

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-211

STATISTICAL REVIEW(S)

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 1, 2009

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SUBJECT: NDA 22-211, ST-605 (Ganciclovir Ophthalmic Gel, 0.15%)
Division Director's evaluation of efficacy results of the Phase III trial

This memorandum evaluates the evidence of efficacy of a Phase III trial presented in NDA 22211 to support the approval of the use of Ganciclovir Ophthalmic Gel, 0.15% in subjects with Acute Herpetic Keratitis. As a background, the main findings of the primary statistical review are first summarized, followed by statistical issues and the Division Director's evaluation of results and conclusions.

Background: The results of the Phase 3 trial (see Table 1, attached) show that the healing rate at day 7 of subjects in the ST-605 arm is 77% (55/71) and in the active comparator Acyclovir arm is 72% (48/67) with a 95% confidence interval for difference in healing rate of -10% to 20%.

The primary statistical reviewer's Meta Analyses (see Table 2, attached), suggest that the historical treatment effect size M1 of the acyclovir comparator and an endpoint of recovery rate at day 7 is in the range of 14% to 31%. These estimates were obtained by the meta-analysis of available historical trials and accounts for uncertainty in the observed treatment effects across trials. These comparator effect sizes were estimated using two different methods and for the "dendritic subpopulation only" or for the composite population of "dendritic and geographic ulcers."

Statistical issues: As indicated in the primary statistical review, the main statistical issue for the Phase III open label trial of this NDA is the inflation of the false positive or the Type 1 error rate for the following reasons:

- The planned primary endpoint for the trial was time to first healing. However, this planned endpoint was changed post-hoc to healing rate at any time.
- Later, after the review of the data, clinical interest changed to the endpoint at day 7 given that the sponsor also analyzed the data at day 14. Interestingly, Day 7 is the time point where the result of this trial appears to be most promising. Such a post-hoc choice of endpoint raises multiplicity issues and increases the chance of the result being on random high.

- The trial was originally planned as a superiority trial, but it was then changed post-hoc to a non-inferiority trial.

Moreover, the comparator control is not approved in the United States. However, Trifluridine, an U.S. approved product is available for this indication. General practice for a non-inferiority trial design is to use an approved comparator whose efficacy in the trial can be reliably assumed from the historical data.

Evaluation of Results: The meta-analyses of available historical Acyclovir trials were conducted for the purpose of evaluating the treatment effect size M1 of Acyclovir comparator for the endpoint of interest at day 7. The results of these analyses suggest treatment effect size M1 of Acyclovir treatment to be in the range of 14% to 31%. The range of this M1 is large because the results are sensitive to which subset of studies is included in the derivation.

Therefore, if these effect sizes can be assumed to be clinically applicable to the current trial, then the data suggest that, the Acyclovir treatment, although unapproved in U.S., is an effective treatment in the current trial for the proposed endpoint and the indication.

The issue of M2, the non-inferiority margin, for the statistical comparison of the new treatment to the control for establishing non-inferiority of the new treatment to the control, is not a statistical issue. It is a matter of clinical judgment. The primary statistical reviewer has provided a range of values M2 that can be set depending on the desired preservation of the treatment effect of Acyclovir. See Table 3 (attached). Table 3 shows that if this preservation of effect can be set at 25%, then the value of M2 can be taken as 10.5 for the day 7 endpoint.

Therefore, if this margin of 10.5 can be clinically justified (relative to M1) and is conservative enough for discounting of the multiplicity issue raised for this trial, then the trial suggests evidence of non-inferiority of ST-605 (Ganciclovir Ophthalmic Gel, 0.15%) in comparison to the Acyclovir treatment for the day 7 endpoint.

Conclusions:

1. Meta-analysis of historical trials of Acyclovir comparator suggests its efficacy (in comparison to placebo) at day 7 is in the range of 14% to 31%. If these results can be assumed to be clinically applicable to the current trial, then one can conclude that the Acyclovir was an effective treatment in the trial for the proposed endpoint and indication.
2. The determination of margin M2, for the non-inferiority testing of ST-605 to Acyclovir, is not a statistical issue. This is to be decided based on clinical considerations. If the value of M2 can be set at 10.5 for the day 7 endpoint and it is conservative enough for discounting the multiplicity issue raised for this trial, then the results of this trial suggest non-inferiority of ST-605 (Ganciclovir

Ophthalmic Gel, 0.15%) in comparison to the Acyclovir treatment for this endpoint.

3. However, this evidence of efficacy of ST-605 coming from a single Phase III confirmatory trial with the above results and issues is not sufficiently persuasive. Therefore, there is a need to replicate the efficacy of ST-605 from other independent sources.

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Appendix Tables:

Table 1: Results of Phase 3 (Study 7) trial on healing rate.

| | Day 3 | Day 7 | Day 10 | Day 14 | Day 21 |
|------------------------------|----------------|----------------|----------------|----------------|----------------|
| ST-605 | 42% (30/71) | 77% (55/71) | 79% (56/71) | 86% (61/71) | 86% (61/71) |
| Acyclovir | 31% (21/67) | 72% (48/67) | 79% (53/67) | 90% (60/67) | 90% (60/67) |
| 95% CI for difference | (-7%, 28%) | (-10%, 20%) | (-14%, 14%) | (-16%, 9%) | (-16%, 9%) |

Table 2: Effect Size M1. Summary results for the two derivation methods Method 1 and Method 2 and for the dendritic subgroup and composite subgroup of dendritic and geographic

| | Number of included studies | Point estimate of difference in healing rates | M1 for difference in healing rates | Point estimate for log odds ratio | M1 for log odds ratio |
|------------------------------------|---|---|------------------------------------|-----------------------------------|-----------------------|
| Method 1- Dendritic | 6 studies for ACV vs IDU and 9 studies for IDU vs Placebo | 63% | 14% | 2.8 | 0.8 |
| Method 2- Dendritic | 10 ACV studies and 12 Placebo studies | 48% | 31% | 2.12 | 1.31 |
| Method 1- Dendritic and Geographic | 7 studies for ACV vs IDU and 9 studies for IDU vs Placebo | 65% | 25% | 2.64 | 1.13 |
| Method 2- Dendritic and Geographic | 15 ACV studies and 12 Placebo studies | 45% | 31% | 1.94 | 1.29 |

Table 3: Non-inferiority margins for difference in healing rate at day 7. Non-inferiority margins were derived for different percent of preservations of treatment effect over placebo.

| Percent Preservation | M1: 0% | 10% | 25% | 50% | 75% | 90% |
|--|---------------|------------|------------|------------|------------|------------|
| Method 1-Dendritic | 14% | 12.6% | 10.5% | 7.0% | 3.5% | 1.4% |
| Method 2-Dendritic | 31% | 27.9% | 23.3% | 15.5% | 7.8% | 3.1% |
| Method 1-Dendritic and Geographic | 25% | 22.5% | 18.8% | 12.5% | 6.3% | 2.5% |
| Method 2-Dendritic and Geographic | 31% | 27.9% | 23.3% | 15.5% | 7.8% | 3.1% |

**APPEARS THIS WAY
ON ORIGINAL**

| Linked Applications | Submission Type/Number | Sponsor Name | Drug Name / Subject |
|---------------------|------------------------|---------------------|--|
| NDA 22211 | ORIG 1 | SIRION THERAPEUTICS | ZIRGAN (GANCICLOVIR OPHTHALMIC GEL)0.15% |

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/s/

MOHAMMAD F HUQUE
09/02/2009



Department of Health and Human Services
Food and Drug Administration
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA # : 22211

Drug Name: Ganciclovir Ophthalmic Gel, 0.15%

Indication(s): Antiviral therapy for treating acute herpetic keratitis (dendritic —
————— ulcers) **b(4)**

Applicant: Sirion Therapeutics, Inc.

Stamp Date: 11/14/08

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TABLE OF CONTENTS

| | |
|---|-----------|
| 1 EXECUTIVE SUMMARY..... | 5 |
| 1.1 CONCLUSIONS AND RECOMMENDATIONS | 5 |
| 1.2 BRIEF OVERVIEW OF CLINICAL STUDIES | 6 |
| 1.3 STATISTICAL ISSUES AND FINDING..... | 6 |
| 2 INTRODUCTION..... | 8 |
| 2.1 CLASS AND INDICATION..... | 8 |
| 2.2 HISTORY OF DRUG DEVELOPMENT | 8 |
| 2.3 SPONSOR'S RATIONALE FOR THE INVESTIGATION OF ST-605 FOR ACUTE HERPETIC KERATITIS | 8 |
| 2.4 STUDIES IN THIS SUBMISSION AND MAJOR STATISTICAL ISSUES..... | 8 |
| 2.4.1 <i>Post-hoc change of hypothesis from superiority to non-inferiority</i> | 10 |
| 2.4.2 <i>Integrated analysis</i> | 11 |
| 2.4.3 <i>Change of primary endpoint</i> | 11 |
| 2.4.4 <i>Choice of historical evidence</i> | 12 |
| 2.4.5 <i>Derivation of non-inferiority margin</i> | 12 |
| 2.5 DATA SOURCES | 12 |
| 2.6 PRIOR REGULATORY GUIDANCE | 12 |
| 3 STATISTICAL EVALUATION..... | 13 |
| 3.1 STUDY DESIGN AND ENDPOINTS (STUDY 7)..... | 13 |
| 3.2 REVIEW OF HISTORICAL DATA ON EFFICACY | 15 |
| 3.3 DERIVATION OF NON-INFERIORITY MARGIN FOR EFFICACY..... | 18 |
| 3.3.1 <i>Method 1: Indirect comparison of Acyclovir to Placebo through Idoxuridine</i> | 18 |
| 3.3.2 <i>Method 2: Indirect comparison of Acyclovir to Placebo through Idoxuridine, Trifluridine and Vidarabine</i> | 28 |
| 3.3.3 <i>Summary of results and non-inferiority margin</i> | 29 |
| 3.3.4 <i>Comparison of Trifluridine to Acyclovir</i> | 30 |
| 3.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS | 32 |
| 3.5 STATISTICAL METHODOLOGIES | 36 |
| 3.5.1 <i>Hypothesis testing</i> | 37 |
| 3.5.2 <i>Missing Data</i> | 37 |
| 3.5.3 <i>Efficacy Analysis Population</i> | 37 |
| 3.6 EVALUATION OF EFFICACY | 38 |
| 3.7 EVALUATION OF SAFETY | 40 |
| 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS | 42 |
| 5 SUMMARY AND CONCLUSIONS | 42 |
| 6 APPENDIX | 45 |
| 6.1 ACYCLOVIR STUDIES | 45 |
| 6.2 PLACEBO STUDIES | 52 |
| 6.3 NON-INFERIORITY MARGIN DERIVATION FOR HEALING AT DAY 14 | 59 |

LIST OF TABLES

| | |
|--|----|
| Table 1. Phase 1, 2, and 3 Trials Contributing Safety Information for ST-605..... | 9 |
| Table 2: Acyclovir historical data | 16 |
| Table 3: Placebo historical data..... | 17 |
| Table 4: Summary of meta analyses in Figures 1-4 comparing Idoxuridine to Placebo. Results in this table report the point estimate and 95% confidence interval..... | 27 |
| Table 5: Summary of meta analyses in Figures 5-8 comparing Acyclovir to Idoxuridine. Results in this table report the point estimate and 95% confidence interval..... | 27 |
| Table 6: Method 2. Results of the 4 logistic regressions (point estimate, 95% confidence interval, overdispersion parameter and degrees of freedom)..... | 28 |
| Table 7: Method 2. Derived estimates for difference in healing rate and log odds ratio..... | 28 |
| Table 8: Effect Size M1. Summary of Results from Method 1 and Method 2..... | 29 |
| Table 9: Non-inferiority margins for difference in healing rate or log odds ratio at day 7. Non-inferiority margins were derived for different percent of preservations of treatment effect over placebo. | 30 |
| Table 10: Number of patients per country..... | 36 |
| Table 11: Results of Phase 3 (Study 7) trial on healing rate difference and log odds ratio..... | 39 |
| Table 12: Healing rates at day 14 for Placebo Studies..... | 59 |
| Table 13: Healing rates at day 14 for Acyclovir studies..... | 59 |
| Table 14: Healing rates at day 14 for studies comparing Acyclovir to Idoxuridine..... | 60 |
| Table 15: Healing rates at day 14 for studies comparing Acyclovir to Trifluridine..... | 60 |
| Table 16: Effect Size M1 for healing rate at day 14..... | 61 |

LIST OF FIGURES

| | |
|---|----|
| Figure 1: Meta analysis for healing rates comparing Placebo to Idoxuridine (IDU). Results for Dendritic ulcer only..... | 20 |
| Figure 2: Meta analysis for healing rates comparing Placebo to Idoxuridine (IDU). Results for combined Dendritic and Geographic ulcers..... | 21 |
| Figure 3: Meta analysis for log odds ratio comparing Placebo to Idoxuridine (IDU). Results for Dendritic ulcer only..... | 22 |
| Figure 4: Meta analysis for log odds ratio comparing Placebo to Idoxuridine (IDU). Dendritic and Geographic ulcer..... | 23 |
| Figure 5: Meta analysis for healing rate comparing Idoxuridine (IDU) to Acyclovir (ACV). Results for Dendritic ulcer only..... | 24 |
| Figure 6: Meta analysis for healing rate comparing Idoxuridine (IDU) to Acyclovir (ACV). Results for pooled Dendritic and Geographic ulcers..... | 25 |
| Figure 7: Meta analysis for log odds ratios comparing Idoxuridine (IDU) to Acyclovir (ACV). Results for Dendritic ulcer only..... | 26 |
| Figure 8: Meta analysis for log odd ratios comparing Idoxuridine (IDU) to Acyclovir (ACV). Results for pooled Dendritic and Geographic ulcers..... | 27 |
| Figure 9: Meta analysis for risk difference comparing Acyclovir to Trifluridine. Dendritic and Geographic ulcer..... | 31 |
| Figure 10: Meta analysis for log odds ratio comparing Acyclovir to Trifluridine. Dendritic and Geographic ulcer..... | 32 |
| Figure 11: Number of recruited male and female in each treatment group. Female are in dark shade, males are in light shade. The sex distribution seems balanced in the treatment groups..... | 33 |
| Figure 12: Distribution of age by treatment group. Distribution of age in the two groups is similar. Minimum age in Acyclovir group is 4 years (patient 240)..... | 34 |
| Figure 13: Baseline ulcer size by treatment group. Although the difference in baseline lesion size is not significant, there are more patients with larger ulcer lesions in the active control group than in the ST-605 group..... | 35 |
| Figure 14: Baseline ulcer size by treatment group. The distribution of lesion size is right skewed in both groups..... | 36 |
| Figure 15: Ulcer size at Day 3 compared to Baseline. Filled circles represent patients in Acyclovir group, open circles represent patients in ST-605 group. We see that there is a positive relationship between ulcer sizes on these two days for both groups..... | 40 |
| Figure 16: Cure at day 7 by Sex and Treatment. Dark shade is uncured counts, light shade is cured count. We do not see a difference in cure rate by sex..... | 42 |

1 EXECUTIVE SUMMARY

Sirion Therapeutics, Inc. has submitted NDA 22211 to support approval of ST-605, Ganciclovir Ophthalmic Gel 0.15%, for antiviral therapy of herpetic keratitis. This submission includes results from seven open label clinical studies: two pharmacokinetic studies with healthy subjects (Study 2 and 3), one pharmacokinetic study in subjects with acute herpetic keratitis (Study 1), three Phase 2b studies (Study 4, 5, and 6) and one Phase 3 study (Study 7). During clinical development, the preservative used in the ST-605 formulation was changed from sodium mercurothiolate 0.006% (used for Studies 1, 4, 5, and 6) to benzalkonium chloride 0.0075% (used for Studies 2, 3, and 7). As change in formulation can affect the efficacy of the product, the statistical review focused on the efficacy results presented from Study 7 only without pooling results from other studies.

