

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-211**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

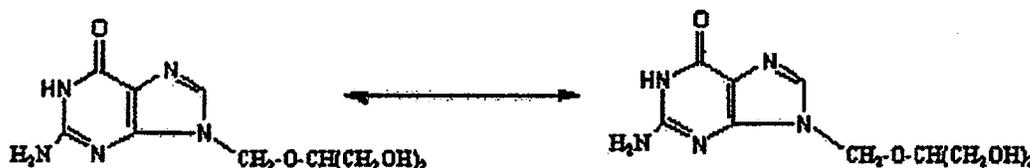
<b>Date</b>	September 10, 2009
<b>From</b>	William M. Boyd, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	22-211
<b>Applicant</b>	Sirion Therapeutics, Inc.
<b>Date of Submission</b>	November 14, 2008
<b>PDUFA Goal Date</b>	September 17, 2009
<b>Type of Application</b>	505(b)(1)
<b>Name</b>	Zirgan (ganciclovir ophthalmic gel) 0.15%
<b>Dosage forms / Strength</b>	Topical ophthalmic gel
<b>Proposed Indication(s)</b>	Indicated for the treatment of acute herpetic keratitis (dendritic ulcers)
<b>Recommended:</b>	Recommended for Approval

### 1. Introduction

The drug product (ganciclovir ophthalmic gel, 0.15%) is a sterile topical ophthalmic gel containing the active ingredient ganciclovir, a synthetic guanine derivative antiviral agent. The aqueous gel is a \_\_\_\_\_, preserved, \_\_\_\_\_ solution. The topical gel is packaged in a multi-dose polyfoil tube. This formulation is for topical ophthalmic use only.

b(4)

The chemical name is 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine. Its structural formula is:



MW 255.23 with a molecular formula of C<sub>9</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub>.

This 505(b)(1) application relies on four clinical studies conducted in Europe, Africa, and Asia between 1990 and 1994 which were originally sponsored by Laboratoires Théa formerly TRANSPHYTO S.A. to support efficacy and safety of ganciclovir ophthalmic gel 0.15% for the recommended indication, treatment of acute herpetic keratitis (dendritic ulcers).

In a correspondence to the FDA from Laboratoires Théa dated August 26, 2009:

Laboratoires Théa has an exclusive licensing agreement with Sirion Therapeutics, Inc. (Sirion) in which Sirion will manufacture, sell and distribute Ganciclovir Ophthalmic

CDTL Review  
William M. Boyd, M.D.  
NDA 22-211  
Zirgan (ganciclovir ophthalmic gel) 0.15%

Gel, 0.15% throughout the United States. Hence, Laboratoires Théa hereby confirms that Sirion has right of reference to all of the clinical data and clinical study reports for Ganciclovir Ophthalmic Gel, 0.15% that support their New Drug Application (NDA 22-211).

Throughout this review, Zirgan (ganciclovir ophthalmic gel) 0.15% may alternately be referred to by various review disciplines as Virgan, ganciclovir, or ST-605 ophthalmic gel formulation.

## 2. Background

The active ingredient, ganciclovir, is a synthetic guanine derivative, which has antiviral activity against HSV. In the United States, ganciclovir is approved for the treatment of CMV retinitis in patients with AIDS (Cytovene -IV, Cytovene capsules, and Vitrasert ocular implant) and for the prevention of CMV disease in patients with kidney, heart, and kidney-pancreas transplants (Valcyte).

Trifluridine ophthalmic solution 1% (NDA 18-299) is approved and marketed for the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to herpes simplex virus, types 1 and 2.

Ganciclovir ophthalmic gel 0.15% was originally approved in 1995 in France for the treatment of acute herpetic keratitis with the same database that has been submitted to support NDA 22-211. Since the initial approval, the drug product has been approved in over 30 countries outside of the United States for this indication.

Orphan drug status for NDA 22-211 (IND 75,762) was granted on March 22, 2007.

The Agency provided responses to questions contained in a request for a Pre-IND/NDA meeting for NDA 22-211 on May 22, 2007. Agency responses to additional questions were provided on June 11, 2007, and October 29, 2007.

NDA 22-211 was originally filed on with the Agency on June 26, 2008, with a formulation (i.e. Formulation C) that was different from that used in the clinical trials. The application was withdrawn on August 26, 2008, and resubmitted on November 17, 2008, with a formulation more consistent with that used in the clinical trials (i.e. Formulation B\*).

## 3. CMC

### DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Ganciclovir ophthalmic gel, 0.15% (ST-605) is currently marketed outside the U.S. by Laboratoires Théa of France for the treatment of acute herpetic keratitis. Ganciclovir is approved in the U.S. and Europe as both an oral and intravenous antiviral agent (Valcyte, NDA 21-304 and Cytovene, NDA 19-661). ST-605 was developed by Transphyto SA (now Laboratoires Théa) as a topical aqueous ophthalmic gel containing ganciclovir, for the treatment of herpetic keratitis.

