CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
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Statistical Review and Evaluation

Clinical Studies

NDA	202408 [505(b)(2) application]
Drug Name:	Acyclovir ophthalmic ointment, 3.0% (tradename AVACLYR)
Indication(s):	Treatment of acute herpetic keratitis (dendritic ulcers)
Applicant:	Fera Pharmaceuticals LLC
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1 EXECUTIVE SUMMARY

The results of five published studies have been submitted as part of a 505(b)(2) NDA (#202408) to support the approval of acyclovir ophthalmic ointment 3% (ACV) for the treatment of dentritic ulcers. All five studies were randomized studies with idoxuridine (IDU) as the active control. See Table 3.1 for a summary of the designs of the five studies and Table 3.2 for a summary of the efficacy results.

Four of the five studies enrolled patients with both dendritic and geographic ulcers; three of these four studies, provided data for dendritic and geographic ulcers separately. The one study that did not separate results for dendritic ulcers and geographic ulcers was not considered as part of the evidence to support the indication for treatment of dendritic ulcers. One study entered patients with only dendritic ulcers. So a total of 4 studies were reviewed as possibly providing evidence of efficacy.

One study (003) of 60 patients showed that ACV was superior to IDU 0.5% with healing rates at Day 7 of 97% (29/30) and 20% (6/30), respectively, and with a treatment difference of +77% and a 95% confidence interval of +57% to +88%. A second study (004) of 54 patients showed that ACV was non-inferior to IDU 1.0% with healing rates at Day 7 of 96% (27/28) and 85% (22/26), respectively, and with a treatment difference of +12% and a 95% confidence interval of -5% to +32%. The latter confidence interval excludes a non-inferiority margin of about -6%; 6% is 50% of M1 computed from a meta-analysis of trials comparing IDU to placebo (see Appendix 5.2). These two studies are sufficient from a statistical perspective to demonstrate the efficacy of acyclovir for the treatment of dendritic ulcers.

Of the other three studies (002, 005 and 006) submitted, none can support efficacy as an independent study for the indication being sought; one study does not present data for dendritic ulcers only, a second study was underpowered to show superiority or non-inferiority with only 10 patients in each arm and the third study appears to be inconsistent with the other studies by design (no use of an anticholinergic) and by results (unusually low healing rate for ACV of 62% at Day 7).

2 INTRODUCTION

2.1 Overview

The applicant (Fera Pharmaceuticals) has submitted a 505(b)(2) NDA for acyclovir ophthalmic ointment, 3% (ACV) for the treatment of acute herpetic keratitis (dendritic ulcers). This submission, according to the applicant, relies on evidence from the published studies and from the following previous applications[1] for acyclovir use for several indications:

- Acyclovir for Injection NDA 01603
- Acyclovir Topical Ointment 5% NDA 18604
- Acyclovir Capsules NDA 18828
- Acyclovir Suspension NDA 19909
- Acyclovir Tablets NDA 20089
- Acyclovir Topical Cream 5% NDA 21478

Acyclovir ophthalmic ointment has been approved in Europe since the early 1980's and studied in a number of clinical trials since that time. The results of five studies submitted by the applicant to demonstrate the safety and efficacy of acyclovir compared to idoxuridine (IDU) were all published in the early 1980"s. Three of the five publications mention that the acyclovir ointment was provided by Welcome Research Laboratories (presently GlaxoSmithKline [GSK]). GSK recently stopped manufacturing acyclovir ointment 3%. The applicant has provided a rationale in Section 3.2.P.1 of Module 3 (submitted 7/24/1013) of the NDA for accepting their product without direct bridging to the product used in the clinical trials.

At the FDA/applicant pre-NDA meeting, FDA referred the applicant to the clinical review of ganciclovir (NDA 22-211) as a guide for preparing their NDA. The five publications submitted for this application are the same five studies presented in the FDA clinical review to quantify the comparison of ACV versus IDU in order to estimate a non-inferiority margin for the comparison of ganciclovir versus ACV.

