giant papillary conjunctivitis and acute anterior uveitis) and allergic conditions. This is supported by evidence from the four, controlled, clinical trials, studies 107, 108, 121, and 122, conducted by the sponsor.

1. *Studies 107 and 108, while not completely independent, do support the conclusion that lotemax is more effective than placebo in treating the 3 signs and symptoms of giant papillary conjunctivitis: papillae, itching, and lens intolerance.*

After removing the patients in question, the average change from baseline for lotemax versus placebo patients is significant for all 3 primary efficacy variables, papillae, itching, and lens

intolerance, for both study 107 ($p = 0.0002$, $p < 0.0001$, and $p = 0.0004$, respectively) and study 108 ($p < 0.0001$, $p < 0.0001$, and $p = 0.0006$, respectively).

2. Study 107 found differences in response to treatment of papillae for females versus males (females fare better; $p = 0.044$) and caucasians versus others (caucasians fare better; $p = 0.062$). Study 108 found no such differences.

3. Studies 107 and 108 suggest that lotemax is a relatively safe treatment for giant papillary conjunctivitis. Three patients using lotemax in study 107 and 1 patient using lotemax in study 108 were discontinued due to an increase in intraocular pressure. All four returned to normal or baseline ranges within one week.

4. Study 121 provides evidence to support the conclusion that lotemax is more effective than placebo in controlling the signs and symptoms of seasonal allergic conjunctivitis: bulbar conjunctival injection and itching, which are combined into a "primary composite score" for analysis.

The 95% confidence interval for the difference between lotemax and placebo patients' peak primary composite score is
 $145,143 (-0.87, -0.47)_{0.88,1.50}$.

5. Response to treatment in study 121, as measured by the peak primary composite score, was found to differ for younger (<30 years) versus older (≥ 30 years) patients (younger patients fare better; $p = 0.047$) and for patients allergic to ragweed versus mountain cedar pollen (patients allergic to ragweed fare better; $p = 0.097$).

6. Safe use of lotemax, as measured by increase in intraocular pressure, was acceptable in study 121. No lotemax patients were discontinued for increase in IOP.

Patients allergic to ragweed had a somewhat lower incidence of increase in intraocular pressure ($p = 0.046$).

7. Study 122 supports the conclusion that lotemax is clinically effective in treating the primary sign and symptom of acute anterior uveitis: cell reaction in the anterior chamber. While lotemax does not perform as well as prednisolone acetate, it is clinically effective and has a better safety profile.

Survival analysis of the time until a "0" cell rating show that

PA patients reach "0" ratings faster (a median of 20 days, versus 23 days for lotemax; $p = 0.003$). However, clinically significant changes of an average increase in cell rating of more than 1 unit were observed in both groups (cell rating decreased an average of 1.6 in the lotemax group and 2.2 in the PA group).

8. In study 122, differences in the median time to a "0" cell rating were found in response to treatment with lotemax for patients with granulomatous versus nongranulomatous anterior chamber reaction (patients with nongranulomatous pathology fare better; $p = 0.032$).

9. Safety was acceptable in study 122. No lotemax patients discontinued treatment due to increased IOP. Survival analysis shows that lotemax patients "survive" longer than prednisolone acetate patients before IOP increases by ≥ 6 mm Hg ($p = 0.012$).

Differences were found in safety outcomes for lotemax patients. Younger patients (<40 years) experience an average decrease in intraocular pressure, which is desired, while older patients (≥ 40 years) experience an increase, $p = 0.031$. Similarly, females experience an average decrease in intraocular pressure, while males experience an increase, $p = 0.106$.

RECOMMENDED REGULATORY ACTION: The objectives of these trials are to show that use of lotemax 0.5% results in lower IOP than a comparable agent while achieving equivalent or better control of giant papillary conjunctivitis, seasonal allergic conjunctivitis, and acute anterior uveitis.

My statistical review shows these studies statistically support the sponsor's claim.