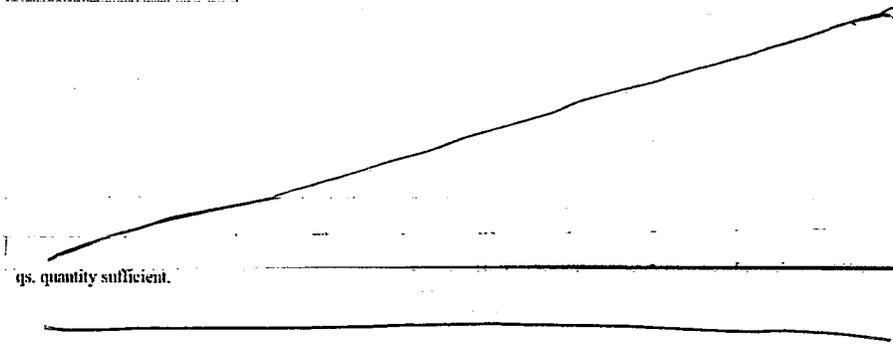
CDTL Review  
 William M. Boyd, M.D.  
 NDA 22-211  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

Four ST-605 formulations will be discussed. All of the clinical studies of ST-605 were conducted outside of the US, by Laboratoires Théa. Formulation A was used in the Phase 2 clinical trials, and Formulation B was used in the Phase 3 clinical trial and was the original commercially marketed formulation (first approved in 1995). Formulation C has been approved and marketed in Europe and internationally since 2001, and Formulation B\* is proposed for U.S. marketing.

**Table 1 – (3.2.P.2.2) Formulation History**

Parameter	Formulation/Variation			
	A	B	B*	C
Ganciclovir concentration	0.05% and 0.15%	0.15%		0.15%
Ganciclovir source				

b(4)



**Table 2 – (3.2.P.2.2) Formulation Usage**

Purpose	Formulation/Variation			
	A	B	B*	C
Phase 1		X		
Phase 2	X			
Phase 3		X		
Commercial		X	X	X
	Clinical development	Clinical development and approved and marketed for use in Europe	Proposed for marketed product in the US	Current marketed product for European and international distribution
Used in Théa clinical studies	1, 4, 5, and 6	2, 3, and 7		

**Formulation A:** The formulation for Formulation A was identical for both dose strengths of ganciclovir evaluated (0.05% and 0.15%), with only the amount of ganciclovir in each formula varying. Both dose strengths of Formula A were used during the Phase 2 studies dose ranging conducted during clinical development.

CDTL Review  
 William M. Boyd, M.D.  
 NDA 22-211  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

**Formulation B:** On the basis of the clinical results obtained from the studies using Formulation A, the 0.15% strength was the dose strength selected for Phase 3 studies with Formulation B. During clinical development, the preservative used in the formulation was changed from sodium mercurothiolate at a concentration of 0.0060% to benzalkonium chloride 0.0075%. After the change to the antimicrobial preservative, additional Phase 1 and Phase 3 controlled clinical studies were performed. Marketing authorization in France was originally granted for Formulation B on August 10, 1995.

In December 2000, a transfer of the marketing authorization from Transphyto to Laboratoires Théa occurred after the merging of the 2 companies.

**Formulation C:** Formulation C is the formula currently marketed in Europe. The transition from Formulation B to Formulation C occurred in 2001. The difference between Formulation B and Formulation C is as follows:



b(4)

The Formulation C change has been in effect since 2001.

**Formulation B\*:** Formulation B\* is the proposed formulation for marketing authorization in the U.S. Formulation B\* will use water for injection instead of \_\_\_\_\_, as in the previous Laboratoires Théa formulations.

b(4)

**Table 1 – (3.2.P.1.2) ST-605 Quantitative and Qualitative Composition of U.S. Market Formula B\***

Component	Quantity (%w/w)	Function	Quality Standard
Ganciclovir	0.15%	Active ingredient	USP
Carbomer ' _____			NF
Mannitol	_____		USP
Benzalkonium chloride ' _____		Antimicrobial preservative	USP / NF
Sodium hydroxide	As needed	pH adjustment	NF
Water for injection	qs	Aqueous vehicle	USP

qs, quantum sufficient, a sufficient quantity; USP, United States Pharmacopeia; NF, National Formulary

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1   Page(s) Withheld

       Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

CDTL Review  
William M. Boyd, M.D.  
NDA 22-211  
Zirgan (ganciclovir ophthalmic gel) 0.15%

#### FACILITIES INSPECTIONS:

The overall recommendation from the Office of Compliance is "Acceptable" in EES.

### 4. Nonclinical Pharmacology/Toxicology

The applicant, Sirion Therapeutics, Inc., has right of reference from Roche to the nonclinical pharmacology and toxicology information in NDA 19-661.

From the original Pharmacology/Toxicology Review finalized 7/8/09:

Ganciclovir IV, ganciclovir capsules, and ganciclovir intravitreal implant are currently marketed in the US. Ganciclovir Ophthalmic Gel 0.15% (Virgan) is approved and marketed in over 30 foreign countries.