Meta-analyses (two Cochrane reviews, one published in 2009 and one in 2011[2]) to compare the efficacy of acyclovir and other therapeutic interventions for the treatment of herpes simplex eye disease were performed by Kirk Wilhelmus. In the 2011 report, he concluded that trifluridine and acyclovir are more effective than idoxuridine or vidarabine and that brivudine and ganciclovir are at least as effective as acyclovir for the healing of herpetic ulcers. Both reviews included meta-analyses of the same nine studies comparing ACV versus IDU. The five studies included in this NDA were all included with those nine studies. According to the FDA statistical review of ganciclovir, three studies included in the Cochrane reviews were primarily excluded because results were not presented for dendritic ulcers separately from geographic ulcers,. Note that a study by Abe (1987) was included in the FDA statistical review but not the FDA clinical review of ganciclovir. Abe was a single-blind study and may have been excluded for that reason.

[1] The list of NDA's was provided by the applicant.

[2] Wilhelmus K. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis (Review) 2011 The Cochrane Collaboration. *The Cochran Library*, Issue 8
Wilhelmus K. Therapeutic interventions for herpes simplex virus epithelial keratitis (Review) 2009 The Cochrane Collaboration. *The Cochran Library*, Issue 1

This statistical review focuses on the five studies submitted by the applicant and deemed acceptable by the FDA clinical staff (based on the FDA clinical ganciclovir reviews and the filing review for this application). Note that the goal of this review is to assess the statistical evidence from each individual study to determine if the published data demonstrate efficacy from more than one well-controlled investigation in accordance with FDA regulation.

2.2 Data Sources and Quality

The full NDA can be accessed in the FDA electronic document room at the following link: \\CDSESUB1\EVSPROD\NDA202408\202408.enx. The NDA is well-organized and contains the necessary information for a statistical review.

No data was submitted for this 505(b)(2) application that depends on literature-based studies to demonstrate efficacy and safety. Summary statistics were provided in the publications and these statistics serve as the basis for the statistical review.

3 STATISTICAL EVALUATION

The applicant has provided publications for five studies comparing ACV to IDU as evidence for the efficacy of ACV in the treatment of dendritic ulcers. The designs for these five studies are summarized in Table 3.1 on the following page.

All five studies are double-blind, randomized trials conducted in the early 1980's and designed to compare ACV to IDU. IDU 0.5% was the comparator in four of the five studies; Study 004 used IDU 1%. All trials used ACV 3%. One study (006) was conducted in the US; with 64 patients, it was the largest study. Three of the five studies were multicenter trials.

Four of the 5 studies enrolled patients with both dendritic and geographic ulcers. Study 003 enrolled only patients with dendritic ulcers. For 4 of the 5 studies, results for dendritic ulcers only are provided. For Study FP-ACV-002, the publication (Colin et al, 1981), the study report and the Cochrane reports all state that patients with dendritic or geographic ulcers could be enrolled in the study; however results by type of ulcer are not provided in the publication. Also there is no mention in the applicant's study report how many of the patients had only dendritic ulcers and it is not stated that the report results are for dendritic ulcers only. The pre-NDA meeting minutes clearly state that dendritic ulcers and geographic ulcers should be considered as separate indications. It appears to this reviewer that Study 002 should not be considered as a study to support the indication for dendritic ulcers.

No two studies used the same treatment regimen with studies differing by type of concomitant medication used and by duration of treatment (see Table 3.1). The proposed labeling recommends applying the ointment 5x/day until healed and then 3x/day for 7 days. None of the 5 studies used the dosing schedule recommended in the applicant's proposed labeling.

None of the publications provided sufficient details with regard to blinding or randomization to assess whether the studies were well-conducted. In addition, very limited data regarding the population baseline demographics was provided with most studies providing data for patients with dendritic and geographic ulcers presented together. Some results by type of ulcer were shown; no other subgroup analyses were conducted.

Table 3.1 Designs for five double-blind, randomized studies of acyclovir versus idoxuridine