The Phase 3 trial was designed and conducted by the original sponsor (Théa Laboratories) as a superiority trial based on some encouraging results from the Phase 2 trials. However, the Phase 3 study failed to demonstrate superiority of ST-605 over Acyclovir 3% using the pre-planned primary endpoint of time to healing. In this submission, the sponsor re-analyzed the failed Phase 3 study with a different endpoint (healing rate at day 14) using a non-inferiority hypothesis with a proposed non-inferiority margin of 18%.

1.1 Conclusions and Recommendations

Both the sponsor's analysis and the reviewer's analysis are post-hoc re-evaluation of the evidence with a post-hoc non-inferiority margin. However, the reviewers' post-hoc exploratory analysis of the evidence differed substantially from the submitted analysis from the sponsor. The differences between the two analyses are: first, the reviewers' analysis used results from the Phase 3 study only whereas the sponsor's analysis used the pooled Phase 2 and Phase 3 data; second, the choice of primary efficacy endpoint was healing rate at day 7 in reviewers' analysis instead of first time healing rate at *anytime* in the sponsor's analysis; third, the subset of historical studies used to derive the non-inferiority margin includes all relevant original published studies in the reviewer's analysis (as suggested by the ophthalmology clinical team) instead of a subsample of studies from the Cochrane review in the sponsor's analysis; fourth, the non-inferiority margin derivation accounts for sampling variability and between study heterogeneity in the reviewer's analysis instead of pooling the point estimates for healing rate in the sponsor's analysis.

Although the reviewer's post-hoc exploratory analysis in study 7 (phase-3) may show that ST-605 is non-inferior to Acyclovir 3% ointment using a NI margin determined post-hoc, we do not think that the current submission is adequate or that it provides substantial evidence of efficacy required for the approval of this indication in the US. Our main objections are two-fold. First, the pre-planned hypothesis of superiority using the pre-planned efficacy endpoint of time to healing, failed to demonstrate superiority using the data from a single, open label Phase 3 trial. The reviewer's analysis used a post-hoc

endpoint and a post-hoc non-inferiority hypothesis, so this analysis has the same potential for multiple testing errors as any post-hoc exploratory analysis. We believe that to avoid multiple testing errors and bias, the choice of primary endpoint and hypothesis test should be pre-planned at the protocol stage and the non-inferiority margin should be pre-specified. Second, the active control used in the Phase 3 trial is not an FDA approved drug, nor the standard of care in the United States. Although the historical evidence may show that the active control used in this trial is effective, the historical evidence fails to show that the active control is superior to the current standard of care in the United States: Trifluridine. Thus, this trial does not provide evidence that ST-605 would be non-inferior, much less superior, to the standard of care Trifluridine. These objections are reinforced by the fact that our own derivation of the non-inferiority margin relies on very heterogeneous historical trials which clearly violate the constancy assumption and are sensitive to the subset of studies included.

Based on the objections cited above, we recommend that at least one prospectively designed, adequate and well-controlled study of ST-605 be conducted for the treatment of acute herpetic keratitis with the comparator Trifluridine to demonstrate that the product is at least as effective as standard of care. The results from the reviewer's exploratory analysis can thus be used as supportive evidence. This new proposed study can be a dose-ranging superiority study or a non-inferiority study comparing ST-605 to Trifluridine or Acyclovir 3% if a clinically meaningful margin can be agreed upon.

1.2 Brief Overview of Clinical Studies

All trials were open label, multi-center, randomized, stratified by study center, with the exception of Study 6, which was conducted at multiple sites within one center. Studies 4 and 6 had three arms comparing ST-605 to Acyclovir and a lower dose of Ganciclovir 0.05%. Studies 5 and 7 were two arm studies comparing ST-605 to Acyclovir. The summary of all clinical studies is presented in Table 1.

1.3 Statistical issues and finding

The two main issues in this application are the re-evaluation of the evidence and the derivation of the non-inferiority margin. The re-evaluation encompasses a change of hypothesis test from pre-planned failed superiority to post-hoc non-inferiority and a change of endpoint from time to first healing to first time healing rate at anytime, and changed again to recovery rate at day 7. In addition, the review of historical data and derivation of the non-inferiority margin conducted by sponsor was inadequate. So, in this statistical review we re-examined the evidence and conducted our own extensive analysis. Our analysis demonstrated that the historical data presents heterogeneous results and the non-inferiority margin should be considered with caution.

In summary, the current submission is not adequate as it does not provide substantial evidence of efficacy required for the approval of this indication in the US. Our main objections are as follows:

- The pre-planned hypothesis of superiority using the efficacy endpoint of time to healing, failed using the data from a single, open label Phase 3 trial.
- Both the current sponsor's analysis, and the reviewer's exploratory analysis used different endpoints and different hypotheses than the ones originally planned. Thus, results of these analyses have the potential for multiple testing errors as any post-hoc exploratory analysis has.
- The reviewer's derivation of the effect size and review of literature showed substantial heterogeneity among historical data. The value of the effect size is highly sensitive to the subset of included studies in the analysis, which reduces the confidence on the validity of the non-inferiority margin.
- The active control used in this trial, Acyclovir 3% ophthalmic ointment is not an FDA approved comparator for this indication. Furthermore, Acyclovir 3% failed to demonstrate superiority to Trifluridine, the current standard of care in the United States. Thus, the current trial does not provide any persuasive evidence that ST-605 would be non-inferior, much less superior, to the standard of care Trifluridine.

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2 INTRODUCTION

2.1 Class and Indication

ST-605 is an ophthalmic gel formulation of ganciclovir 0.15% for topical instillation. Ganciclovir (9-(1,3-dihydroxy-2-propoxymethyl) is a synthetic guanine derivative antiviral drug that is active in vitro and in vivo against herpes simplex viruses (HSV), the cause of acute herpetic keratitis.

2.2 History of drug development

ST-605 is marketed outside of the US under the trade name Virgan[®] by Laboratoires Théa (formerly Transphyto). Marketing authorization was first granted in August 1995, under the sponsorship of Laboratoires Transphyto SA (MA No. 339-512-8 NL 19679). In December 2000, Transphyto SA and Laboratoires Théa merged and the marketing authorization for Virgan was transferred to Laboratoires Théa. Since this initial approval, Virgan (ST-605) has been approved in over 30 countries for the treatment of acute herpetic keratitis. Postmarketing data are available from 10 years of patient exposure to more than 1.1 million units of ST-605. This NDA contains all of the nonclinical and clinical data previously submitted by Transphyto SA in support of their European marketing authorizations for ST605 for the treatment of acute herpetic keratitis. Ganciclovir is also marketed internationally as both an oral and intravenous antiviral drug product by Roche, and is marketed under the trade name Cytovene[®] in the US for the treatment of cytomegalovirus retinitis in immunocompromised patients, including patients with AIDS.

2.3 Sponsor's Rationale for the Investigation of ST-605 for Acute Herpetic Keratitis

According to the sponsor, ST-605 was initially developed to address a need for an antiviral therapy for herpetic keratitis that did not show the cytotoxicity of early antivirals (e.g. idoxuridine and vidarabine) or trifluridine. The active comparator was chosen to be Acyclovir 3%.

HSV invades host cells and replicates in the host cell nucleus, causing the death of the cell and the subsequent release of viral particles that may then infect surrounding cells. In the infected host cell, ganciclovir is phosphorylated to ganciclovir triphosphate, the active form of the drug, which inhibits DNA polymerase and is incorporated into the DNA, blocking the synthesis of viral DNA.

2.4 Studies in this submission and major statistical issues

The clinical efficacy results presented by the sponsor are based on the data from three Phase 2 (Study 4,5, 6) and one open label Phase 3 clinical trials (study 7), which were

part of the EU marketing application. All trials were conducted prior to 1995, multi-sites with centers in Europe, Africa and Pakistan. Acyclovir 3% ophthalmic ointment was used as the active control in all these studies. All trials were open label, multi-center, randomized, stratified by study center with the exception of Study 6, which was conducted at multiple sites within one center. Studies 4 and 6 had three arms comparing ST-605 to Acyclovir and a lower dose of Ganciclovir 0.05%. Studies 5 and 7 were two arm studies comparing ST-605 to Acyclovir. The dosing regimen for ST-605 was the same in Studies 4, 5, and 7 (i.e. 5 times per day until the ulcer healed, then 3 times per day for 7 days), which corresponds with the dosing regimen that is proposed for the marketed product. Study 6 maintained dosing at 5 times per day for 10 days.

Table 1 shows the location, design and treatment duration for all clinical trials submitted in this NDA. The main statistical issues are with re-evaluation the evidence, change of hypothesis test, change of primary endpoint, choice of historical evidence findings, and derivation of the non-inferiority margin.

Table 1. Phase 1, 2, and 3 Trials Contributing Safety Information for ST-605

| Study ID/Protocol No. | Locations | Study Designs | Treatment/Duration |
|--|---|--|--|
| Study 1 Protocol No.: 64.GV550/04.92 | Hôtel-Dieu Hospital, Paris, France | Single-center, open-label ST-605 or GCV 0.05% | 1 drop 5×/day until the ulcer healed, then 3×/day for 7 days (11-15 days) N=24 ST-605: n=11 |
| Study 2 Protocol No.: F-94-02 | Centre d'Investigation Clinique, Toulouse, France | Single-center, open label ST-605 | 1 drop 4×/day for 1 day |
| Study 3 Protocol No.: F-94-01 | Centre d'Investigation Clinique, Toulouse, France | Single-center, double-masked, randomized, intra-individual (right vs left eye) ST-605 in 1 eye and vehicle in opposite eye | 1 drop in conjunctival sac 5×/day for 7 days |
| Study 4 Protocol No.: 42-2.GV550/02.90 | Mali (Bamako); Senegal (Dakar); Tunisia (Sousse, Tunis) | Comparative, multicenter, randomized ST-605 or ACV 3% or GCV 0.05% | 1 drop 5×/day until the ulcer healed, then 3×/day for 7 days for a maximum of 21 days N=67 ST-605: n=23 ACV 3%: n=22 GCV 0.05%: n=22 |

| | | | |
|--|--|---|---|
| Study 5 Protocol Nos.: 44.GV550/ 12.90 46.GV550/ 07.90 | France (Brest, Clermont-Ferrand); Switzerland (Lausanne); United Kingdom (Bristol) | Comparative, multicenter, randomized ST- 605 or ACV 3% | 1 drop 5×/day until the ulcer healed, then 3×/day for 7 days for a maximum of 21 days N=35 ST-605: n=18 ACV 3%: n=17 |
| Study 6 Protocol No.: 47.GV550/ 09.90 | Pakistan (Karachi) | Comparative, multicenter, randomized, single-masked ST-605 or ACV 3% or GCV 0.05% | 1 drop 5×/day for 10 days. N=109 ST-605: n=36 ACV 3%: n=38 GCV 0.05%: n=45 |
| Study 7 Protocol Nos.: 64.GV550/ 04.92 66.GV550/ 06.92 | France (Aulnay-Sous- Bois, Bobigny, Bordeaux [2 sites], Brest, Chambéry, Chateaulin, Clermont- Ferrand [5 sites], Cournon, Le Golfe Juan, Lesneven, Marseille, Palaiseau, Paris [2 sites], Thiers, Toulon); Mali (Bamako); Madagascar (Tananarivo); Switzerland (Sousse); United Kingdom (Birmingham, Bristol, Dublin, London) | Comparative, multicenter, randomized, stratified by ulcer type ST-605 or ACV 3% | 1 drop 5×/day until ulcer healed, then 3×/day for 7 days for a maximum of 21 days for dendritic ulcers and 35 days for geographic ulcers N=164 ST-605: n=84 ACV 3%: n=80 |

2.4.1 Post-hoc change of hypothesis from superiority to non-inferiority

The sponsor's justification of the change of hypothesis is as follows:

“The original statistical analysis conducted for Study 7 was based on a superiority hypothesis, with a 20% improvement in recovery rate postulated for ST-605 compared with topical ophthalmic acyclovir 3%. The sample size was calculated on this basis, but the results of the efficacy analysis showed that efficacy was comparable between the 2 treatment groups, and thus the study failed to meet the superiority margin required. A strong argument can be made that the original statistical analysis should have been designed to show noninferiority, with the possibility of superiority, based on the results of previous trials of ST-605 against acyclovir 3%. Although the results were not statistically significant for the superiority of ST-605 in comparison with acyclovir 3%, it was clear that ST-605 was as effective as acyclovir 3% in healing acute herpetic ulcers.”

This sponsor's rationale goes against our recommendation to pre-specify non-inferiority hypothesis to protect against possible sources of bias and multiple testing as stated in the ICH E10 guidance for industry

"Historical evidence of sensitivity to drug effects can, and should, be evaluated before beginning a non-inferiority trial. Specifically, it should be determined that, in the specific therapeutic area under study, appropriately designed and conducted trials that used a specific active treatment, or other treatments with similar effects, reliably showed an effect. Optimally, this is demonstrated by finding that the active treatment intended for use as the active control was reliably found superior to placebo. If this is the case, there is historical evidence of sensitivity to drug effects for similarly designed active control." (page 9 of ICH E-10 report).

2.4.2 Integrated analysis

The original sponsor claim of non-inferiority relied on failing to show superiority in the Phase 3 trial (Study 7). The current sponsor based their non-inferiority claim on the integrated analysis pooling the data from all three Phase 2 studies and the Phase 3 study. However, during clinical development, the preservative used in the ST-605 formulation was changed from sodium mercurothiolate 0.006% (used for Studies 1, 4, 5, and 6) to benzalkonium chloride 0.0075% (used for Studies 2, 3, and 7). Since changing the preservative could have an effect on the efficacy of an ophthalmic drug, the reviewer's analysis presents the results based on the data from Study 7 only.