Most nonclinical safety information in support of this NDA has been previously submitted for Cytovene (ganciclovir sodium for injection – Roche Laboratories, NDA 19-661). The systemic toxicity of ganciclovir in animals was investigated in Good Laboratory Practice (GLP)-compliant toxicity studies conducted by Syntex and Roche Pharmaceutical Companies, in support of ganciclovir for injection. Additional GLP safety studies have been conducted by Laboratoires Théa to evaluate the safety and tolerability of the ST-605 ophthalmic formulation of ganciclovir (approved in other countries under the brand name Virgan), for the treatment of herpetic keratitis.

The repeat-dose intravenous and oral toxicity studies in animals showed that ganciclovir caused anemia and testicular toxicity. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes *in vitro* at concentrations of 50 to 500 and 250 to 2000 µg/mL, respectively. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg but not 50 mg/kg. Ganciclovir was not mutagenic in the Ames Salmonella assay at concentrations of 500 to 5000 µg/mL. Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 mg/kg/day. There was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vagina) and liver in females. No carcinogenic effect was observed in mice administered at 1 mg/kg/day.

Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day, respectively. Effects observed in rabbits included: fetal growth retardation, embryoletality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryoletality.

CDTL Review  
William M. Boyd, M.D.  
NDA 22-211  
Zirgan (ganciclovir ophthalmic gel) 0.15%

Seven local ocular tolerance studies have been conducted with ganciclovir, when administered in the ST-605 ophthalmic gel formulation. Three of the local tolerance studies compared the effects of ST-605 eye gel containing either BAC 0.0075% as the preservative or sodium mercuriothiolate 0.006% (thimerisol) as the preservative. The BAC preservative was selected prior to the Phase 3 clinical study and was also present in the initially marketed Virgan formulation. In these studies, there appeared to be no differences between gel formulations with respect to irritancy to the conjunctiva, iris or cornea, or corneal sensitivity after single instillation, or wound-healing time after repeat instillation. The ocular toxicity information from the above studies has been previously used in the marketing approval of ST-605 ophthalmic formulation of ganciclovir (Virgan) in foreign countries. Two additional studies have been conducted evaluating the local tolerance and corneal toxicity of ST-605 and trifluridine 1% in rabbits with intact corneas or with total corneal epithelial defects.

None of the ocular studies showed any systemic adverse reactions resulting from ocular topical instillation of ST-605, regardless of formulation tested. The only noted ocular finding was slight irritation and redness post instillation. However, each morning the signs of the previous day had disappeared, showing reversibility of the irritation.

The clinical dosing regimen of ST-605 (0.15%) is 1 drop per eye, 5 times a day, for up to 42 days. The animal ocular tolerance studies with ST-605 (0.15%) included regimen of 1 drop per eye, 5 times a day, for up to 42 days. Therefore, it appears that there is a sufficient margin of safety.

b(4)

## 5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 6/29/09:

ST-605 is an ophthalmic gel formulation of ganciclovir 0.15% for topical instillation. ST-605 is proposed for the treatment of acute herpetic keratitis (dendritic ~~ulcers~~ ulcers). A total of seven (7) clinical studies were conducted to support ST-605 for the treatment of acute herpetic keratitis: one pharmacokinetic study in subjects with acute herpetic keratitis (Study 1, based on a subset of the subjects in Study 4), two pharmacokinetic studies in healthy subjects (Studies 2 and 3), three Phase 2 studies in herpetic keratitis patients (Studies 4, 5, and 6) and one Phase 3 study in herpetic keratitis patients (Study 7). Pharmacokinetic data was obtained in Studies 1, 2, 3, 5 and 7. The clinical pharmacology findings from these studies are summarized as follows:

b(4)

- The extent of local and systemic exposure to ganciclovir from topical ophthalmic administration of ST-605 ganciclovir 0.15% was evaluated in four clinical studies: two multiple dose studies in healthy volunteers (Studies 2 and 3) and two studies in patients with acute herpetic keratitis as part of the Phase 2 and Phase 3 clinical development program (Studies 4 and 7). Systemic exposure to ganciclovir appears to be minimal following multiple administration of ganciclovir 0.15% gel, as evidenced by plasma and urine concentrations following multiple administration.

CDTL Review  
William M. Boyd, M.D.  
NDA 22-211  
Zirgan (ganciclovir ophthalmic gel) 0.15%

- In tear samples collected from six healthy volunteers following multiple dose administration of ganciclovir 0.15% gel, the concentrations of ganciclovir were below the limit of detection in 33% of samples. For the remaining samples, a high variability in ganciclovir concentrations was found within and between individuals. The clinical relevance of ganciclovir tear concentrations or their variability is unknown.
- Although urine samples collected from herpetic keratitis patients following multiple doses of ganciclovir 0.15% gel yielded no detectable ganciclovir, conclusions regarding systemic absorption following ophthalmic administration of ganciclovir gel cannot be made due to the lack of sensitivity of the urine assay (LLOQ of 100 ng/mL).
- A dose-response relationship for efficacy was suggested in both the phase 2 studies which compared ganciclovir 0.05% and 0.15%. Although numerical differences in response rates were observed, the sponsor's statistical analysis showed no statistically significant differences between the ganciclovir 0.05% and 0.15% treatments. No dose-response relationship for safety was observed in the phase 2 studies which compared ganciclovir 0.05% and 0.15%.