	FP-ACV-002	FP-ACV-003	FP-ACV-004	FP-ACV-005	FP-ACV-006
Reference	Colin, 1981	Collum, 1980	Coster, 1980	Klauber, 1982	McCulley, 1982
Centers	3 (France)	2 (Dublin)	1 (London)	1 (Copenhagen)	5 (USA)
# randomized ACV IDU	 ACV 3% 25 IDU 0.5% 27	 ACV 3% 30 IDU 0.5% 30	 ACV 3% 30 IDU 1% 30	 ACV 3% 18 IDU 0.5% 20	 ACV 3% 30 IDU 0.5% 34
Pt diagnosis	Superficial dendritic or geographic corneal ulceration.	Superficial dendritic corneal ulceration	Superficial dendritic or geographic corneal ulceration	Superficial dendritic or geographic corneal ulceration	Superficial dendritic or geographic corneal ulceration
% with dendritic ulcers	NA	100%	ACV 28/30 (93%) IDU 26/30 (87%)	ACV 10/18 (56%) IDU 10/20 (50%)	ACV 26/30 (87%) IDU 26/34 (76%)
Trt regimen	5x/day atropine 1% 2x/day	5x/day homatropine 1% 2x/day	5x/day until healing, then 3x/day for 3 days atropine 1% 1x/day	5x/day until improved, then 3x/day 0.2% scopolamine 2x/day	5x/day Concomitant medication information not available
Duration of trt	7 days if no improvement by Day 7, Or until healed	4 days if no improvement by Day 4, Or until healed	Until healed plus 3 days	Until healed or a maximum of 14 days	14 days
Demographics Mean Age % males	 NA for dendritic only	 41 yrs 73%	 NA	 NA for dendritic only	 NA for dendritic only
Healing Endpoint	No epithelial ulceration based on fluorescein staining	Healed when there was "no fluorescein uptake"	No epithelial defect based on rose Bengal and fluorescein staining	No epithelial defect based on rose Bengal and fluorescein staining	No epithelial defect based on fluorescein staining
Details wrt blinding	NA	Packed in identical tubes	Ophthalmologist & patient were blinded	NA	NA
Details wrt randomization	NA	NA	Stratified on type and size of ulcer, use of topical corticosteroids and degree of inflammation	NA	"Random code list"

NA indicates information neither available in the reference nor in the NDA study report.

The healing rates at Day 7 are considered the primary endpoint. The presentation of results differed across the studies but a Day 7 healing rate could be computed from the data provided with either the data provided explicitly or interpolated from graphs of healing rates. End of study data was always provided but the definition of end of study varied across studies. This reviewer did not consider summarizing time to healing since schedules for following patients during the trial varied considerably. In some studies, patients were seen on specific follow-up days while in others patients were seen twice a week or every other day. Also length of follow-up varied as can be seen from Table 3.1.

The results for all 5 studies are provided in Table 3.2. As stated earlier, Study 002 included results for dendritic and geographic ulcers combined; so this reviewer is presenting the results for that study for completion but not including this study in the overall statistical assessment of efficacy of acyclovir for the treatment of dendritic ulcers. Healing rates were ascertained from the publications and treatment differences with 95% confidence intervals were computed by the reviewer.

Studies 003, 004 and 005 showed higher healing rates at Day 7 for ACV than IDU; the treatment difference was statistically significant in one study (Study 003, $p<0.0001$, Fisher's exact test). The US study (006) showed Day 7 healing rates for both ACV and IDU that were 20-30% lower than what was seen in the other 3 studies. Also the US study showed slightly higher rates for IDU than ACV; 4% higher on Day 7 and 7% higher on Day 14. One difference between the report for the US study and the other 3 studies is that the other three study reports all mention that an anticholinergic was given with the randomized treatment. There may also be patient population differences that could explain the difference in rates between the US study and the other studies but there is insufficient information to assess this.

Table 3.2 Results for five double-blind, randomized studies of acyclovir versus idoxuridine; Study 002 results are for dendritic and geographic ulcers while results for Studies 003, 004, 005 and 006 are for dendritic ulcers only

	FP-ACV-002	FP-ACV-003	FP-ACV-004	FP-ACV-005	FP-ACV-006
Reference	Colin, 1981	Collum, 1980	Coster, 1980	Klauber, 1982	McCulley, 1982
Healing rates[1]					
Day 7					
ACV	*19/25 (76%)*	29/30 (97%)	27/28 (96%)	8/10 (80%)	16/26 (62%)
IDU	*11/27 (41%)*	6/30 (20%)	22/26 (85%)[2]	5/10 (50%)	17/26 (65%)
Risk Difference[3]					
ACV-IDU	*+35%*	**+77%**	**+12%**	**+30%**	**-3.8%**
(95%CI)	*(+8%, +60%)*	**(+57%, +88%)**	**(-5%, +32%)**	**(-15%, +67%)**	**(-30%, +23%)**
End of study					
ACV	*23/25 (92%)*	30/30 (100%)	28/28 (100%)	10/10 (100%)	22/26 (85%)
IDU	*22/27 (81%)*	22/30 (73%)	26/26 (100%)	10/10 (100%)	24/26 (92%)

[1]The healing rates were extracted from the literature and study reports. When 7 day results were not available, the applicant interpolated the 7 day results from a graph of time to healing found in the publication; this reviewer checked the interpolation.
[2] The high rate of 85% for IDU in this study is for a dosage of 1% for IDU compared to 0.5% in the rest of the studies.
[3]Risk differences were computed by this reviewer and are based on an exact test to compare proportions. Positive risk differences favor ACV.