2.4.3 Change of primary endpoint

The data on HSV progression, in Study 7, was collected over time for two types of ulcers: Dendritic and Geographic. Three questions of interest to determine an appropriate endpoint are: (1) what is a success for HSV keratitis? (2) when to determine the success which is clinically meaningful? and (3) for which patient group? The answers to these three questions were different in the pre-planned design by the original sponsor, in the re-analysis submitted by the current sponsor and in the reviewer's analysis. The original sponsor answered these three questions by the endpoint time to first healing, within the first 3 weeks of treatment for Dendritic ulcer. The current sponsor answers these same questions by the endpoint first time healing rate, at *anytime*, for Dendritic and Geographic ulcers. The current sponsor used yet another endpoint, first time healing rate at day 14, for deriving the non-inferiority margin. The clinical review team considered the current sponsor's endpoints inappropriate and instead answered the questions of interest by the endpoint healing rate at day 7 for Dendritic ulcer. In the reviewers' definition, recurrence of the lesions or breakdown of the epithelium on or after day 7 is a failure. The choice of day 7 instead of day 14 was motivated by the disease evolution over time as presented in the published literature. The choice of looking at Dendritic ulcer only for primary endpoint was motivated by the great clinical differences between the two types of ulcer: Dendritic and Geographic. Missing observations before healing were considered failures, whereas missing observations after healing were considered successes.

2.4.4 Choice of historical evidence

The current sponsor's and the reviewer's analyses used the 2008 Cochrane review, "Therapeutic interventions for herpes simplex virus epithelial Keratitis" by Wilhemus K. R., to identify the relevant studies for the derivation of the non-inferiority margin. However, the sponsor was interested in a different endpoint: recovery rate at day 14, and has used the numbers reported in the review, not the numbers in the original articles. We reviewed the original publications in each study to derive the recovery rate at day 7.

2.4.5 Derivation of non-inferiority margin

The sponsor obtained the non-inferiority margin by deriving the pooled placebo recovery rate at day 14 from 3 different studies (48%), then deriving the pooled active comparator recovery rate at day 14 from several studies (87%). The sponsor finally claims "Therefore, a noninferiority limit of 18.5% was prospectively chosen, which preserves 50% of the advantage of active (i.e. acyclovir) over placebo."

As stated in the ICH E10 guidance for industry, the margin in a non-inferiority trial should find the smallest effect size that the active drug would be reliably expected to have compared with placebo. Since the margin should reflect the smallest effect size, the margin calculation should account for the sampling variability in each trial and the possible heterogeneities between trials. The sponsor's derivation simply pooled point estimates from different selected historical studies and completely ignored sources of variability. By contrast, our analysis accounts for these sources of variation.

2.5 Data sources

Sponsor's data sets are available in [\CDSESUB1\EVSPROD\NDA022211\0005](#)

2.6 Prior Regulatory Guidance

Orphan Drug Designation in the US was granted on March 22, 2007 for ST-605 for the treatment of acute herpetic keratitis (dendritic and geographic ulcers). The Orphan Designation number is 07-2376. Subsequently, Sirion requested a Type B meeting, which was scheduled for May 23, 2007, to obtain the FDA feedback on the existing clinical database in support of an NDA for ST-605. The FDA provided a written response containing questions about the microbiology, clinical, and statistical portions of the package. To respond to these questions, Sirion requested a second Type B meeting, which was scheduled for November 5, 2007, and prepared a briefing package which included an integrated summary of efficacy and an integrated summary of safety for the product.

3 STATISTICAL EVALUATION

3.1 Study Design and Endpoints (Study 7)

Study 7 was an open label study, multicenter, two arms, stratified by center and ulcer type (Dendritic or Geographic).

Exclusion criteria

Exclusion criteria were as follows

At the ophthalmic level

1. development period greater than 7 days,
2. antiviral treatment in the preceding 14 days,
3. severe stromal damage,
4. kerato-uveitis,
5. keratoplasty of the affected eye,
6. bacterial corneal or conjunctival secondary infection,
7. recent ocular traumatism, except phototraumatism,
8. contralateral visual acuity of the eye less than 2/10

At the general level

1. age less than 18 years,
2. person of age under care,
3. known hypersensitivity to acyclovir or ganciclovir,
4. known leukopenia, anaemia, thrombocytopenia,
5. pregnant or breastfeeding woman, or who is not using an effective means of contraception (In Ireland, this criterion was replaced with "non-menopausal woman")
6. patient treated with zidovudine (RETROVIR®).

Frequency and duration of treatment

The two arms have same treatment frequency and duration of treatment.

ST-605

First, administer of one drop of ST-605, 5 times per day until complete healing of the ulcer. Then, continue administering one drop of ST-605 but only 3 times a day for 7 days.

Acyclovir 3% ointment

First, administer a strip of acyclovir ointment in 5 applications per day until complete healing of the ulcer. Then, continue with 1 application but only 3 times per day for 7 days.

The total duration of each treatment is not to exceed three weeks for Dendritic ulcers and five weeks for Geographic ulcer.

Planned control dates

During this clinical trial, three visits on D3, D7 and D10 were mandatory. Any later visits were dependent on recovery date, with it being necessary to see the patient one week after recovery.

Planned sample size

The study initially planned to recruit a total of 100 Dendritic ulcers, with Geographic ulcers recruited in addition. The number of cases necessary was later increased, by amendment (Amendment of March 1994), to 130 Dendritic ulcers.

Sponsor's justification of the amendment is as follows: "This amendment related to the increasing in the number of Patients required, following the re-evaluation of this figure on the basis of the results from previous studies....The favourable recommendation of the Brest CCPPRB, included as Annex A, was given on 12 April 1994."

Reviewer's comment: the mathematical derivation of sample size accompanying the request for increase of sample size was poorly written without reference to the methodology used in the derivation. In addition, the guesses for effect size assumed a 20% difference in recovery rates between the two groups with a superiority hypothesis. This large difference was grossly overstating the observed recovery rate observed in the Phase 2 trials.

Primary endpoint

The data on HSV progression, in Study 7, was collected over time for two types of ulcers: Dendritic and Geographic. Three questions of interest to determine an appropriate endpoint are: (1) what is a success for HSV keratitis? (2) when to determine the success which is clinically meaningful? and (3) for which patient group? The answers to these three questions were different in the pre-planned design by the original sponsor, in the re-analysis submitted by the current sponsor and in the reviewer's analysis. The original sponsor answered these three questions by the endpoint time to first healing, within the first 3 weeks of treatment for Dendritic ulcer. The current sponsor answers these same questions by the endpoint first time healing rate, at *anytime*, for Dendritic and Geographic ulcers. The current sponsor used yet another endpoint, first time healing rate at day 14, for deriving the non-inferiority margin. The clinical review team considered the current sponsor's endpoints inappropriate and instead answered the questions of interest by the endpoint healing rate at day 7 for Dendritic ulcer. In the reviewers' definition, recurrence of the lesions or breakdown of the epithelium on or after day 7 is a failure. The choice of day 7 instead of day 14 was motivated by the disease evolution over time as presented in the published literature. The choice of looking at Dendritic ulcer only for primary endpoint was motivated by the great clinical differences between the two types of ulcer: Dendritic and Geographic. Missing observations before healing were considered failures, whereas missing observations after healing were considered successes.

Other endpoints

In addition to the three endpoints discussed above: time to 1st healing, recovery rate at day 7, recovery rate at day 14, recovery rate at anytime, sponsor considered the number of relapses, and investigator assessment of efficacy.

3.2 Review of historical data on efficacy

The 2008 Cochrane review “Therapeutic interventions for herpes simplex virus epithelial Keratitis” by Wilhemus K. R. compared different treatments of HSV. These findings were based on published results from 99 trials that randomized a total of 5363 participants. From the published results, Wilhemus extracted the recovery rates at day 7 and recovery rates at day 14, when they were available.

Sponsor’s review of historical data

There are some similarities and some important differences between our review of historical data and the sponsor’s review of historical data submitted as part of this NDA. The commonality is that the two analyses used the Cochrane review study to identify the relevant subset of trials which included either Placebo or Acyclovir in one of the arms of their design. Sponsor also provided narratives on all Placebo trials as supportive evidence, but did not use the numbers from most trials to derive the non-inferiority margin. The differences in the sponsor’s derivations and ours are: first, sponsor was interested in a different endpoint to derive the non-inferiority margin: recovery rate at day 14. Second, sponsor used the numbers reported in the Cochrane review, not the numbers in the original articles, to derive the margin. Third, sponsor did not include all the trials cited in Wilhemus. Fourth, sponsor included the studies presented in this NDA in its derivation. Fifth, the endpoint used for the non-inferiority derivation (healing rate at day 14) is different from the endpoint used for efficacy assessment (1st time healing rate at anytime). Last but not least, the derivation of the effect size M1 was simply a difference between the pooled recovery rate for Acyclovir and the pooled recovery rate for Placebo. This estimate ignores the heterogeneity between studies and does not account for sampling variability.

Our review of historical data

In our review, we used the trials which included either Placebo or Acyclovir in one of the arms of their design. While checking the original publications, we noticed that some of the recovery rates quoted in the Cochrane review did not match the original publications. These discrepancies were discussed with Wilhemus, the author of the review, and he agreed to our corrections. Thus, we used a relevant subset of publications from the set of publications identified by the Cochrane review, but the recovery rates presented in our review are the ones derived from the original publications. We used these publications to derive healing rate estimates at day 7 for Dendritic ulcer, the same endpoint we use for efficacy analysis.

Our summary of the studies’ design as well as a reference for the accompanying publication are presented in Table 2, Table 3 and Section 6. Due to the seriousness of the disease and availability of first generation anti-virals when Acyclovir was developed, this drug was never compared to Placebo. Instead of a direct comparison to Placebo,

Acyclovir was compared to first generation drugs Idoxuridine and Vidarabine and second generation drugs Trifluridine and Ganciclovir. The published studies comparing Acyclovir to Ganciclovir were excluded from our non-inferiority margin derivation because all the published studies comparing these two drugs are the same studies as in this NDA. As we see in Table 2 and Table 3, for the endpoint of interest: healing at 7 days, 13 studies had placebo in one arm and 15 studies had Acyclovir in one arm. Among the Placebo studies, Placebo was compared to Idoxuridine in the majority of studies (10 studies) and the remaining studies were comparing Placebo to Interferon (3 studies). Among the Acyclovir studies, Acyclovir was compared either to Idoxuridine (7 studies), vidarabine (4 studies), Trifluridine (3 studies) or Iododesoxycytidine (1 study). Four of the Acyclovir publications did not provide enough information to separate the Dendritic ulcer's recovery rate from the Geographic ulcer's recovery rate.

The validity of any conclusion from a NI study depends on the choice of the historical active control effect over placebo (MI) and the determination of the NI margin based on the preservation of the control effect using clinical judgment. A non-inferiority margin is meaningful when the following two assumptions are valid: *assay sensitivity* of current trial(s) and the *constancy* of the active control treatment effect in the historical studies and the current trials. There was no evidence of lack of assay sensitivity in the trials submitted in this NDA. However, the constancy assumption is hard to claim in this case as the design of the historical studies differed from each other and from the current design. As mentioned above a direct comparison of Acyclovir to Placebo is impossible as no study investigated Acyclovir arm and Placebo arm in the same trial. The meaning of placebo differed among the Placebo studies as shown in the last column of Table 3. Moreover, the quality and the published information on the studies vary widely in the extensive study summary in Section 6. The treatment assignment was not randomized or was unspecified in half of the Placebo studies. All published historical studies were small with most of them having less than 20 patients per arm and conducted in one center. The study centers locations varied widely from Japan (7 studies), Europe (4 studies in France, 5 studies in the United Kingdom, 3 studies in the United States and 1 study in each of Ireland, Norway, Denmark, Netherlands, Canada and the Australia). All studies reported the per protocol efficacy rate and very few give enough information to derive the intent to treat efficacy rate. The primary endpoint adjudication also varied with most of the Acyclovir trials determining healing by fluorescein dye, but most of the Placebo studies being vague on how healing was determined. Most studies report the aggregate primary and recurrent infection recovery rate and the recovery rate is known to be different in each of these subgroups. The use of concomitant medication including corticosteroids also varied from study to study and this concomitant drug is known to affect the healing rate.

Table 2: Acyclovir historical data

| Acyclovir | Healing rate-Dendritic and Geographic | Healing rate-Dendritic only | Comparator |
|-----------|---------------------------------------|-----------------------------|------------|
| Abe 1987 | 61% (11/18) | 60% (9/15) | IDU |

| | | | |
|---------------|-------------|-------------|-------|
| Colin 1981 | 76% (19/25) | 76% (19/25) | IDU |
| Colin 1984 | 67% (10/15) | NA | IDO |
| Collum 1980 | 97% (29/30) | 97% (29/30) | IDU |
| Coster 1980 | 90% (26/29) | 96% (27/28) | IDU |
| Denis 83 | 90% (6/24) | NA | Ara-A |
| Hoang Xuan 84 | 43% (9/18) | NA | TFT |
| Hovding 89 | 72% (18/25) | 72% (18/25) | TFT |
| Jackson 84 | 81% (26/32) | NA | Ara-A |
| Kitano 83 | 74% (40/54) | NA | IDU |
| Klauber 1982 | 67% (12/18) | 80% (8/10) | IDU |
| La Lau 82 | 68% (21/31) | 68% (21/31) | TFT |
| McCulley 1982 | 63% (19/30) | 62% (16/26) | IDU |
| Yeakley 81 | 89% (17/19) | 94% (17/18) | Ara-A |
| Young 82 | 69% (33/48) | 68% (27/40) | Ara-A |

Ara-A: Vidarabine; TFT: Trifluridine; IDU: Idoxuridine; IDO: Iododesoxycytidine

Table 3: Placebo historical data

| Study | Healing rate-Dendritic only | Healing rate-Dendritic and Geographic | Comparator | Meaning of Placebo |
|------------------|-----------------------------|---------------------------------------|------------|--------------------------|
| Burns 1963 | 33% (5/15) | 33% (5/15) | IDU | Water |
| Davidson 1964 | 32% (8/25) | 32% (8/25) | IDU | Gamma Globulin |
| Hart 1965 | 15% (2/13) | 15% (2/13) | IDU | Neosporin |
| Laibson 1964 | 27% (7/26) | 25% (13/53) | IDU | Water and Thimersol |
| Markham 1977 | 21% (4/19) | 20% (4/20) | IDU | Ointment and homatropine |
| Luntz 1963 | 45% (5/11) | 45% (5/11) | IDU | Neosporin |
| Patterson-a 1963 | 38% (5/13) | 38% (5/13) | IDU | Culture medium |
| Patterson-b 1963 | 13% (2/15) | 13% (2/15) | IDU | Phenyl mercuric nitrate |
| Patterson-c 1963 | 0% (0/14) | 0% (0/14) | IDU | Occlusive dressing |
| Uchida 1981 | 25% (1/4) | 25% (1/4) | INT | Gentamycin and albumine |
| Yamazaki-b 1984 | 41% (17/41) | 41% (17/41) | INT | Albumin solution |
| Yamazaki-c 1984 | 30% (6/20) | 30% (6/20) | INT | Low dose interferon |

IDU: idoxuridine; INT: Interferon

3.3 Derivation of Non-inferiority margin for efficacy

To derive the NI margin based on the log odds ratio or the difference in proportions requires comparing Acyclovir to Placebo. Since this direct comparison is not available in any of the published studies, we used two different indirect comparison methods to derive the estimated effect size M1. In both methods, M1 was derived

- for the difference in healing rate as well as for the log odds ratio between the two treatments: Acyclovir and Placebo,
- as the lower bound of a 95% confidence interval for difference in healing rate or log odds ratio respectively;
- for Dendritic ulcer only or for Dendritic and Geographic ulcer.