In comparison to systemic concentrations following IV administration of ganciclovir, plasma concentrations following ophthalmic administration are much lower; concentrations ranged between 0 to 37 ng/mL with ganciclovir gel versus a reported mean C<sub>max</sub> value of  $9.46 \pm 2.02$  µg/mL with the intravenous formulation. Similarly, systemic concentrations following instillation of ganciclovir gel are much lower than the reported mean ganciclovir C<sub>max</sub> value of  $5.61 \pm 1.52$  µg/mL following oral administration of valganciclovir tablets.

Although the current application included multiple assessments of systemic exposure of ganciclovir 0.15% gel in both healthy subjects and acute herpetic keratitis patients, the Applicant did not submit adequate validation data to support the bioanalytical methods used in the pharmacokinetic studies. Thus, pharmacokinetic data from the ganciclovir 0.15% gel development program should be used for informational purposes only and should not be used for regulatory decisions (e.g. product labeling).

## 6. Sterility Assurance

From the Product Quality Microbiology Reviews finalized 8/4/09 and 9/9/09:

The drug product is formulated at 1.5 mg of ganciclovir per gram of clear colorless gel with benzalkonium chloride as preservative. The bulk formulation is sterilized \_\_\_\_\_

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The primary Container Closure System (CCS) for US commercial ST-605 consists of a \_\_\_\_\_ mL multidose polyfoil tube, a tip, and a cap. The polyfoil tube with tip and cap is supplied by \_\_\_\_\_  
The tube contains little or no headspace due to the filling and is closed using a \_\_\_\_\_ process by the contract manufacturer, Allied Medical Products (AMP)

b(4)

CDTL Review  
William M. Boyd, M.D.  
NDA 22-211  
Zirgan (ganciclovir ophthalmic gel) 0.15%

Laboratoires Théa (European manufacturer of the same product), evaluated the antimicrobial effectiveness of benzalkonium chloride and found that benzalkonium chloride at a concentration of 0.0075% was capable of ensuring a level of antimicrobial protection that satisfied the efficacy of the antimicrobial preservation.

On August 6, 2009, Sirion modified the Control of Drug Product Specifications section (3.2.P.5.1) to include a USP LAL Method MTM-200033 indicating an acceptable endotoxin specification for ganciclovir at  $< \frac{1}{10}$  EU/mL. This response is acceptable.

b(4)

## 7. Clinical/Statistical - Efficacy

From the original Medical Officer Review finalized 9/11/2009:

This 505(b)(1) application relies on four clinical studies (Study 4, 5, 6, and 7) conducted in Europe, Africa, and Asia between 1990 and 1994 which were originally sponsored by Laboratoires Thea formerly TRANSPHYTO S.A. to support efficacy and safety of ganciclovir ophthalmic gel 0.15% for the proposed indication, treatment of acute herpetic keratitis (dendritic ~~ulcers~~ ulcers).

b(4)

### Analyses of Endpoints

The primary efficacy endpoint used in the review of this NDA is cure rate (healed ulcers) at Day 7. This review analyzed the submitted clinical data as though the phase 2 and phase 3 studies were designed as non-inferiority trials.

### Efficacy Findings for Study 7 – Protocol Nos. 64.GV550/04.92 and 66.GV550/06.92

#### Median Time to Recovery (Days) – ITT Population

Treatment	Median
Ganciclovir 0.15%	7.0
Acyclovir 3%	7.0

Source: Sirion 5.3.5.1 Integrated Summary of Efficacy, 4.2.5 Median Time to Recovery (Days) – ITT Population

Although time to healing of ulcer (dendritic or geographic) was the specified primary efficacy endpoint for these protocols (see above), the primary efficacy endpoint used in the review of this NDA is cure rate (healed ulcers) at Day 7.

The statistical plan was written without an understanding of how to write a non-inferiority statistical plan. The assumption of a cure rate of 20% in 6 days for acyclovir and a 20% improvement for ganciclovir on this cure rate is not supported by the literature or the results from the ganciclovir phase 2 clinical trials. The cure rate for acyclovir is approximately 80%. This review analyzed the submitted clinical data as though study 7 was designed as non-inferiority trial. There is sufficient data in the literature to justify a non-inferiority margin for dendritic ulcers ~~\_\_\_\_\_~~.

b(4)

CDTL Review  
 William M. Boyd, M.D.  
 NDA 22-211  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

**Idoxuridine (IDU) vs Placebo – Day 7 Cure (Dendritic Ulcers)**

First Author	Year	Control	IDU Cures n/N (%)	Control Cures n/N (%)
Burns	1963	Water ± Mydriatics, Steroids	15/23 (65)	5/15 (33)
Davidson	1964	Gamma globulin 1%	12/25 (48)	8/25 (32)
Hart	1965	Neosporin 0.3% with 0.5% Chlorbutol	14/19 (74)	2/13 (15)
Laibson	1964	Water + Thimersol	15/22 (66)	7/26 (27)
Markham	1977	Ointment and Homatropine	4/20 (20)	4/19 (21)
Lutz	1963	Neosporin 1%	3/11 (27)	5/11 (45)
Patterson	1963	Culture medium	5/10 (50)	5/13 (38)
Patterson	1963	Phenyl mercuric nitrate	13/17 (76)	2/15 (13)
Patterson	1963	Occlusive dressing	11/16 (69)	0/14 (0)
Average (95% CI)			92/163 (56) (49%-64%)	38/151 (25) (18%-32%)