Ph.D. 6/29/95
 Nancy L. Paul, ^{Simmen} Ph.D.
 Biomedical Statistician, Group 7

Ph.D. 6/29/95
 Concur: Ralph Harkins, Ph.D.
 Supervisory Statistician, Group 7

Satya D. Dubey, Ph.D.
 Branch Chief, SERB

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 6/29/95

cc:
Orig. NDA #20-583
HFD-540
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HFD-540/Dr. Wiley Chambers
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HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Dr. Harkins
HFD-713/Dr. Paul
HFD-344/Dr. Lisook
Chron.
This review contains 17 pages.

**APPEARS THIS WAY
ON ORIGINAL**

Addendum to Statistical Review and Evaluation

APR 10 1996

NDA#: 20-583

Applicant: Pharmos Corporation

Name of Drug: Loteprednol etabonate ophthalmic suspension (LOTEMAX[®]), 0.5%

Drug Class: 1S

Documents Reviewed: Volumes 1 and 41-62, stamp dated March 29, 1995, and data on disk.

Indications: (1) Treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye (such as seasonal allergic conjunctivitis and acute anterior uveitis). (2) Also for use in the treatment of giant papillary conjunctivitis.

Medical Officer: Wiley Chambers, M.D., HFD-540

Statistical Reviewer: Nancy Paul Silliman, Ph.D., HFD-725

Study 122

In my review of the sponsor's study #122 of lotemax versus prednisolone acetate for the treatment of acute anterior uveitis, "clinically effective" is used to mean that the drug (either lotemax or prednisolone acetate) is able to achieve an average reduction in cell rating of at least 1 unit. Both lotemax and prednisolone acetate are shown to be clinically effective in the ITT analysis of all patients (lotemax achieves an average reduction of 1.6, prednisolone acetate of 2.2). However, lotemax is statistically inferior to prednisolone acetate in the same analysis for three of four comparisons of cell rating (i.e., median time to 0 rating, $p=0.003$; proportion of patients with 0 rating by the final visit, 95% confidence interval $_{81,75}(-0.39, -0.12)_{0,64,0,89}$ and $p<0.001$; and proportion of patients with a reduction of at least 1 unit, 95% confidence interval $_{81,75}(-0.37, -0.12)_{0,69,0,93}$ and $p<0.001$ -- the difference between average reduction is not statistically significant, $p=0.075$). As for the main safety variable, elevation in IOP, lotemax is statistically superior to prednisolone acetate. Lotemax patients "survive" a longer time until their IOP increases by at least 6 mm Hg ($p=0.012$). As for increases of 10 mm Hg or more, 1/81 (1%) lotemax and 5/75 (7%) prednisolone acetate patients experienced such an increase.

Recall that there were differences in outcome between the centers in the U.S. and the centers in the U.K. due to the differential drop-out rate (i.e., investigators in the U.K. dropped 11 patients early, on days 2 and 3, who were not responding sufficiently to treatment -- 9 of these patients were receiving lotemax -- and all patients lost to follow-up are carried forward as failures in the ITT-LOCF analysis). In the U.S., 81% of lotemax and 85% of prednisolone acetate patients completed the study ($p=0.67$). In the U.K., 60% of lotemax and 87% of prednisolone acetate patients completed the study ($p=0.004$). The following tables summarize results in the U.S. and U.K. separately. Note that in the U.S.,

efficacy tends to be the same for lotemax and prednisolone acetate, although there are too few patients for the confidence intervals to meet the usual FDA requirements on the lower bound. In the U.S., safety is significantly better on lotemax than on prednisolone acetate. In the U.K., efficacy and safety conclusions are reversed, i.e., lotemax is inferior in terms of efficacy and there is no difference in safety profile.