The results are summarized in Table 8 with values of M1 ranging from 14% to 30% for healing rate difference and from 0.8 to 1.29 for log odds ratio. Details of these derivations are given in the following two subsections. As indicated by the wide range of these estimations, this result is sensitive to the subset of studies included and to the derivation used.

Determination of the non-inferiority margin depends on the estimate of M1 as well as the fraction of M1 that should be preserved based on clinical judgment. Table 9 shows what the non-inferiority margin would be based on the percent preservation of the entire treatment effect over placebo.

3.3.1 Method 1: Indirect comparison of Acyclovir to Placebo through Idoxuridine

In this method, the effect size M1 of Acyclovir versus Placebo is derived by combining the results of two meta analyses. The first meta analysis derives the effect size of Idoxuridine over Placebo using only the studies comparing these two treatments in Table 3. The second meta analysis derives the effect size of Acyclovir over Idoxuridine using only the studies comparing these two treatments in Table 2. By combining these two meta analyses, we can then derive the effect size of Acyclovir over Placebo. More specifically, the estimated effect size M1 using this method is simply the sum of the two lower bounds of the two 95% confidence intervals. By looking at the lower bound of a confidence interval derived from a meta analysis, we take into account the sampling variability of the results as well as heterogeneity between studies.

We used both the difference in healing rate and the log-odds ratio to measure effect size. The effect size was also derived for Dendritic ulcer only and for the pooled Dendritic and Geographic ulcer.

Results for the comparison of Idoxuridine to Placebo are shown in Figures 1-4 and summarized in Table 4. We see in each figure the results of each study as well as the point estimate and confidence interval from the meta analysis. We see from these meta analyses that Idoxuridine is significantly better than Placebo whether we use difference in

healing rates or log odds ratio, whether we are looking at Dendritic or combined Dendritic and Geographic ulcers. The 95% confidence interval for Dendritic ulcer only is (12% to 51%) for difference in healing rate and (0.43 to 2) for log odds ratio. The results are almost identical for the pooled Dendritic and Geographic ulcer.

Results for the comparison of Acyclovir to Idoxuridine are shown in Figures 5-8 and summarized in Table 5. We see in each figure the results of each study as well as the point estimate and confidence interval from the meta analysis. We see from these meta analyses that Acyclovir is significantly better than Placebo whether we use difference in healing rates or log odds ratio, whether we are looking at Dendritic or combined Dendritic and Geographic ulcers. However, the strength of the evidence varies depending on the subset of studies we use. One would expect that the effect size from the pooled Dendritic and Geographic ulcer estimate would be lower because Geographic ulcers are harder to treat. However, this was not the case in this derivation because the subset of study used in the Dendritic analysis on one hand and the pooled Dendritic and Geographic analysis on the other hand is not the same. The Kitano 1983 study only provided pooled estimates of healing rates without distinction of whether the ulcer was Dendritic or Geographic. This study was excluded from the Dendritic ulcer analysis but included in the Dendritic and Geographic ulcer analysis. As summarized in Table 5, including or excluding this study changes both the point estimate and lower bound of the confidence interval in the opposite direction to the one expected. Although the point estimate changes by only 3% from 31% to 34%, the lower bound of the confidence interval changes by 11% (from 2% to 13%). This shows that the results of this derivation are highly sensitive to the subset of studies included in the analysis and that the Kitano 1983 is highly influencing the results.

The heterogeneity in the design that we noted from our literature review were also observed in the numerical results. We see in Figures 1-8 that there is a lot of heterogeneity in the results of the studies. More specifically, we see in each forest plot comparing Idoxuridine to Placebo that some studies favor Idoxuridine whereas others favor Placebo. We see also in each forest plot comparing Acyclovir to Idoxuridine that most studies do not show a significant difference and have a very large confidence interval due to their small sample size. The Collum 1980 study shows a much higher difference than the other studies which is not explained by the design. This study heterogeneity was somewhat accounted for in the meta analysis by deriving the random effect confidence interval.

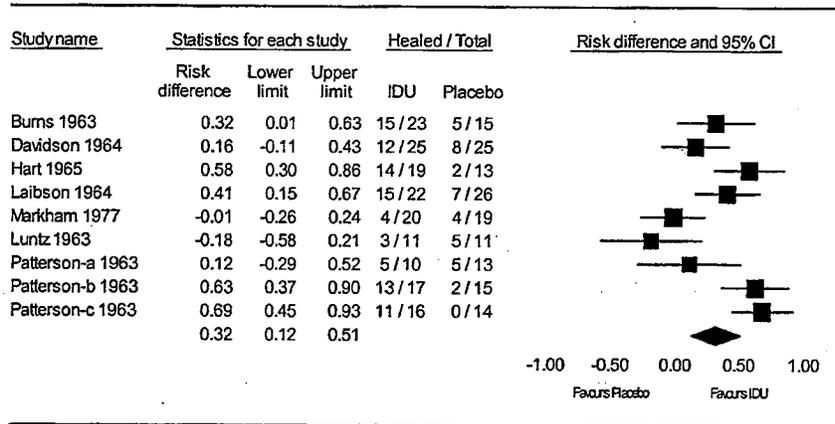


Figure 1: Meta analysis for healing rates comparing Placebo to Idoxuridine (IDU). Results for Dendritic ulcer only.

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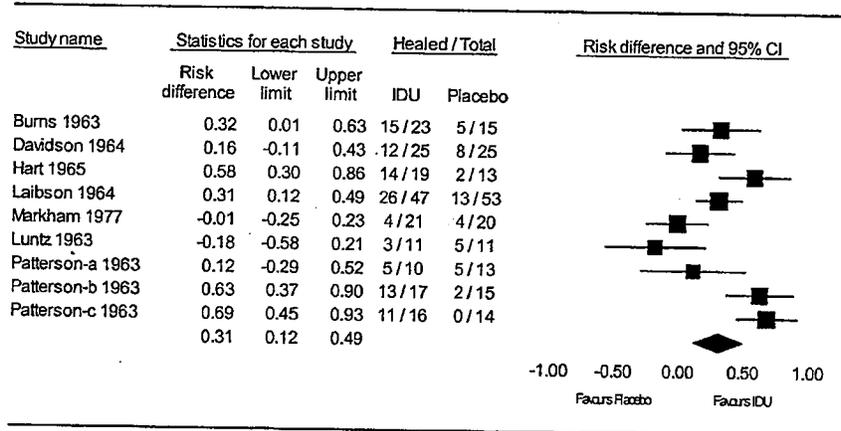


Figure 2: Meta analysis for healing rates comparing Placebo to Idoxuridine (IDU). Results for combined Dendritic and Geographic ulcers.

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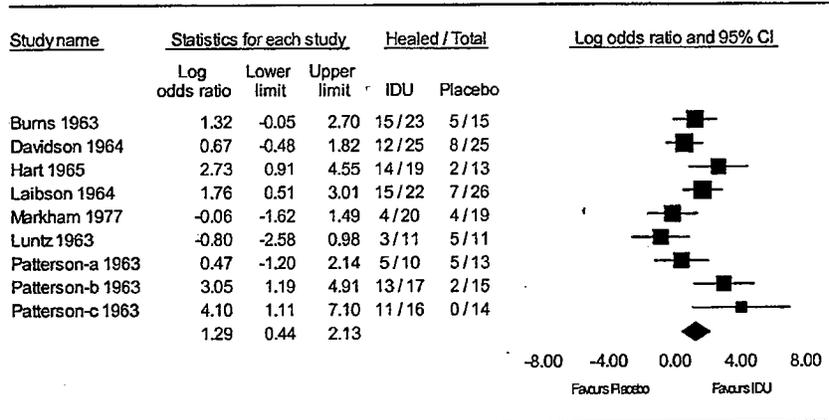


Figure 3: Meta analysis for log odds ratio comparing Placebo to Idoxuridine (IDU). Results for Dendritic ulcer only.

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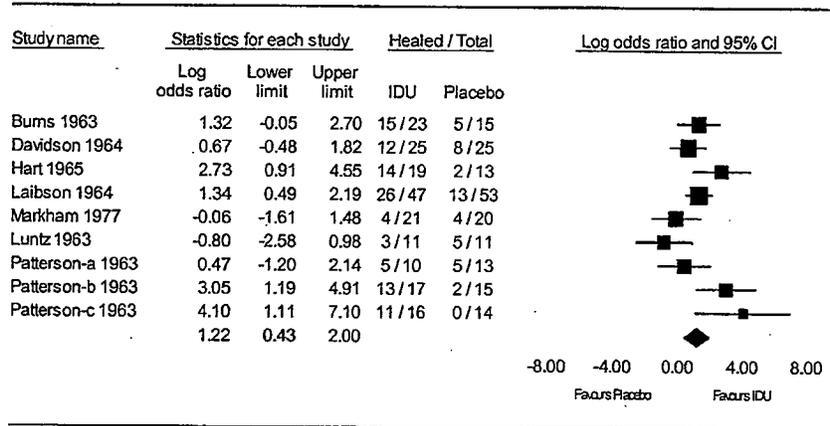


Figure 4: Meta analysis for log odds ratio comparing Placebo to Idoxuridine (IDU). Dendritic and Geographic ulcer.

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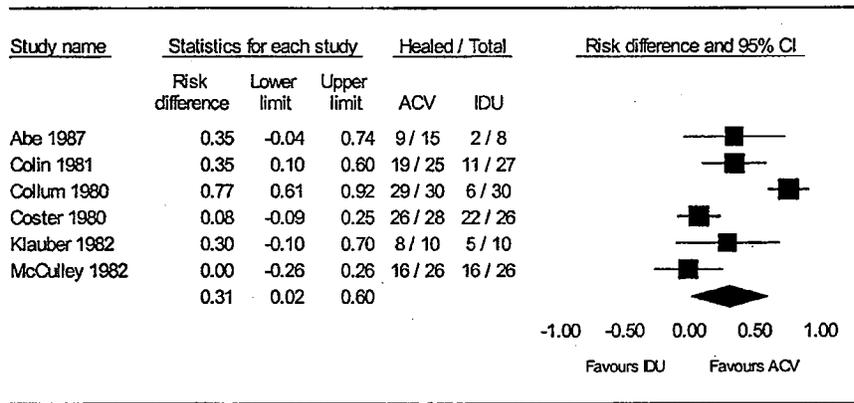


Figure 5: Meta analysis for healing rate comparing Idoxuridine (IDU) to Acyclovir (ACV). Results for Dendritic ulcer only.

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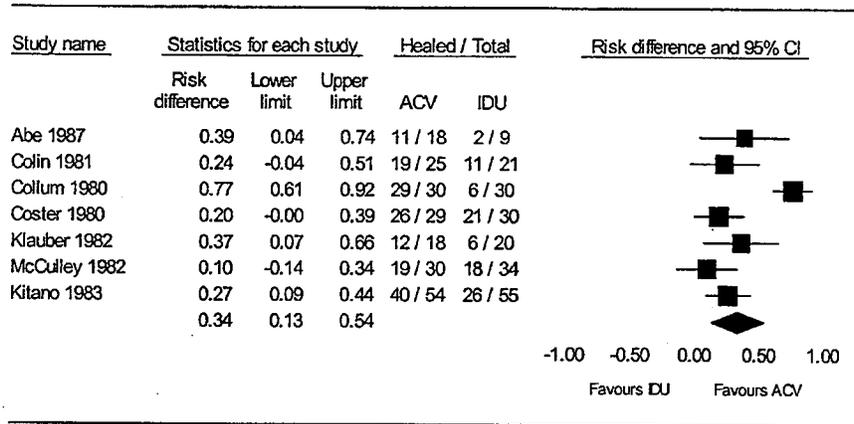


Figure 6: Meta analysis for healing rate comparing Idoxuridine (IDU) to Acyclovir (ACV). Results for pooled Dendritic and Geographic ulcers.

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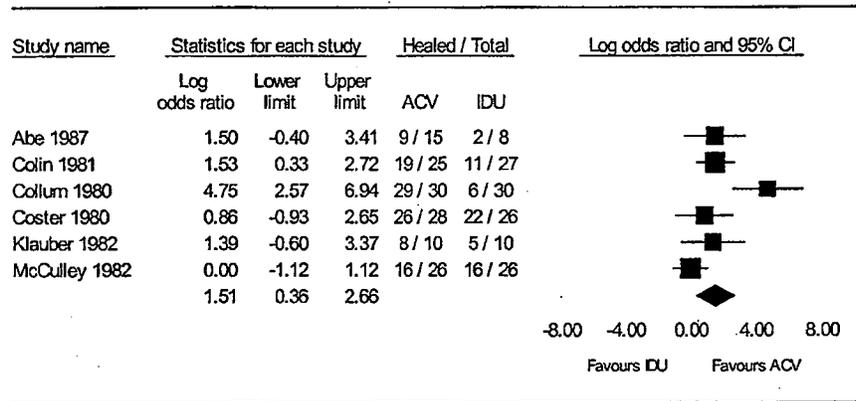


Figure 7: Meta analysis for log odds ratios comparing Idoxuridine (IDU) to Acyclovir (ACV). Results for Dendritic ulcer only.

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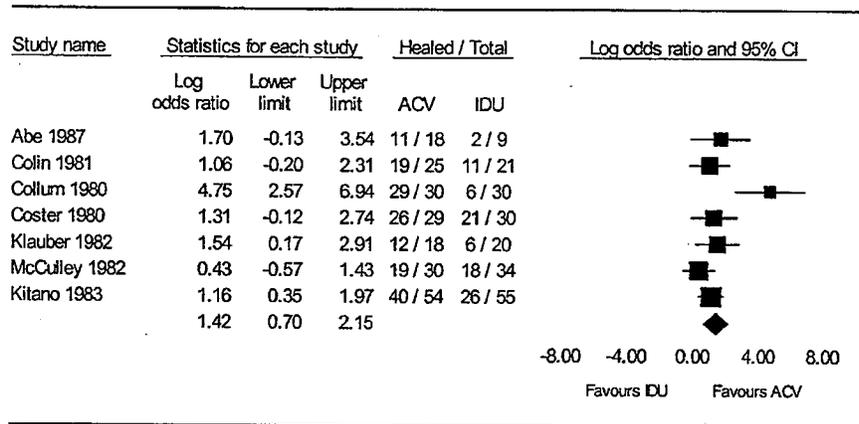


Figure 8: Meta analysis for log odd ratios comparing Idoxuridine (IDU) to Acyclovir (ACV). Results for pooled Dendritic and Geographic ulcers.