**Acyclovir vs IDU – Day 7 Cure (Dendritic Ulcers)**

First Author	Year	Control	Acyclovir Cures n/N (%)	IDU Cures n/N (%)
Colin	1981	IDU	19/25 (76)	11/27 (41)
Collum	1980	IDU	29/30 (97)	6/30 (20)
Coster	1980	IDU	27/28 (96)	22/26 (85)
Klauber	1982	IDU	8/10 (80)	5/10 (50)
McCulley	1982	IDU	16/26 (62)	16/26 (62)
Average (95% CI)			99/119 (83) (76%-90%)	60/119 (50) (41%-59%)

IDU is superior to placebo for the treatment of dendritic ulcers. Acyclovir 3% is superior to IDU for the treatment of dendritic ulcers. The data from the literature supports a non-inferiority margin of 44% for the active control, acyclovir 3%, over vehicle and 17% over IDU (typically referred to as M1).

CDTL Review  
 William M. Boyd, M.D.  
 NDA 22-211  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

**Study 7 – Cure Rate at Day 7 (Dendritic Ulcers)**

Treatment	n/N (%)	95 % CI
Ganciclovir 0.15%	55/71 (77)	68%-87%
Acyclovir 3%	48/67 (72)	64.2%-85.0%
Difference	5.8%	(-9.6%-18.3%)

The non-inferiority analysis showed that the lower 95% confidence interval around the difference between ganciclovir 0.15% and acyclovir 3% (9.6%) was no greater than the non-inferiority margin (10%).

**Efficacy Findings for Study 4 (Protocol No.: 42-2.GV550/02.90), Study 5 (Protocol Nos.: 44.GV550/12.90 and 46.GV 550/07.90), and Study 6 (Protocol No.: 47.GV550/09.90)**

**Study 4 – Cure Rate at Day 7 (Dendritic Ulcers)**

Treatment	n/N (%)
Acyclovir 3%	11/17 (65)
Ganciclovir 0.15%	13/20 (65)
Ganciclovir 0.05%	13/20 (65)

**Study 5 – Cure Rate at Day 7 (Dendritic Ulcers)**

Treatment	n/N (%)
Acyclovir 3%	10/17 (59)
Ganciclovir 0.15%	14/17 (82)

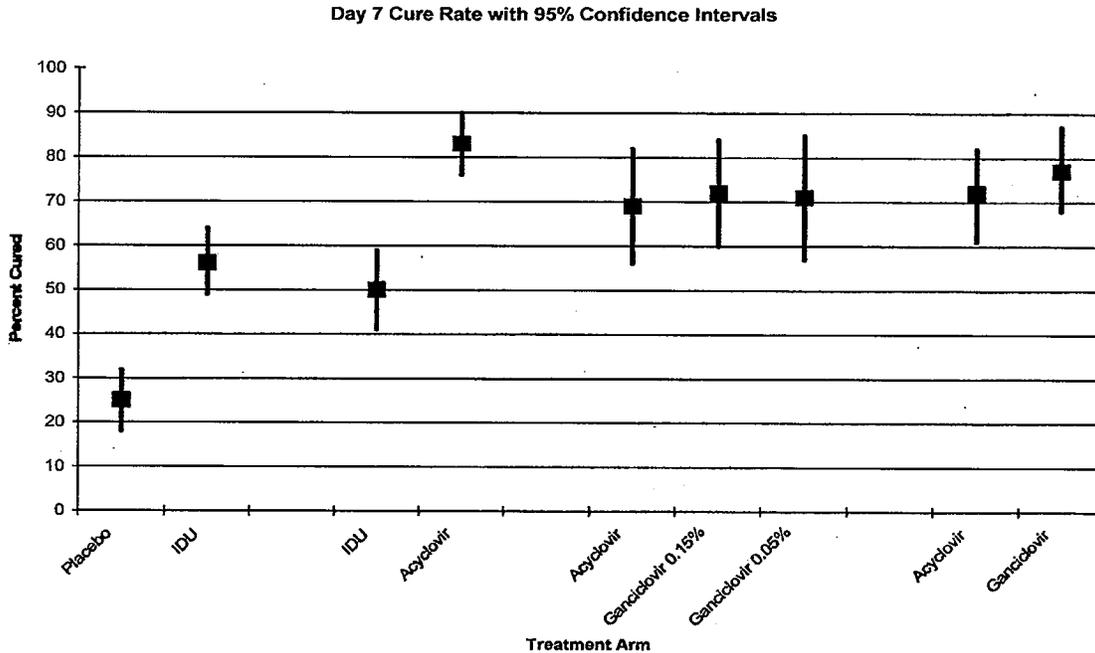
**Study 6 – Cure Rate at Day 7 (Dendritic Ulcers)**