Table 1: Median Time to 0 Rating

	Lotemax	Prednisolone Acetate	p-value
U.S.	19 days	15 days	p = 0.28
U.K.	27 days	21 days	p = 0.002

Table 2: Proportion Achieving 0 Rating by Final Visit

	Lotemax	Prednisolone Acetate	95% Confidence Interval	p-value
U.S.	25/34 (74%)	28/32 (88%)	(-33.2%, 5.2%)	p = 0.15
U.K.	27/47 (57%)	39/43 (91%)	(-51.5%, -15.0%)	p < 0.001

Table 3: Proportion Improving > 1 Unit by Final Visit

	Lotemax	Prednisolone Acetate	95% Confidence Interval	p-value
U.S.	27/34 (79%)	29/32 (91%)	(-28.5%, 6.1%)	p = 0.22
U.K.	29/47 (62%)	41/43 (95%)	(-50.8%, -16.5%)	p < 0.001

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ON ORIGINAL

Table 4: Time Until 25% of Patients Reached IOP Increase > 6 mm Hg*

	Lotemax	Prednisolone Acetate	p-value
U.S.	25 days	12 days	p < 0.001
U.K.	20 days	19 days	p = 0.99

*Note that this is used instead of median time as less than 50% of the patients in each arm had an increase of > 6 mm Hg.

4/9/96

Nancy Paul Silliman, Ph.D.
Statistical Reviewer, Division of Biometrics IV

PHD
4/10/96
Ralph Harkins, Ph.D.
Acting Division Director, Division of Biometrics IV

cc:
Orig. NDA #20-583
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HFD-725/Dr. Harkins
HFD-725/Dr. Silliman
HFD-344/Dr. Lisook
Chron.

This addendum contains 3 pages and 4 tables.

APPEARS THIS WAY
ON ORIGINAL

Statistical Review and Evaluation
(Consult)

NDA#: 20-583

Applicant: Pharmos Corporation

Name of Drug: Loteprednol Etabonate Ophthalmic Suspension (Lotemax^R), 0.5%

Drug Class: 1 S

Indication: Inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye.

Introduction:

The question asked is: "Are these procedures applicable to a dose ranging type study?" The material provided is for a studies using a placebo plus three escalating doses of the active agent. The hypothesis of interest is whether there is an increase in adverse events as the dose increases. The information provided is very incomplete. However, from the tables provided it appears adverse events are measured as the proportion of litters showing reproductive toxicologic effects.

Evaluation

Fisher's Exact test is when sample sizes are so small that usual asymptotic statistical procedures are not applicable. Bonferroni adjustments, or similar adjustments in the test level, are made when multiple, non-independent comparisons are used. Both situations apply in this case.

The sponsor's Tables 5, 6 and 7, under tab 2, which give the frequency of occurrence of a given parameter by litter is based on the assumption that if an effect occurs, it will affect every pup in the litter equally. If this assumption is false, this approach has a distinct potential for masking the relative seriousness of a given parameter's occurrence, i.e., there is little chance of detecting a statistically significant difference even when there is one.

The results under tab 3 are similarly presented and have the same problems.

The sponsor's "BRIEF CONCLUSIONS" section indicates they provided analyses in a previous submission based on individual foetus counts. Again, this is not the correct analysis. This ignores the potential effect of dam on the outcome as well as the fact that litter is the experimental unit.

The particular designs provided should be handled as a nested design where affected pups are nested under dam. Due to inequality of litter size and other factors, this will necessarily fit in the messy data evaluation class. This means many statisticians do not like to do these analyses.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

The analyses, as presented, are not applicable to the trial design used. In fact, the two analyses provided may miss important trends due to increased dose due to this use of inappropriate statistical procedures.

RH

Ralph Harkins, Ph.D. Group Leader
Biomedical Statistician, Group 7

cc:

Orig. NDA-20-583

HFD-540

HFD-540/Dr. Wilkin

HFD-540/Dr. Shriver

HFD-540/Ms. Chapman

HFD-713/Dr. Dubey [File: DRU 1.3.2]

HFD-713/Dr. Harkins

Chron.

This review contains 2 pages.

APPEARS THIS WAY
ON ORIGINAL