Table 4: Summary of meta analyses in Figures 1-4 comparing Idoxuridine to Placebo. Results in this table report the point estimate and 95% confidence interval.

| Comparison | Type of ulcer | point estimate | lower bound | upper bound |
|-----------------------------|--------------------------|----------------|-------------|-------------|
| Difference in healing rates | Dendritic only | 32% | 12% | 51% |
| | Dendritic and Geographic | 31% | 12% | 49% |
| log-odds ratios | Dendritic only | 1.29 | 0.44 | 2.13 |
| | Dendritic and Geographic | 1.22 | 0.43 | 2 |

Table 5: Summary of meta analyses in Figures 5-8 comparing Acyclovir to Idoxuridine. Results in this table report the point estimate and 95% confidence interval.

| Comparison | Type of ulcer | point estimate | lower bound | upper bound |
|-----------------------------|--------------------------|----------------|-------------|-------------|
| Difference in healing rates | Dendritic only | 31% | 2% | 60% |
| | Dendritic and Geographic | 34% | 13% | 54% |

| | | | | |
|-----------------|--------------------------|------|------|------|
| log-odds ratios | Dendritic only | 1.51 | 0.36 | 2.66 |
| | Dendritic and Geographic | 1.42 | 0.7 | 2.15 |

3.3.2 Method 2: Indirect comparison of Acyclovir to Placebo through Idoxuridine, Trifluridine and Vidarabine

In this method, the healing rate for Placebo is first derived using all the studies with placebo in one arm, regardless of what the comparator is in the other arm (i.e. all studies identified in Table 3). Similarly, the Acyclovir healing rate is derived using all the studies with Acyclovir in one arm, whether the comparator is Idoxuridine, Vidarabine, or Trifluridine (i.e. all studies identified in Table 2). The rate pooling in this method was done in each case using a logistic regression. This regression was fit with a random effect to account for the over-dispersion due to the heterogeneity between the studies. The logistic regression fits are shown in Table 6. These fits were used to derive the estimates and confidence intervals for the difference in healing rate estimates as well as the log odds ratios. The result of these derivations is shown in Table 7. Finally, the estimate of the effect size M1 is the lower bound of the derived estimates shown in Table 7. We see from this table that M1 is 31% for difference in healing rate with Dendritic only or pooled Dendritic and Geographic. The log odds ratio for M1 is 1.31 for Dendritic only and 1.29 for Dendritic and Geographic.

Table 6: Method 2. Results of the 4 logistic regressions (point estimate, 95% confidence interval, overdispersion parameter and degrees of freedom).

| Logit of healing rate | | point estimate | Lower bound | upper bound | Overdispersion (df) |
|-----------------------|--------------------------|----------------|-------------|-------------|---------------------|
| Placebo | Dendritic only | -0.91 | -1.26 | -0.57 | 1.34 (11) |
| | Dendritic and Geographic | -0.95 | -1.29 | -0.62 | 1.42 (11) |
| Acyclovir | Dendritic only | 1.21 | 0.73 | 1.73 | 2.84 (9) |
| | Dendritic and Geographic | 0.99 | 0.67 | 1.33 | 2.28 (14) |

Table 7: Method 2. Derived estimates for difference in healing rate and log odds ratio.

| Derived estimates | | Point estimate | lower bound | upper bound |
|----------------------------|--------------------------|----------------|-------------|-------------|
| Difference in healing rate | Dendritic only | 48% | 31% | 63% |
| | Dendritic and Geographic | 45% | 31% | 58% |
| Log odds ratio | Dendritic only | 2.12 | 1.31 | 2.99 |
| | Dendritic and Geographic | 1.94 | 1.29 | 2.63 |

3.3.3 Summary of results and non-inferiority margin

By construct, the studies used to derive the estimates of Method 1 are a subset of the studies used to derive the estimates in Method 2. Method 1 controls for within study variation by estimating the treatment effect difference whereas Method 2 does not control for this variability. We see in Table 8 that although M1 does not vary between the two methods, the point estimates for the difference in healing rate between Acyclovir and Placebo vary by as much as 15%. The reason for this apparent contradiction is that the second method uses a larger number of studies which result in smaller confidence intervals than Method 1.

From the results in Table 8, it is hard to draw an appropriate Non-inferiority margin as it is clear that study results are heterogeneous and sensitive to the methodology used. The non-inferiority margin takes into account the value of M1 as well as a discounting factor. We show in Table 9 the value of non-inferiority margin for different discounting factors. For example, for a 50% discounting factor, the non-inferiority margin varies from 7% to 15.5% for difference in healing rate and from 0.4 to 0.66 for log odds ratio depending on the method used for the derivation.

Table 8: Effect Size M1. Summary of Results from Method 1 and Method 2

| | Number of included studies | Point estimate of difference in healing rates | M1 for difference in healing rates | Point estimate for log odds ratio | M1 for log odds ratio |
|-----------------------------------|---|---|------------------------------------|-----------------------------------|-----------------------|
| Method 1-Dendritic | 6 studies for ACV vs IDU and 9 studies for IDU vs Placebo | 63% | 14% | 2.8 | 0.8 |
| Method 2-Dendritic | 10 ACV studies and 12 Placebo studies | 48% | 31% | 2.12 | 1.31 |
| Method 1-Dendritic and Geographic | 7 studies for ACV vs IDU and 9 studies for IDU vs Placebo | 65% | 25% | 2.64 | 1.13 |
| Method 2-Dendritic and | 15 ACV studies and 12 Placebo | 45% | 31% | 1.94 | 1.29 |

| | | | | | | |
|------------|---------|--|--|--|--|--|
| Geographic | studies | | | | | |
|------------|---------|--|--|--|--|--|

M1 is the estimated effect size

Table 9: Non-inferiority margins for difference in healing rate or log odds ratio at day 7. Non-inferiority margins were derived for different percent of preservations of treatment effect over placebo.

| Measure of healing | Percent Preservation | M1: 0% | 10% | 25% | 50% | 75% | 90% |
|-----------------------------------|-----------------------------------|--------|-------|-------|-------|------|------|
| Difference in healing rate | Method 1-Dendritic | 14% | 12.6% | 10.5% | 7.0% | 3.5% | 1.4% |
| | Method 2-Dendritic | 31% | 27.9% | 23.3% | 15.5% | 7.8% | 3.1% |
| | Method 1-Dendritic and Geographic | 25% | 22.5% | 18.8% | 12.5% | 6.3% | 2.5% |
| | Method 2-Dendritic and Geographic | 31% | 27.9% | 23.3% | 15.5% | 7.8% | 3.1% |
| Log odds ratio | Method 1-Dendritic | 0.80 | 0.72 | 0.60 | 0.40 | 0.20 | 0.08 |
| | Method 2-Dendritic | 1.31 | 1.18 | 0.98 | 0.66 | 0.33 | 0.13 |
| | Method 1-Dendritic and Geographic | 1.13 | 1.02 | 0.85 | 0.57 | 0.28 | 0.11 |
| | Method 2-Dendritic and Geographic | 1.29 | 1.16 | 0.97 | 0.65 | 0.32 | 0.13 |

3.3.4 Comparison of Trifluridine to Acyclovir

Trifluridine is the standard of care in the United States. There are 3 studies comparing Acyclovir to Trifluridine for healing rate at day 7. We see from the meta-analyses shown

in Figure 9 and Figure 10 that the three studies fail to show a significant difference between Acyclovir and Trifluridine.

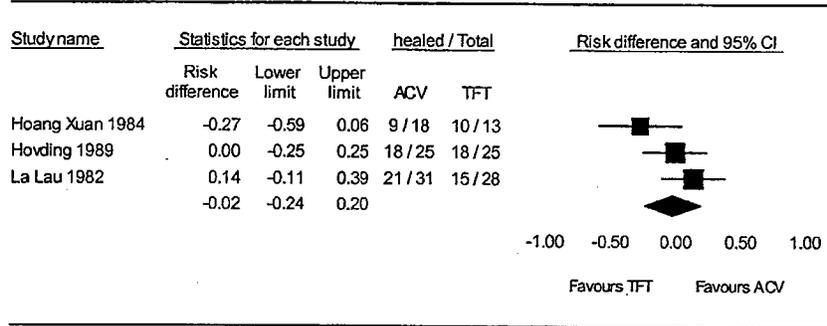


Figure 9: Meta analysis for risk difference comparing Acyclovir to Trifluridine. Dendritic and Geographic ulcer.

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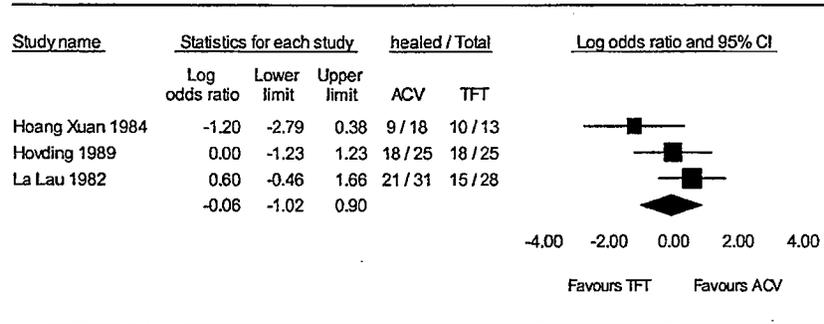


Figure 10: Meta analysis for log odds ratio comparing Acyclovir to Trifluridine. Dendritic and Geographic ulcer.

3.4 Demographic and Baseline Characteristics

There were no significant differences in demographics and baseline characteristics collected by sponsor (sex, age and baseline ulcer size) in Study 7. As shown in Figure 11, 20 out of 67 subjects were female in the Acyclovir group versus 22 out of 71 subjects in the ST-605 group. We see in Figure 12 that the age distribution is similar in both treatment groups. Note that a patient in the Acyclovir group is 4 years old (Patient ID 240). Although the difference in baseline ulcer size is not significant between the two groups, we see in Figure 13 and Figure 14 that the ulcer sizes at baseline are higher in the Acyclovir group. We see from Table 10 that the majority of patients recruited in the trial came from a large number of centers in France while a few centers in each country recruited the remaining number of patients.

Male/Female by treatment group

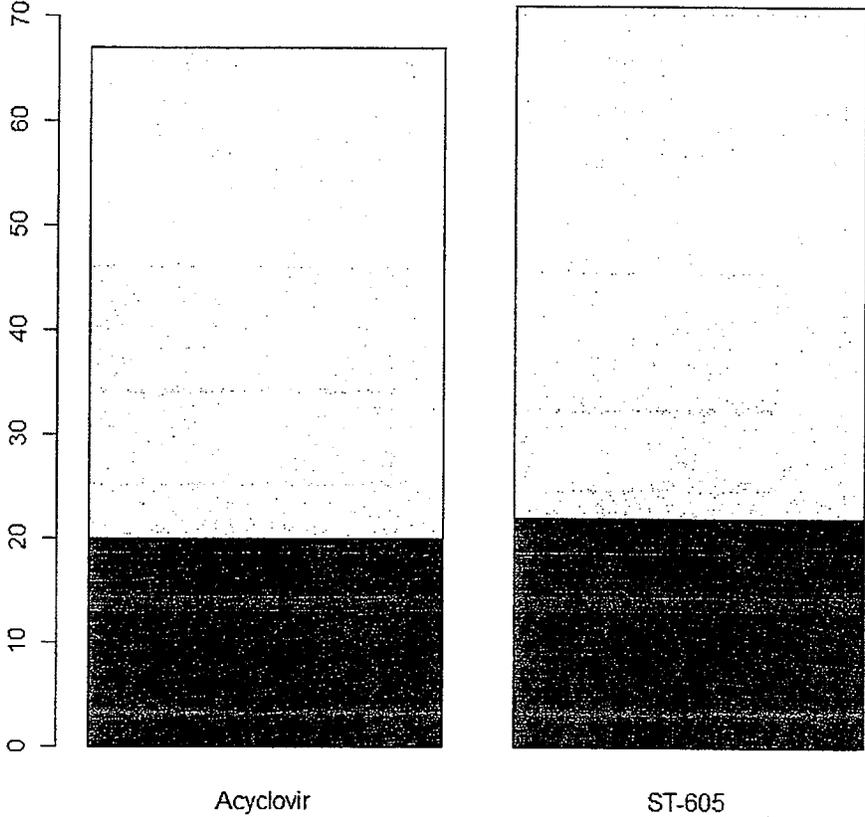


Figure 11: Number of recruited male and female in each treatment group. Female are in dark shade, males are in light shade. The sex distribution seems balanced in the treatment groups.

Age by treatment group

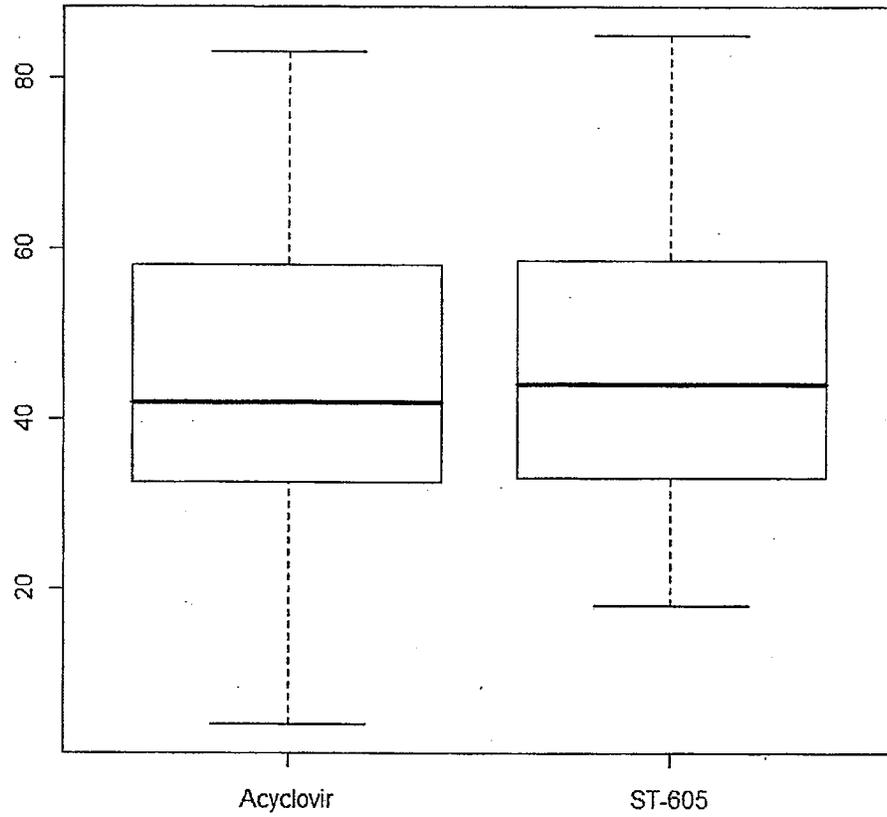


Figure 12: Distribution of age by treatment group. Distribution of age in the two groups is similar. Minimum age in Acyclovir group is 4 years (patient 240).