Treatment	n/N (%)
Acyclovir 3%	13/15 (87)
Ganciclovir 0.15%	14/20 (70)
Ganciclovir 0.05%	16/21 (76)

**Combined Phase 2 Studies – Cure Rate at Day & (Dendritic Ulcers)**

Treatment	n/N (%)	95 % CI
Acyclovir 3%	34/49 (69)	56%-82%
Ganciclovir 0.15%	41/57 (72)	60%-84%
Ganciclovir 0.05%	29/41 (71)	57%-85%
Difference between Acyclovir and ganciclovir 0.15%	2.5%	-15.6%-20.9%

The cure rate at Day 7 (dendritic ulcers) for ganciclovir and acyclovir 3% are similar. The phase 2 study data (Study 4, 5, and 6) demonstrate that ganciclovir is not inferior to acyclovir 3% for dendritic ulcers, non-inferiority margin 16%.



IDU is superior to placebo; acyclovir is superior to IDU; and ganciclovir is not inferior to acyclovir.

### Efficacy Summary Statement

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Zirgan (ganciclovir ophthalmic solution) 0.15% is effective in the treatment of acute herpetic keratitis (dendritic ulcers). Study 7 demonstrated that that the lower 95% confidence interval around the difference between ganciclovir 0.15% and acyclovir 3% (9.6%) was no greater than the non-inferiority margin (10%). Studies 4, 5, and 6 demonstrated that the cure rate at Day 7 (dendritic ulcers) for ganciclovir and acyclovir 3% was similar, i.e. ganciclovir is not inferior to acyclovir 3% for dendritic ulcers (non-inferiority margin 16%).

b(4)

### 8. Safety

From the original Medical Officer Review finalized 9/11/2009:

The patient exposure and safety assessments were adequate.

CDTL Review  
 William M. Boyd, M.D.  
 NDA 22-211  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

A total of 161 and 57 subjects were exposed to ganciclovir 0.15% and ganciclovir 0.05%, respectively in three phase 2 (studies 4, 5, and 6) and one phase 3 studies (study 7). The mean days of exposure were 11.5 days for ganciclovir 0.15% and 9.1 days for ganciclovir 0.05%.

Pooled data may be presented because of the small number of adverse events reported.

**Drop-outs for Studies 4, 5, 6, and 7**

Study	Treatment		
	Ganciclovir 0.15% n/N (%)	Acyclovir 3% n/N (%)	Ganciclovir 0.05% n/N (%)
4	3/23 (13.0)	7/22 (31.8)	6/22 (27.3)
5	2/18 (11.1)	7/17 (41.2)	
6	2/36 (5.6)	8/38 (22.2)	4/35 (11.4)
7	11/71 (15.5)	8/67 (11.9)	

Source: Sirion 5.3.5.1 Integrated Summary of Efficacy, Study 7-Table 3, Study 6-Table 4.A, Study 5-Table 4.A, Study 4-Table 4.A

**Drop-outs Due to Adverse Events for Studies 4, 5, 6, and 7**

Study	Treatment		
	Ganciclovir 0.15% n/N (%)	Acyclovir 3% n/N (%)	Ganciclovir 0.05% n/N (%)
4	0/23 (0.0)	0/22 (0.0)	0/22 (0.0)
5	0/18 (0.0)	0/17 (0.0)	
6	0/36 (0.0)	0/38 (0.0)	0/35 (0.0)
7	2/71 (2.8)	1/67 (1.5)	

Source: Sirion 2.7.4.6.2 Treatment-Related Withdrawals Due to Adverse Events

**Study 7 – Drop-outs Due to Adverse Event**

Subject No.	Ganciclovir 0.15%	Acyclovir 3%
074	Foreign body in eye, resulting in palpebral and conjunctival disorders, superficial punctate keratitis (SPK), and epithelial abrasion	
537	Bilateral conjunctival hyperemia recorded 48 hours after cessation of treatment (so it was not possible at the study visit to determine whether the subject applied the product to both eyes), minimal SPK, burning	
032		SPK, initial signs of punctuate keratitis

Source: Sirion 2.7.4.6.2 Summary of Clinical Safety, Table 4. Withdrawal Due to Adverse Events

CDTL Review  
 William M. Boyd, M.D.  
 NDA 22-211  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