The results for Studies 004, 005 and 006 can be assessed for the non-inferiority of ACV compared to IDU. A meta-analysis of trials comparing IDU to placebo performed by the statistical reviewer (Dr. Rima Izem) of ganciclovir (see Appendix 5.2) yielded a treatment effect for IDU over placebo of +31% with a 95% confidence interval of +12% to +49%. This confidence interval suggests that the probable smallest important difference (M1) between IDU and placebo is 12%. In an active control study, a new

product should be no more than 12% worse than IDU to demonstrate efficacy over the putative placebo. The non-inferiority margin should then be -12% or larger with the chosen magnitude dependent on clinical input. (For example, discounting by 50% would suggest a non-inferiority margin of -6%.) Regardless of the amount of adjustment to M1, only the data for Study 004 yields a confidence interval that rules out a margin of -12% or larger. For Studies 005 and 006, the lower bounds to the confidence intervals are -15% and -30% and do not rule out a difference of 12% or larger in favor of IDU.

Of the five studies submitted by the applicant, two studies demonstrate the efficacy of acyclovir for the treatment of dendritic ulcers. Study 003 (Collum, 1980) showed that acyclovir was superior to idoxuridine 0.5% while Study 004 (Coster, 1980) showed that acyclovir was non-inferior to idoxuridine 1.0%.

4 SUMMARY AND CONCLUSIONS

4.1 Conclusions and Recommendations

For this 505(b)(2) application, the results of 5 published studies were presented to support the efficacy of acyclovir in the treatment of dendritic ulcers. The results for these 5 studies are summarized in Table 3.2 on the previous page. The table below summarizes this reviewer's statistical interpretation of each study.

Table 4.1.1 Reviewer's statistical interpretation of 5 studies submitted to support the efficacy of acyclovir

Study	ACV-IDU Diff (95% CI)	Interpretation
002 (Colin, 1981)	Results for dendritic and geographic ulcers combined	Not useful since the data for dendritic ulcers only were not presented
003 (Collum, 1980)	+77% (+57%, +88%)	ACV 3% superior to IDU 0.5%
004 (Coster, 1980)	+12% (-5%, +32%)	ACV 3% non-inferior to IDU 1.0% Non-inferiority margin>-12%
005 (Klauber, 1982)	+30% (-15%, +67%)	Study underpowered with only 20 patients
006 (McCulley, 1982)	-3.8% (-30%, +23%)	Low healing rates for both groups suggests some significant differences in study design from the other studies. One difference between this study and others was the lack of use of an anticholinergic

Two well-controlled studies (003 and 004) demonstrate the efficacy of acyclovir for the treatment of dentritic ulcers. The reviewer would recommend including the results for Studies 003 and 004 in labeling.

4.2 Labeling Comments

The proposed labeling recommends applying the ointment 5x/day until healed and then 3x/day for 7 days as shown below:

(b) (4)

The applicant has proposed the following labeling for the clinical studies section.

14 CLINICAL STUDIES

(b) (4)

The applicant's annotation for the clinical studies section above refers to Section 2.7.3 in Module 2 Summary of Clinical Efficacy. It appears that the numbers proposed for the labeling were extracted from Table 2 of Section 2.7.3. However, the numbers in that table do not match numbers reported for the five studies in the publications, in the study reports, in the applicant's summaries (including the text of 2.7.3), in FDA reviews of ganciclovir or in this statistical review (Table 3.2). Following a correspondence from FDA, the applicant acknowledged that their Table 2 contained errors and they updated their Table 2 with the correct numbers.

This reviewer suggests the following edits to the applicant's labeling proposal based on the results from Studies 003 (Colin 1981) and 004 (Coster 1980):

In two randomized, double masked clinical studies which enrolled a total of 114 subjects with herpetic keratitis Acyclovir Ophthalmic Ointment, 3% was either superior or as effective as idoxuridine ophthalmic ointment in subjects with dendritic ulcers.