Baseline lesion size by treatment group

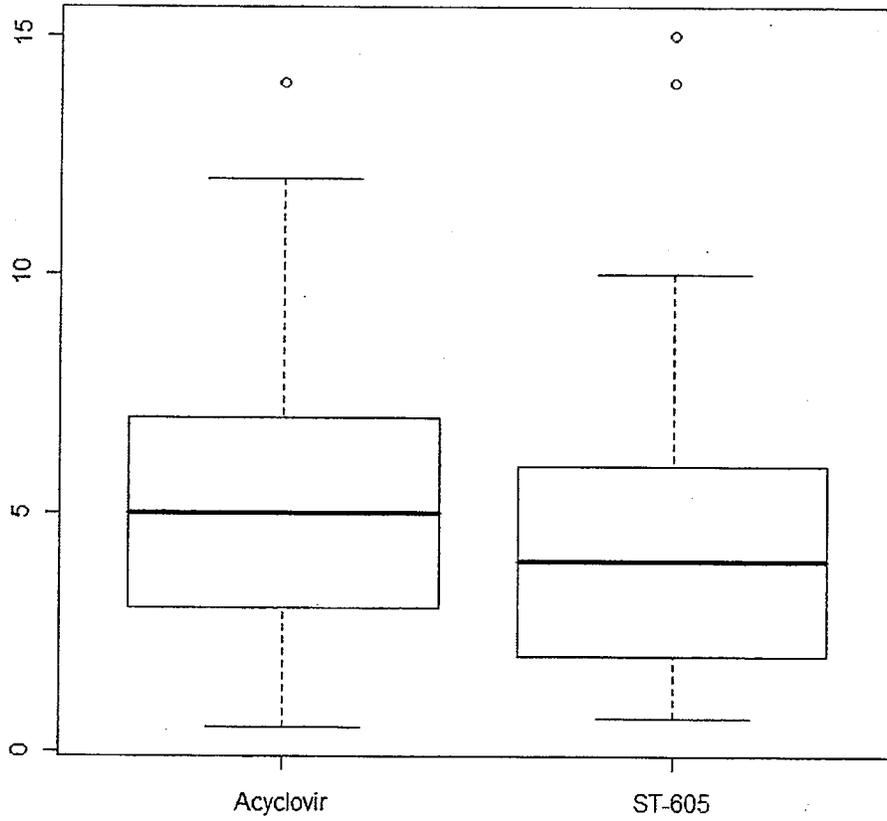


Figure 13: Baseline ulcer size by treatment group. Although the difference in baseline lesion size is not significant, there are more patients with larger ulcer lesions in the active control group than in the ST-605 group.

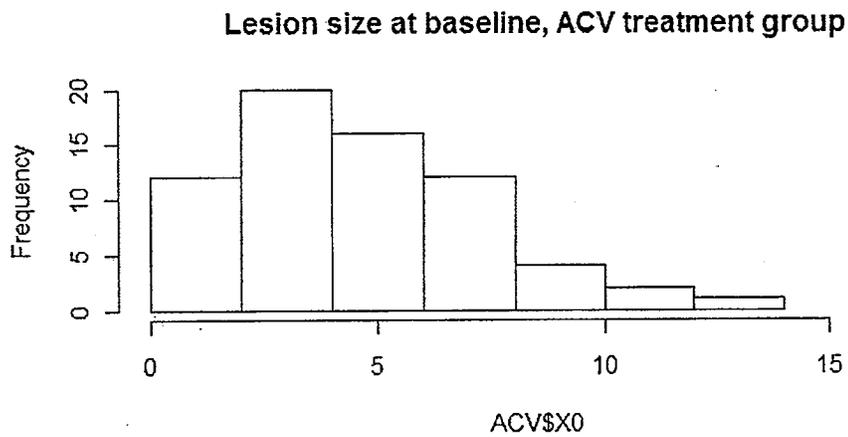
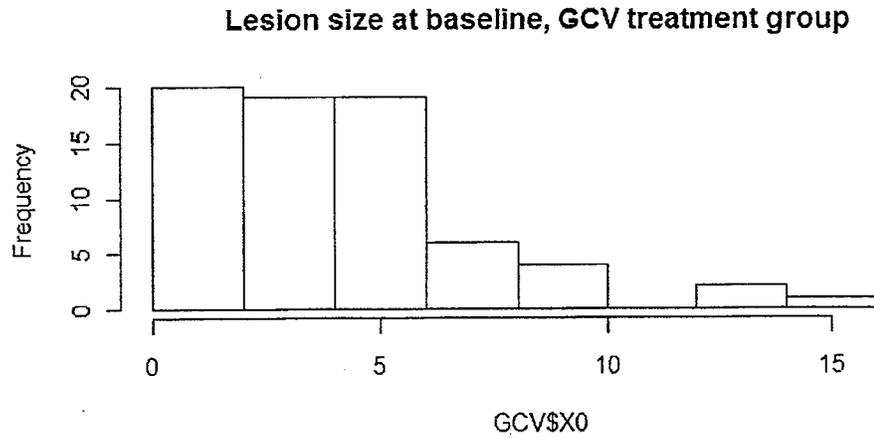


Figure 14: Baseline ulcer size by treatment group. The distribution of lesion size is right skewed in both groups.

Table 10: Number of patients per country

| Country | Numbers of Centers | Number of Patients |
|---------|--------------------|--------------------|
| France | 20 | 57 |
| UK | 3 | 27 |
| Ireland | 1 | 16 |
| Tunisia | 1 | 16 |
| Mali | 1 | 18 |

3.5 Statistical Methodologies

The endpoint used by current sponsor is different from the primary endpoint that was planned and conducted by previous sponsor and these two endpoints are different from

the reviewers' preferred primary endpoint. Thus, the statistical analysis of efficacy was different in each case. We discuss in this section what was decided by the original sponsor as well as the current sponsor and in our analysis

3.5.1 Hypothesis testing

Sponsor's hypothesis testing

The original statistical analysis conducted for Study 7 was based on a superiority hypothesis of time to first healing of Dendritic ulcer, with a 20% improvement in recovery rate postulated for ST-605 compared with topical ophthalmic acyclovir 3%.

The current sponsor post-hoc hypothesis is that of non-inferiority of first time healing rate at anytime of both Dendritic and Geographic ulcers with a non-inferiority margin of 18% (derived for healing rate at day 14).

Reviewer's hypothesis testing

The reviewer' post-hoc hypothesis testing is that of non-inferiority of healing rate at day 7 for Dendritic ulcer with an effect size varying from 14% to 31% for difference in healing rate and from 0.8 to 1.31 for log odds ratio. A non-inferiority margin preserving 50% of this effect would vary from 7% to 15% for difference in healing rate and from 0.4 to 0.75 for log odds ratio.

3.5.2 Missing Data

Sponsor's analysis

In cases where the subject left the study but the recovery criterion was not met, the observation was considered as a treatment failure (selection of maximum bias). Scores were imputed by carrying forward the previous observed score. If an ulcer was recovered at any time, it was considered a treatment success, even if relapse occurred at a later time point during the study period. Both the Sponsor's analyses and Laboratoires Théa's analysis counted only the first recovery of the ulcer, not relapses.

Reviewer's analysis

Relapses were counted as failures. Missing observations prior to healing were considered as failures whereas missing observations after day 7 and after healing were considered successes.

3.5.3 Efficacy Analysis Population

Sponsor's analysis

In the original analysis, two types of statistical analysis were carried out: an analysis in intention to treat, taking into consideration all patients included, and an analysis per protocol excluding those files for which a significant protocol deviation existed (significant inclusion error, lost from view after DO, insufficient frequency of application). The ITT analysis included all 130 observations (67 in the Acyclovir group and 71 in the ST-605 group). The total number of observations in accordance with the

protocol and therefore incorporated in the analysis as per protocol was 62 for the Acyclovir group and 64 for the ST-605 group.

In the current sponsor's analysis, only the intent to treat population was considered for the efficacy analysis.

Reviewer's analysis

An intent to treat analysis was carried out and is presented in Section 3.6.

The per protocol analysis, excluding the same individuals as the ones excluded by the original sponsor, was carried out and shows similar results to the intent to treat analysis.

3.6 Evaluation of Efficacy

Sponsor's analysis

The original sponsor's analysis failed to show superiority of ST-605 to Acyclovir. Testing for differences in 1st time healing rate of Dendritic ulcer did not show significant difference.

The current sponsor's analysis post-hoc non-inferiority showed that ST-605 was non-inferior to Acyclovir for 1st time healing rate of Dendritic and Geographic ulcer at anytime. The non-inferiority testing relied on an 18% non-inferiority margin derived by the sponsor.

Reviewer's comment: the non-inferiority margin of 18% is invalid as the derivation does not account for heterogeneity in the studies and sampling uncertainty. Using the endpoint of healing rate at day 14, we derived a non-inferiority margin from historical data and the results are shown in Section 6.3. The derived effect size shown in Table 16 is of 14% using Method 1 and 18% using Method 2. Thus, a non-inferiority margin of 18% would not discount any of the effect size. Note that the estimated effect sizes at day 14 are about half the estimated effect sizes at day 7, which suggests that the active control effect over placebo diminishes over time.

Reviewer's analysis

Table 11 shows the point estimate for each treatment group as well as the 95% confidence interval for difference in healing rates and for log odds ratio over time. As shown in this table, at day 7 the lower bound of the confidence interval for difference in healing rate is -10% and the lower bound of the confidence interval for log odds ratio is -0.45. The value of these lower bounds have to be compared to the non-inferiority margin. The conclusion on non-inferiority depends on the method used for deriving the effect size as well as the percent preservation. These results fail to show non-inferiority with a 50%

preservation using Method 1 for Dendritic ulcer only. These same results could show non-inferiority with a 25% preservation using any of the methods used above.

Table 11: Results of Phase 3 (Study 7) trial on healing rate difference and log odds ratio.

| | Day 3 | Day 7 | Day 10 | Day 14 | Day 21 |
|-----------------------|----------------------|----------------------|-----------------------|----------------------|-----------------------|
| ST-605 | 42% (30/71) | 77% (55/71) | 79% (56/71) | 86% (61/71) | 86 (61/71) |
| Acyclovir | 31% (21/67) | 72% (48/67) | 79% (53/67) | 90% (60/67) | 90% (60/67) |
| CI for difference | (-7%, 28%) | (-10%, 20%) | (-14%, 14%) | (-16%, 9%) | (-16%, 9%) |
| CI for log odds ratio | 0.47 (-0.22,0.47) | 0.31 (-0.45,1.07) | -0.01 (-0.82,0.79) | -0.34 (1.34,0.66) | -0.34 (-1.34,0.66) |

Reviewer's comment: Note that although the difference between the two treatments failed to show significance at anytime, the point estimate for ST-605 is better than Acyclovir at day 3 then the difference between the two treatments decreases over time. The initial difference may be a carry-over effect of the baseline difference observed at Day 0 between Acyclovir and ST-605 (not significant). Although the difference is not significant, the correlation between day 3 and day 0 is of 44% and the scatter plot in Figure 15 shows a clear relationship between ulcer size at baseline and ulcer size at day 3 after initiation of treatment. It may be necessary in future trials to control for this covariate, ulcer size at baseline, before randomization.

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Ulcer size at baseline and day 3

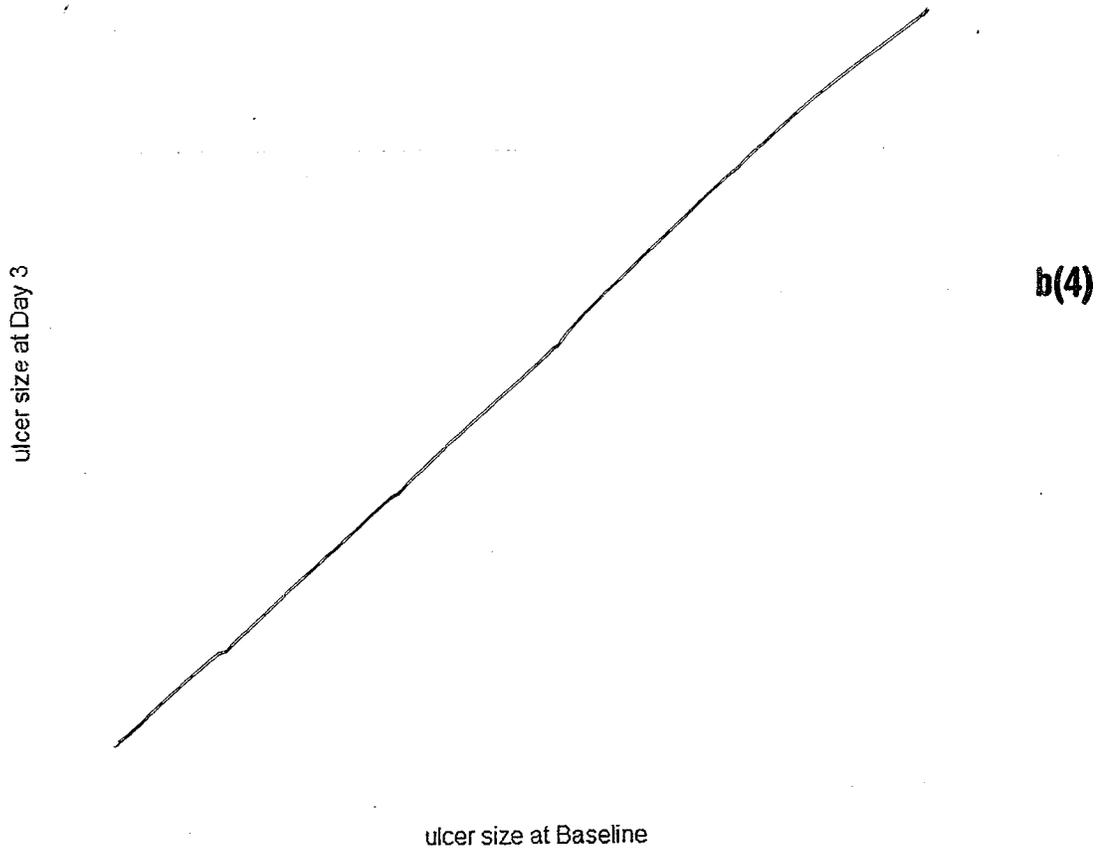


Figure 15: Ulcer size at Day 3 compared to Baseline. Filled circles represent patients in Acyclovir group, open circles represent patients in ST-605 group. We see that there is a positive relationship between ulcer sizes on these two days for both groups.

3.7 Evaluation of Safety

The following is a summary of safety provided by the sponsor; please refer to clinical review for details on safety.

The safety data presented by the sponsor shows that Ganciclovir Ophthalmic gel is safe and well tolerated. The data on AEs from studies 4, 5, 6, and 7 supported this claim. In addition, there has been no safety concern in post marketing since the launch of Virgan outside the US in 1995.