### Common Adverse Events – Studies 4, 5, 6 & 7 Pooled – Safety Population

Measure	Study 4		Study 5		Study 6		Study 7		Total			
	GAN 0.15%	ACY	GAN 0.05%	GAN 0.15%	ACY	GAN 0.15%	ACY	GAN 0.15%	ACY	GAN 0.15% & 0.05% N=218	ACY	
	N=23	N=22	N=22	N=18	N=17	N=36	N=38	N=35	N=84	N=80	N=167	
Ocular												
Vision blurred	3 13%	3 13.6%	3 13.6%	14 77.8%	16 94.1%	33 91.7%	37 97.4%	33 94.3%	43 51.2%	56 70%	129 59.2%	112 71.3%
Eye irritation	4 17.4%	10 45.5%	5 22.7%	3 16.7%	10 58.8%	1 2.8%	2 5.3%	1 2.9%	25 29.8%	35 43.8%	39 17.9%	55 46.2%
Punctate keratitis	3 13%	2 9.1%	0	0	0	0	0	0	8 9.5%	17 21.3%	11 5.0%	19 11.4%
Conjunctival hyperemia	1 4.3%	0	1 4.5%	4 22.2%	2 11.8%	0	0	2 5.7%	2 2.4%	4 5%	10 4.6%	6 3.6%
Erythema of the eyelid	1 4.3%	0	1 4.5%	2 11.1%	2 11.8%	0	0	0	1 1.2%	2 2.5%	5 2.3%	4 2.4%
Corneal disorder	0	0	0	0	1 5.9%	0	0	0	1 1.2%	0	1 0.5%	1 0.6%
Eye pain	0	0	0	0	0	0	1 2.6%	1 2.9%	0	0	1 0.5%	1 0.6%
Dry eye	0	0	0	0	0	0	0	1 2.9%	0	0	1 0.5%	0
Lacrimation increased	0	0	0	0	0	0	0	1 2.9%	0	0	1 0.5%	0
Foreign body sensation	0	0	0	0	0	0	0	1 2.9%	0	0	1 0.5%	0
Non-ocular												
Dysgeusia	0	0	0	0	0	0	0	0	1 1.2%	0	0	1 0.6%
Headache	0	0	0	0	0	0	1 2.6%	0	0	0	0	1 0.6%

GAN=ganciclovir, ACY=acyclovir 3%  
 Source: Sirion 2.7.4.4.4 – Summary of Clinical Safety, Tables 2 and 3

Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%). No non-ocular adverse events occurred at a rate of 5% or more.

### Safety Summary Statement

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Zirgan, dosed 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until corneal ulcer heals, and then 1 drop 3 times per day for 7 days, is safe for the treatment of treatment of acute herpetic keratitis (dendritic ulcers).

CDTL Review  
William M. Boyd, M.D.  
NDA 22-211  
Zirgan (ganciclovir ophthalmic gel) 0.15%

## 9. Advisory Committee Meeting

No Advisory Committee Meeting was necessary for Zirgan (ganciclovir ophthalmic gel) 0.15%.

## 10. Pediatrics

This drug product has been designated an orphan drug and hence, is exempt from the pediatric assessment requirement under 21 CFR 314.55(d). Safety and efficacy in pediatric patients below the age of 2 years have not been established.

## 11. Other Relevant Regulatory Issues

### DSI

A Division of Scientific Investigations (DSI) audit was not requested.

The NDA studies were not conducted under an IND, and the data was gathered solely from foreign sites.

### FINANCIAL DISCLOSURE

All clinical studies included in this application were conducted in Europe, Africa, and Asia between 1990 and 1994 and were originally sponsored by Laboratoires Théa formerly (TRANSPHYTO S.A.). Laboratoires Théa, a pharmaceutical company based in Clermont-Ferrand, France, was not required to collect financial disclosure information from the investigators in those studies.

### DMEPA

The Division of Medication Error Prevention and Analysis objected to the Applicant's primary name, Virgan (OSE Review #2007-1171, dated June 14, 2007) due to potential orthographic and phonetic confusion with Veregen, an approved drug product in the U.S. Subsequently, DMEPA objected to the Applicant's second and third name choices, \_\_\_\_\_ due to the inclusion of the USAN stems -vir and -vir-, respectively, as well as potential orthographic confusion between \_\_\_\_\_ and Denavir and between \_\_\_\_\_ and Zovirax OSE Review # 2008-1300/2008-1302, dated April 6, 2009). Zirgan is the Applicant's fourth name choice. b(4)

DAIOP concurred with DMEPA's objection to the proposed names, \_\_\_\_\_, based on the orthographic similarity arguments. However, DAIOP disagreed with DMEPA's position regarding USAN stems. b(4)

The Proprietary Name Risk Assessment findings indicated that the proposed name, Zirgan, is not vulnerable to name confusion that could lead to medication errors. Thus the Division of Medication Error Prevention and Analysis (DMEPA) had no objection to the proprietary name, Zirgan, for this

CDTL Review  
William M. Boyd, M.D.  
NDA 22-211  
Zirgan (ganciclovir ophthalmic gel) 0.15%

product at this time. Additionally, DDMAC did not object to the proposed name, Zirgan, from a promotional perspective.

DMEPA also provided recommendations on the packaging configuration and the package insert labeling. These are incorporated into the Medical Officer's labeling where appropriate. DMEPA was present at the wrap-up meeting/pre-approval safety meeting for this application, held on September 2, 2009. DMEPA was in agreement with the comments proposed to the applicant regarding the final package insert, carton, and container labeling.

#### **DDMAC**

DDMAC reviewed the proposed product labeling for Zirgan (ganciclovir ophthalmic gel) 0.15% submitted by the applicant in July 2009, and offered the following comments.

Regarding the Dosage and Administration Section:

- Please consider adding more elaboration on what defines a corneal ulcer as healed.