In one multicenter, randomized, double masked clinical study which enrolled a total of 60 subjects with herpetic keratitis Acyclovir Ophthalmic Ointment, 3% was superior to idoxuridine ophthalmic ointment 0.5% in subjects with dendritic ulcers. Clinical resolution (healed ulcers) at Day 7 was 97% (29/30) for Acyclovir compared to 20% (6/30) for idoxuridine 0.5%.

In one single center, randomized, double masked clinical study which enrolled 54 subjects with herpetic keratitis, Acyclovir Ophthalmic Ointment, 3% was as effective as idoxuridine ophthalmic ointment 1% in subjects with dendritic ulcers. Clinical resolution (healed ulcers) at Day 7 was 96% (27/28) for Acyclovir compared to 85% (22/26) for idoxuridine 1.0%.

5 APPENDICES

5.1 Literature References

Colin J, Tournoux A, Chastel C, Renard G. Superficial herpetic keratitis. Comparative treatment in a double-blind trial using acyclovir and idoxuridine. Nouv. Presse Med., 1981, 10, 2969-2975.

Collum L, Benedict-Smith I, Hillary I. Randomized double-blind trial of acyclovir and idoxuridine in dendritic corneal ulceration. British Journal of Ophthalmology, 1980, 64, 766-769.

Coster D, Wilhelmus K, Michaud R, Jones B. A comparison of acyclovir and idoxuridine as treatment for ulcerative herpetic keratitis, British Journal of Ophthalmology, 1980, 64, 763-765.

Klauber A, Ottovay E. Acyclovir and Idoxuridine Treatment of Herpes Simplex Keratitis-A Double Blind Clinical Study, ACTA Ophthakmologica, 60 (1982) 838-844.

McCulley J, Binder P, Kaufman H, O'Day D, Poirer R. A Double-blind, Multicenter Clinical Trial of Acyclovir vs. Idoxuridine for Treatment of Epithelial Herpes Simplex Keratitis, Ophthalmology 89:1195-1200, 1982.

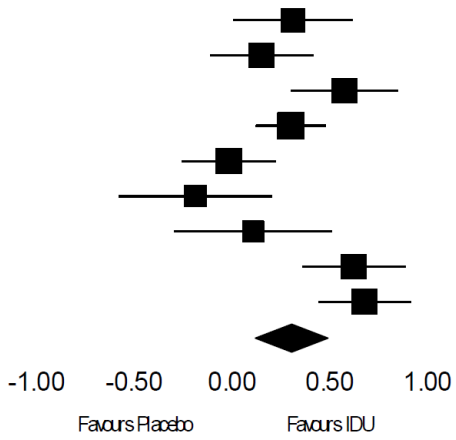
Wilhelmus KR. 2009. The Cochrane Collaboration, The Cochran Library, Issue 1.

Wilhelmus KR. 2011. The Cochrane Collaboration, The Cochran Library, Issue 8.

5.2 Meta-analysis of idoxuridine versus placebo

Meta-analysis results for IDU versus placebo from page 20 of the statistical review of Dr. Rima Izem dated 7/7/2009 are shown below. This analysis yielded a 95% confidence interval of 12% to 49% suggesting the smallest clinically important difference between IDU and placebo is 12% and thereby a non-inferiority margin of 12% or smaller for comparisons of an active drug to IDU would be acceptable.

Study name	Statistics for each study			Healed / Total	
	Risk difference	Lower limit	Upper limit	IDU	Placebo
Burns 1963	0.32	0.01	0.63	15 / 23	5 / 15
Davidson 1964	0.16	-0.11	0.43	12 / 25	8 / 25
Hart 1965	0.58	0.30	0.86	14 / 19	2 / 13
Laibson 1964	0.31	0.12	0.49	26 / 47	13 / 53
Markham 1977	-0.01	-0.25	0.23	4 / 21	4 / 20
Luntz 1963	-0.18	-0.58	0.21	3 / 11	5 / 11
Patterson-a 1963	0.12	-0.29	0.52	5 / 10	5 / 13
Patterson-b 1963	0.63	0.37	0.90	13 / 17	2 / 15
Patterson-c 1963	0.69	0.45	0.93	11 / 16	0 / 14
	0.31	0.12	0.49		



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/s/

JOY D MELE
10/30/2013

YAN WANG
10/30/2013
I concur.