All clinical studies submitted in this NDA were conducted outside the US and enrolled a total of 16 healthy subjects and 377 subjects with acute herpetic keratitis across multiple clinical investigative sites in Africa, Europe, and Asia. There were no serious AEs (SAEs) and no deaths reported for any of the clinical trials. The safety and tolerability AEs that were treatment-emergent and not due to disease progression were blurred vision, eye irritation, punctate keratitis, conjunctival hyperaemia, erythema of the eyelid, corneal disorders, and dacryostenosis acquired. Of the 161 subjects who were treated with ST-605 in these clinical trials, the most frequently reported ocular AEs were blurred vision upon instillation (57.8%), eye irritation (burning and stinging) upon instillation (25.6%), and punctate keratitis (8.8%). However, all these ocular AEs were rated mild to moderate in severity, were transient, and resolved without sequelae. The same AEs were seen in the acyclovir 3% treated group, in the same order of frequency, but at a higher incidence: blurred vision upon instillation (71.3%), eye irritation (burning and stinging) upon instillation (46.2%), and punctate keratitis (16%). There were no withdrawals of subjects due to AEs in Studies 4, 5, and 6. In Study 7, 2 subjects treated with ST-605 and 1 subject treated with acyclovir 3% were withdrawn due to AEs.

Laboratoires Théa has only registered 1 report of a nonserious spontaneous adverse reaction associated with the use of Virgan. In addition, 1 suspected adverse reaction was reported that was considered to be due to a misuse of the product because the product was not prescribed for the approved indication.

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ON ORIGINAL**

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No special subgroup was investigated by sponsor. The bar plot in Figure 16 shows that there is no apparent difference between male and females in their response to treatment.

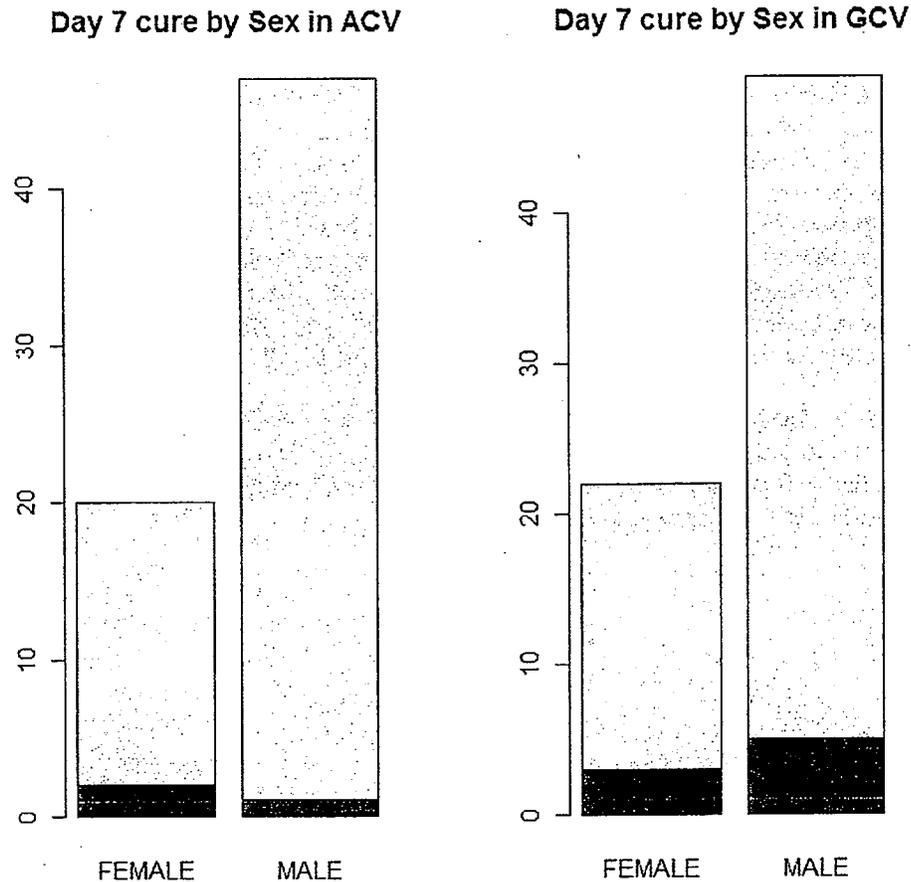


Figure 16: Cure at day 7 by Sex and Treatment. Dark shade is uncured counts, light shade is cured count. We do not see a difference in cure rate by sex.

5 SUMMARY AND CONCLUSIONS

Both the sponsor's analysis and the reviewer's analysis are post-hoc re-evaluation of the evidence with a post-hoc non-inferiority margin. However, the reviewers' post-hoc exploratory analysis of the evidence differed substantially from the submitted analysis from the sponsor. The differences between the two analyses are: first, the reviewers' analysis used results from the Phase 3 study only whereas the sponsor's analysis used the pooled Phase 2 and Phase 3 data; second, the choice of primary efficacy endpoint was

healing rate at day 7 in reviewers' analysis instead of first time healing rate at *anytime* in the sponsor's analysis; third, the subset of historical studies used to derive the non-inferiority margin includes all relevant original published studies in the reviewer's analysis (as suggested by the ophthalmology clinical team) instead of a subsample of studies from the Cochrane review in the sponsor's analysis; fourth, the non-inferiority margin derivation accounts for sampling variability and between study heterogeneity in the reviewer's analysis instead of pooling the point estimates for healing rate in the sponsor's analysis.

Although the reviewer's post-hoc exploratory analysis in study 7 (phase-3) may show that ST-605 is non-inferior to Acyclovir 3% ointment using a NI margin determined post-hoc, we do not think that the current submission is adequate or that it provides substantial evidence of efficacy required for the approval of this indication in the US. Our main objections are two-fold. First, the pre-planned hypothesis of superiority using the pre-planned efficacy endpoint of time to healing, failed to demonstrate superiority using the data from a single, open label Phase 3 trial. The reviewer's analysis used a post-hoc endpoint and a post-hoc non-inferiority hypothesis, so this analysis has the same potential for multiple testing errors as any post-hoc exploratory analysis. We believe that to avoid multiple testing errors and bias, the choice of primary endpoint and hypothesis test should be pre-planned at the protocol stage and the non-inferiority margin should be pre-specified. Second, the active control used in the Phase 3 trial is not an FDA approved drug, nor the standard of care in the United States. Although the historical evidence may show that the active control used in this trial is effective, the historical evidence fails to show that the active control is superior to the current standard of care in the United States: Trifluridine. Thus, this trial does not provide evidence that ST-605 would be non-inferior, much less superior, to the standard of care Trifluridine. These objections are reinforced by the fact that our own derivation of the non-inferiority margin relies on very heterogeneous historical trials which clearly violate the constancy assumption and are sensitive to the subset of studies included.

Based on the objections cited above, we recommend that at least one prospectively designed, adequate and well-controlled study of ST-605 be conducted for the treatment of acute herpetic keratitis with the comparator Trifluridine to demonstrate that the product is at least as effective as standard of care. The results from the reviewer's exploratory analysis can thus be used as supportive evidence. This new proposed study can be a dose-ranging superiority study or a non-inferiority study comparing ST-605 to Trifluridine or Acyclovir 3% if a clinically meaningful margin can be agreed upon.

SIGNATURES/DISTRIBUTION LIST

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Date: July 7th, 2009

Concurring Reviewer: Thamban Valappil, Ph.D, Statistical Team Leader

cc:

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HFD-700/Mathematical Statistician/Lillian Patrician, MS, MBA

6 APPENDIX

Below is a summary of all the publications reviewed to derive the non-inferiority margin at day 7. The publications are divided into two groups, the Acyclovir studies and the Placebo studies. In each group, the studies are listed in alphabetical order.

6.1 Acyclovir Studies

| | |
|--|---|
| Study name | Abe 1987 |
| Reference: | Abe T, Hara S. Use of acyclovir in herpetic ocular infections. Japanese Journal of Clinical Ophthalmology 1987; 41:73-7. |
| Research center: | one center in Japan |
| Period of Study: | not given |
| Objective: | comparing idoxuridine to acyclovir |
| Design: | single masking; method of allocation not available |
| Number of subjects: | 27 |
| Diagnostic: | Dendritic or geographic epithelial keratitis; primary or recurrent infections. |
| Concomitant treatments: | None |
| Evaluation criteria (endpoint): | complete resolution or partial resolution of superficial inflammation. |
| Study | Colin, 1981 |
| Reference | Colin J, Tournoux A, Chastel C, Renard G. Superficial herpes simplex keratitis. Double-blind comparative trial of acyclovir and idoxuridine [Kératite herpétique superficielle. Traitement comparatif en double insu par acyclovir et idoxuridine]. La Nouvelle Presse Médicale 1981; 10:2969-70, 2975. |
| Research center: | one in France |
| Period of Study: | not given |
| Objective: | Comparison of the efficacy of acyclovir and idoxuridine in the treatment of human herpetic keratitis |
| Design: | double blind; randomized. |

| | |
|---------------------------------|--|
| Number of subjects: | 52 |
| Diagnostic: | Dendritic or geographic epithelial keratitis; primary or recurrent infection |
| Concomitant treatments: | Atropine |
| Evaluation criteria (endpoint): | absence of epithelial ulceration after instillation of fluorescein |
| Study | Colin, 1984 Colin J. Superficial herpetic keratitis: comparative double-blind treatment with iododeoxycytidine and acyclovir [Kératite herpétique superficielle: traitement comparatif en double-insu pour iododesoxycytidine et acyclovir]. Bulletin des Societes d' Ophthalmologie de France 1984;84:1283-6. |
| Reference | |
| Research center: | One in France |
| Period of Study: | not given |
| Objective: | Comparison of iododesoxycytidine and acyclovir |
| Design: | double-blind; randomized. |
| Number of subjects: | 32 |
| Diagnostic: | Dendritic or geographic epithelial keratitis |
| Concomitant treatments: | Atropine |
| Evaluation criteria (endpoint): | no epithelial ulceration after fluorescein instillation |
| Study | Collum 1980 Collum LMT, Benedict Smith A, Hillary IB. Randomised doubleblind trial of acyclovir and idoxuridine in dendritic corneal ulceration. British Journal of Ophthalmology 1980;64: 766-9. |
| Reference | |
| Research center: | one, Ireland |
| Period of Study: | not given |
| Objective: | comparison of acyclovir to Idoxuridine |

| | |
|------------------------------------|--|
| Design: | double blind; randomized |
| Number of subjects: | 60 |
| Diagnostic: | Dendritic epithelial keratitis only |
| Concomitant treatments: | homatropine, pad |
| Evaluation criteria (endpoint): | no fluorescein uptake |
| Study | Coster, 1980 Coster DJ, McKinnon JR, McGill JJ, Jones BR, Fraunfelder FT. Clinical evaluation of adenine arabioside and trifluorothymidine in the treatment of corneal ulcers caused by herpes simplex virus. Journal of Infectious Diseases 1976;133 Suppl:A173-7. |
| Reference | Moorfields Eye Hospital, London |
| Research center: | not given |
| Period of Study: | |
| Objective: | Comparison of acyclovir to Idoxuridine |
| Design: | double-blind; randomized; stratified (size of ulcer, type, degree of inflammation, steroid use) |
| Number of subjects: | 60 |
| Diagnostic: | Dendritic or geographic epithelial keratitis |
| Concomitant treatments: | 1% atropine (once per day until cicatrisation 'of the ulcer) and corticosteroids |
| Evaluation criteria (endpoint): | absence of fluorescein coloration and Rose Bengal |
| Study | Denis, 1983 Denis J, Thenault-Giono S, Ray-Cohen M-L, Tournoux A, Pouliquen Y. Double-blind treatment of ocular herpes simplex: Vira-A and acyclovir [Traitement de l'herpes oculaire en double insu: Vira- A et acyclovir]. Bulletin des Societes d' Ophtalmologie de France 1983; 83:25-9. |
| Reference | one, france |
| Research center: | |
| Period of Study: | |

Objective: comparing vidarabine to acyclovir

Design: single blind; randomized

Number of subjects: 23

Diagnostic: Dendritic or geographic epithelial keratitis

Concomitant treatments: mydriatic, antibiotic, local corticoid

Evaluation criteria (endpoint): Scarification

Study

Hoang-Xuan, 1984

Hoang-Xuan T, Frot P, Denis J, Pouliquen Y. Acyclovir and trifluorothymidine in herpetic kerato-uveitis. A comparative clinical study. Indications for corticoid therapy [Aciclovir et trifluorothymidine dans la kérato-uvéite herpétique. Une étude comparative en Clinique humaine. Indications de la corticothérapie]. Journal Francais d' Ophtalmologie 1984;7:125-31.

Reference

Research center: one, france

Period of Study: 1980-1982

Objective: comparing trifluorothymidine to acyclovir

Design: open label, not randomized

Number of subjects: 29

Diagnostic: Dendritic or geographic epithelial keratitis

Concomitant treatments: cycloplegic, antibiotic, timolol, corticosteroids

Evaluation criteria (endpoint): no fluorescein staining

Study

Hovding, 1989

Hovding G. A comparison between acyclovir and trifluorothymidine ophthalmic ointment in the treatment of epithelial dendritic keratitis. A double blind, randomized parallel group trial. Acta Ophthalmologica 1989;67:51-4.