The addition of this information to the Dosage and Administration Section is not recommended. It has the potential to promote off label use of the product for either re-epithelialization of the cornea or prevention of corneal scarring.

Regarding the Adverse Events Section:

- Please include an adequate description of the data sources for the adverse event data, as outlined in the guidance. For example, please include information on whether the trials were double blinded, randomized, and placebo controlled trials, if available. Also, please include the dosage, frequency, and duration of therapy that patients received.
- Identify adverse reactions, if any, that resulted in a significant rate of discontinuation or other clinical intervention (e.g., dosage adjustment, need for other therapy to treat an adverse reaction) in clinical trials.

The addition of these statements to the Adverse Events Section is not recommended. The adverse events noted in Section 6 of the labeling were seen in multiple trials conducted in Europe outside an IND application; these trials varied in duration, design, dosing, and control arm. There were no adverse reactions resulting in a significant rate of discontinuation.

Regarding the Clinical Studies Section:

- The description of the clinical studies is vague and may be used by the sponsor to promote in a misleading manner. We suggest rewriting this section with the following information: number of patients studied in each arm of the trial(s), age ranges of the patients, major study endpoints, descriptions of the measurement tools used to evaluate the outcomes (the measurable signs of clinical resolution), actual results in tabular format, and any appropriate accompanying statistics.

CDTL Review  
William M. Boyd, M.D.  
NDA 22-211  
Zirgan (ganciclovir ophthalmic gel) 0.15%

- Specifically, please provide more information on the definition of clinical resolution (healed ulcers). Please be aware that there have been promotional issues with sponsors using a different definition of "clinical resolution" than the FDA used for analysis of results.

The addition of these statements to the Clinical Trials Section is not recommended. The results noted in Section 14 of the labeling were seen in multiple trials conducted in Europe outside an IND application; these trials varied in duration, design, dosing, and used unapproved products as active control arms. Supplying a tabular format would likely overstate the efficacy of the drug in promotional materials or promote off-label use of the control product.

Regarding the Patient Counseling Information Section:

- Please consider adding the information that patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with Zirgan.

The final package insert contains the statement, "Patients should be advised not to wear contact lenses when using ZIRGAN."

Regarding the Draft Carton Label, Draft Container Label:

0(4)

DDMAC was invited to the wrap-up meeting/pre-approval safety meeting for this application, held on September 2, 2009, but did not attend. Final labeling was discussed at this meeting.

## **BIOSTATISTICS**

Per the Biostatistics consultative review finalized 7/6/09:

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

CDTL Review  
William M. Boyd, M.D.  
NDA 22-211  
Zirgan (ganciclovir ophthalmic gel) 0.15%

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.

These conclusions by the Biostatistics Reviewer **are not in agreement** with the conclusions reached between Clinical and Biostatistics disciplines at the CDER Regulatory Briefing held March 27, 2009. In a separate memorandum dated September 1, 2009, from the Director, Division of Biometrics IV/Office of Biostatistics/OTS:

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.

In agreement with the Director, Division of Biometrics IV, Study 7 is not the sole basis to support efficacy of Zirgan. Studies 4, 5, and 6 have also been considered and determined to be supportive of efficacy.

## 12. Labeling

NDA 22-211, Zirgan (ganciclovir ophthalmic gel) 0.15% is recommended for approval for the treatment of acute herpetic keratitis (dendritic ulcers) with the labeling submitted on September 9, 2009, and found in the Appendix at the end of this CDTL review.

CDTL Review  
William M. Boyd, M.D.  
NDA 22-211  
Zirgan (ganciclovir ophthalmic gel) 0.15%

### **13. Recommendations/Risk Benefit Assessment**

#### **RECOMMENDED REGULATORY ACTION:**

NDA 22-211, Zirgan (ganciclovir ophthalmic gel) 0.15% is recommended for approval for the treatment of acute herpetic keratitis (dendritic ulcers). There is substantial evidence consisting of adequate and well controlled studies which demonstrate that Zirgan, dosed 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until corneal ulcer heals, and then 1 drop 3 times per day for 7 days, is safe and effective for the treatment of acute herpetic keratitis (dendritic ulcers).

Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%).

#### **RISK BENEFIT ASSESSMENT:**

The submitted studies in this NDA support a favorable risk/benefit profile regarding the safety and efficacy of ganciclovir in the treatment of acute herpes simplex keratitis (dendritic ulcer). The most common adverse events were blurred vision (60%) and eye irritation (20%).

Pharmacology/Toxicology, CMC, Clinical, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

The Biostatistics reviewer does not recommend approval; however, the Division Director of Biometrics IV has written a separate memorandum supporting approval by taking into account multiple studies.

#### **RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:**

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

6 Page(s) Withheld

         Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

         Draft Labeling (b5)

         Deliberative Process (b5)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22211	ORIG-1	SIRION THERAPEUTICS	ZIRGAN (GANCICLOVIR OPHTHALMIC GEL)0.15%

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/s/

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WILLIAM M BOYD  
09/15/2009

WILEY A CHAMBERS  
09/15/2009