Reference

Research center: one, Bergen (Norway)

Period of Study: not given

Objective: Comparison of acyclovir and trifluorothymidine in the treatment of dendritic keratitis

| | |
|---------------------------------|--|
| Design: | Double-blind; randomized |
| Number of subjects: | 55 |
| Diagnostic: | Dendritic epithelial keratitis; primary or recurrent infection |
| Concomitant treatments: | None |
| Evaluation criteria (endpoint): | disappearance of epithelial ulceration fixing fluorescein |
| Study | Jackson, 1984 |
| Reference | Jackson WB, Breslin CW, Lorenzetti DWC, Michaud R, Dubé I. Treatment of herpes simplex keratitis: comparison of acyclovir and vidarabine. Canadian Journal of Ophthalmology 1984;19:107-11. |
| Research center: | one, Canada |
| Period of Study: | not given |
| Objective: | Comparison of acyclovir and adenine arabinoside (vidarabine) |
| Design: | Double-blind; randomized. |
| Number of subjects: | 66 |
| Diagnostic: | dendritic or geographic epithelial keratitis; primary or recurrent infection |
| Concomitant treatments: | None |
| Evaluation criteria (endpoint): | no fluorescein reaction in relation to the former ulcer |
| Study | Kitano,1985 |
| Reference | Kitano S, Yamanishi M, Matsuda H, et al. Clinical results of topical human fibroblast interferon for herpetic keratitis. Comparison with IDU eyedrops. Japanese Review of Clinical Ophthalmology 1983;77: 1777-86. |
| Research center: | one, japan |
| Period of Study: | August 1981 - May 1982 |
| Objective: | comparison of Idoxuridine and Acyclovir |

| | |
|------------------------------------|--|
| Design: | Double blind; randomized |
| Number of subjects: | 109 |
| Diagnostic: | dendritic or geographic epithelial keratitis |
| Concomitant treatments: | None |
| Evaluation criteria (endpoint): | no fluorescein staining |
| Study | Klauber, 1982 Klauber A, Ottovay E. Acyclovir and idoxiuridine treatment of herpes simplex keratitis -a double blind clinical study. Acta Ophthalmologica 1982;60:838-44. |
| Reference | |
| Research center: | one, denmark |
| Period of Study: | not given |
| Objective: | Comparison of Idoxuridine and Acyclovir |
| Design: | Double blind; allocation NA |
| Number of subjects: | 38 |
| Diagnostic: | dendritic or geographic epithelial keratitis; primary or recurrent infection; stromal affection |
| Concomitant treatments: | Scopolamine |
| Evaluation criteria (endpoint): | fluorescein and bengal staining |
| Study | La Lau, 1982 La Lau C, Oosterhuis JA, Versteeg J, van Rij G, Renardel de Lavalette JGC, et al. Acyclovir and trifluorothymidine in herpetic keratitis: a multicentre trial. British Journal of Ophthalmology 1982; 66:506-8. |
| Reference | |
| Research center: | four, Netherlands |
| Period of Study: | not given |
| Objective: | TFT and acyclovir |

Design: Double blind; randomized
Number of subjects: 59

Diagnostic: dendritic epithelial keratitis

Concomitant treatments: None
Evaluation criteria
(endpoint): fluorescein staining

Study

McCulley, 1982

McCulley JP, Binder PS, Kaufman HE, O'Day DM, Poirier RH. A double-blind, multicenter clinical trial of acyclovir vs idoxuridine for treatment of epithelial herpes simplex keratitis. *Ophthalmology* 1982; 89:1195-200.

Reference
Research center: five, USA
Period of Study: not given

Objective: Compare IDU to Acyclovir

Design: Double blind; randomized
Number of subjects: 64

Diagnostic: Dendritic (26) or geographic (4) epithelial keratitis;
primary or recurrent infection

Concomitant treatments: None
Evaluation criteria
(endpoint): fluorescein staining

Study

Yeakley, 1981

Yeakley WR, Laibson PR, Michelson MA, Arentsen JJ. A double controlled evaluation of acyclovir and vidarabine for the treatment of herpes simplex epithelial keratitis. *Transactions of the American Ophthalmological Society* 1981;79:168-79.

Reference
Research center: one, USA
Period of Study: not given

Objective: acyclovir and vidarabine

| | |
|---------------------------------|---|
| Design: | Double blind, randomized |
| Number of subjects: | 40 |
| Diagnostic: | dendritic or geographic epithelial keratitis; primary or recurrent infection |
| Concomitant treatments: | None |
| Evaluation criteria (endpoint): | absence of fluorescein staining |
| used by sponsor? | Yes |
| Study | Young, 1982 |
| | Young BJ, Patterson A, Ravenscroft T. A randomised double-blind clinical trial of acyclovir (Zovirax) and adenine arabinoside in herpes simplex corneal ulceration. <i>British Journal of Ophthalmology</i> 1982; 66:361-3. |
| Reference | |
| Research center: | One, UK |
| Period of Study: | not given |
| Objective: | acyclovir and vidarabine |
| Design: | Double blind, randomized |
| Number of subjects: | 93 |
| Diagnostic: | dendritic or geographic epithelial keratitis; primary or recurrent infection |
| Concomitant treatments: | Atropine |
| Evaluation criteria (endpoint): | Not given |

6.2 Placebo Studies

| | |
|------------------|--|
| Study | Burns 1963 |
| | Burns RP. A double-blind study of IDU in human herpes simplex keratitis. <i>Archives of Ophthalmology</i> 1963;70:381-4. |
| Reference | |
| Research center: | 42 centers, USA |

Period of Study: not given

Objective: Compare Idoxuridine to placebo, where placebo is distilled water

Design: double blind, randomized

Number of subjects: 38

Diagnosis: acute epithelial keratitis

Concomitant treatments: Unknown

Evaluation criteria (endpoint): Fluorescein staining

Study **Davidson 1964**
 Davidson SI, Jameson Evans P. IDU and the treatment of herpes simplex keratitis. British Journal of Ophthalmology 1964;48:678-83.

Reference
 Research center: one in UK
 Period of Study: not given

Objective: compare Idoxuridine to debridement and placebo. Placebo is gamma globulin 1% solution.

Design: open label, randomized

Number of subjects: 75

Diagnosis: not given

Concomitant treatments: Unknown

Evaluation criteria (endpoint): absence of staining with 2% fluorescein

Study **Hart 1965**
 Hart DRL, Brightman VJF, Readshaw GG, Porter GTJ, Tully MJ. Treatment of human herpes simplex keratitis with idoxuridine. A sequential double-blind controlled study. Archives of Ophthalmology 1965;73:623-34.

Reference
 Research center: one in Australia
 Period of Study: Unknown

Objective: Compare idoxuridine to placebo. Placebo is neomycin 0.3%

Design: double blind, randomized

Number of subjects: 32

Diagnosis: dendritic epithelial keratitis

Concomitant treatments: mydriatic, pad

Evaluation criteria (endpoint): absence of discrete fluorescein staining of the cornea

Study

Laibson 1964

Laibson PR, Leopold IH. An evaluation of double-blind IDU therapy in 100 cases of herpetic keratitis. Transactions of the American Academy of Ophthalmology and Otolaryngology 1964;68:22-34.

Reference
Research center: one in USA
Period of Study: 1962-1963

Objective: Compare Idoxuridine to placebo. Placebo is distilled water.

Design: double blind, randomized

Number of subjects: 100

Diagnosis: dendritic or geographic epithelial keratitis, without or with stromal keratitis

Concomitant treatments: None

Evaluation criteria (endpoint): Fluroscein staining

Study

Luntz 1963

Luntz MH, MacCallum FO. Treatment of herpes simplex keratitis with 5-iodo-2'-deoxyuridine. British Journal of Ophthalmology 1963; 47:449-56.

Reference
Research center: one in UK
Period of Study: unknown

Objective: Compare idoxuridine to placebo. Placebo is neomycin 1% ointment.

Design: open label, alternate patients

Number of subjects: 22

Diagnosis: dendritic epithelial keratitis

Concomitant treatments: atropine, pad, small scraping

Evaluation criteria (endpoint): fluorescein staining

Study

Markham, 1977

Markham RH, Carter C, Scobie MA, Metcalf C, Easty DL. Doubleblind clinical trial of adenine arabinoside and idoxuridine in herpetic corneal ulcers. Transactions of the Ophthalmological Societies of the United Kingdom 1977;97:333-40

Reference

Research center:

Period of Study:

Year of Publication:

one, UK

not given

1977

Objective:

compare vidarabine and idoxuridine to placebo

Methodology

Double blind; randomized

Number of subjects

41

Diagnosis

epithelial keratitis

concomitant

treatment/combined

debridement

Homatropine

Evaluation criteria (endpoint) Rose-Bengal staining

Study

Patterson 1963a

Patterson A, Fox AD, Davies G, Maguire C, Holmes Sellers PJ, Wright P, et al. Controlled studies of IDU in the treatment of herpetic keratitis.

Transactions of the Ophthalmological Societies of the United Kingdom 1963;83:583-91.

Reference

Research center:

Period of Study:

one in UK

1962

Objective: Compare Idoxuridine to placebo

Design: double blind

Number of subjects: 23

Diagnosis: dendritic epithelial keratitis

Concomitant treatments: atropine, pad

Evaluation criteria (endpoint): Fluoresceing and rose bengal staining

Study

Patterson 1963b

Patterson A, Fox AD, Davies G, Maguire C, Holmes Sellers PJ, Wright P, et al. Controlled studies of IDU in the treatment of herpetic keratitis.

Transactions of the Ophthalmological Societies of the United Kingdom 1963;83:583-91.

Reference

Research center:

one in UK

Period of Study:

1962

Objective: Compare Idoxurine to Placebo

Design: double blind

Number of subjects: 32

Diagnosis: dendritic epithelial keratitis

Concomitant treatments: atropine, pad

Evaluation criteria (endpoint): Fluoresceing and rose bengal staining

Study

Patterson 1963c

Patterson A, Fox AD, Davies G, Maguire C, Holmes Sellers PJ, Wright P, et al. Controlled studies of IDU in the treatment of herpetic keratitis.

Transactions of the Ophthalmological Societies of the United Kingdom 1963;83:583-91.

Reference

Research center:

one in UK

Period of Study: 1962
 Objective: compare Idoxuridine to placebo
 Design: double blind
 Number of subjects: 30
 Diagnosis: dendritic epithelial keratitis
 Concomitant treatments: atropine, pad
 Evaluation criteria (endpoint): Fluorescein and rose bengal staining

Study **Uchida, 1981**
 Uchida Y, Kaneko M, Yamanishi R, Kobayashi S.
 Effect of human fibroblast interferon on dendritic
 keratitis. In: Sundmacher R editor(s). Herpetic
 Augenerkrankungen. München: JF Bergmann, 1981:
 409–13.
 Reference
 Research center: eight in Japan
 Period of Study: Unspecified

Objective: Compare idoxuridine to placebo, where placebo is
 albumin
 Methodology: double blind randomized
 Number of subjects: 54
 Diagnosis: dendritic epithelial keratitis
 concomitant
 treatment/combined
 debridement: gentamicin solution
 Evaluation criteria (endpoint): Disappearance of gross staining areas with
 fluorescein

Study **Yamazaki, 1984 b**
 Yamazaki S. Further studies on clinical trials of
 interferon in Japan. Japanese Journal of Medical
 Science and Biology 1984;37:209–23.
 Reference
 Research center: one, Japan

| | |
|---|--|
| Period of Study: | not given |
| Objective: | compare interferon to Placebo, where placebo is an albumin solution |
| Methodology | Unspecified |
| Number of subjects | 41 |
| Diagnosis concomitant treatment/combined debridement | dendritic epithelial keratitis not given |
| Evaluation criteria (endpoint) | complete cure in a week or lesion regressed by 50% in a week or complete cure in 2 weeks |
| Study | Yamazaki, 1984 c |
| Reference | Yamazaki S. Further studies on clinical trials of interferon in Japan. Japanese Journal of Medical Science and Biology 1984;37:209-23. |
| Research center: | one, japan |
| Period of Study: | not given |
| Objective: | Compare interferon to Placebo, where placebo is a low dose interferon |
| Methodology | Unspecified |
| Number of subjects | 20 |
| Diagnosis concomitant treatment/combined debridement | dendritic epithelial keratitis not given |
| Evaluation criteria (endpoint) | complete cure in a week or lesion regressed by 50% in a week or complete cure in 2 weeks |

6.3 Non-inferiority margin derivation for healing at day 14

The effect size was estimated for the difference in healing rate at day 14, using the pooled Dendritic and Geographic data, and the results are shown in Table 16. The M1 values are 14% using Method 1 and 18% using Method 2. Tables 12-15 provide summary information used to derive these estimates from the corresponding studies.

Table 12: Healing rates at day 14 for Placebo Studies

| Placebo Studies | Recovery rate of Placebo arm at day 14: n/N (%) | Comparator name, recovery rate at day 14: n/N (%) |
|--|---|---|
| Yamazaki, 1984 b Placebo = Albumin solution | 28/41 (68%) | INT |
| Luntz, 1963 Placebo = neomycin ointment | 7/11 (64%) | IDU 10/11 (91%) |
| Haut, 1983 Placebo = oral placebo | 6/12 (50%) | |
| Markham, 1977 Placebo = placebo ointment | 8/20 (40%) | IDU 15/21 (71%) |
| Overall Placebo rate (Method 2) | 58% (45,71) | |

Table 13: Healing rates at day 14 for Acyclovir studies

| ACV Studies | Rate (n/N, %) | |
|-----------------|---------------|-----|
| Abe 1987 | 18/18 | 100 |
| Altinisik 1987 | 5/10 | 50 |
| Cellini 1994 | 20/20 | 100 |
| Colin 1981 | 23/25 | 92 |
| Colin 1984 | 15/15 | 100 |
| Colin 1987 | 16/16 | 100 |
| Collum 1980 | 30/30 | 100 |
| Coster 1980 | 27/29 | 93 |
| Denis 1983 | 13/14 | 93 |
| Genee 1987 | 11/14 | 79 |
| Hoang-Xuan 1984 | 17/18 | 94 |
| Hovding 1989 | 23/25 | 92 |

| | | |
|---------------------|-------|-----|
| Jackson 1984 | 31/32 | 97 |
| Kitano 1985 | 50/54 | 93 |
| Klauber 1982 | 15/18 | 83 |
| Kumar 1987 | 19/19 | 100 |
| La Lau 1982 | 27/31 | 87 |
| McCulley1982 | 25/30 | 83 |
| Maychuk 1988 | 35/39 | 90 |
| Panda 1995 | 19/20 | 95 |
| Pavan-langston 1981 | 19/20 | 95 |
| Yeakley 1981 | 19/19 | 100 |
| Young 1982 | 46/48 | 96 |

Table 14: Healing rates at day 14 for studies comparing Acyclovir to Idoxuridine.

| Study | Acyclovir | IDU |
|----------------|-----------|-------|
| Abe 1987 | 18/18 | 5/9 |
| Altinisik 1987 | 5/10 | 1/9 |
| Colin 1981 | 23/25 | 22/27 |
| Collum 1980 | 30/30 | 21/22 |
| Coster 1980 | 27/29 | 29/30 |
| Kitano 1985 | 50/54 | 43/55 |
| Klauber 1982 | 15/18 | 12/20 |
| Kumar 1987 | 19/19 | 13/17 |
| Maychuk 1988 | 35/39 | 26/38 |
| McCulley1982 | 25/30 | 29/34 |
| Panda 1995 | 19/30 | 12/20 |

Table 15: Healing rates at day 14 for studies comparing Acyclovir to Trifluridine.

| Study | Acyclovir | TFT |
|-----------------|-----------|-------|
| Hoang-Xuan 1984 | 17/18 | 10/11 |
| Hovding 1989 | 23/25 | 24/25 |
| La Lau 1982 | 27/31 | 23/28 |
| Panda 1995 | 19/20 | 19/20 |

Table 16: Effect Size M1 for healing rate at day 14.

| Results | Description | M1 day 14 |
|---------|--|--------------|
| 1 | ACV-IDU. Meta analysis comparing Acyclovir to Idoxuridine. | 6% |
| 2 | Method 1: ACV - P= IDU- P + ACV-IDU Two meta analyses. The first compares Idoxuridine to Placebo and the second compares Acyclovir to Idoxuridine. | 14% |
| 3 | Method 2: Pooled (ACV-P). Fitting two logistic regressions and correcting for overdispersion. | 18% |

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