

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-211

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	22-211
Submission Date(s):	17NOV2008
Brand Name	Zirgan
Generic Name	ST-605; ganciclovir ophthalmic gel, 0.15%
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Applicant	Allergan, Inc.
Relevant IND(s)	IND 75,762
Submission Type; Code	Original NDA; 505(b)(1) application
Formulation; Strength(s)	Ganciclovir ophthalmic gel, 0.15%
Indication	Treatment of acute herpetic keratitis (dendritic ulcers)

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1. EXECUTIVE SUMMARY

ST-605 is an ophthalmic gel formulation of ganciclovir 0.15% for topical instillation. Ganciclovir is a synthetic guanine derivative antiviral drug that, upon phosphorylation, inhibits DNA replication by herpes simplex viruses (HSV). ST-605 is proposed for the treatment of acute herpetic keratitis (dendritic ~~ulcers~~ ulcers). The proposed dosage and route of administration for ST-605 is as follows: 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until the corneal ulcer heals, and then 1 drop 3 times per day for 7 days.

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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. In December 2000, Transphyto SA and Laboratoires Théa merged and the marketing authorization for ST-605 was transferred to Laboratoires Théa. Since this initial approval, ST-605 has been approved in over 30 countries 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.

On March 27, 2009 a CDER regulatory briefing was held to discuss the findings from the Phase 3 development program for ganciclovir 0.15% gel, specifically efficacy results using topical ophthalmic acyclovir 3%, a product not approved in the US, as an active comparator. Trifluridine is the only currently marketed topical ophthalmic antiviral agent in the US. Acyclovir 3% was used as the comparator in the ganciclovir development program because placebo-controlled trials were considered unethical at the time the clinical trials were conducted and acyclovir 3% has efficacy similar to that of trifluridine. In addition, the dosing regimen for acyclovir is less frequent than that of trifluridine and identical to that of ganciclovir. The briefing focused on acceptance of trials with non-FDA active controls and reassessment of primary hypotheses from pre-planned superiority trials to post-hoc non-inferiority analysis.

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).

1.1. Recommendation

The clinical pharmacology information provided by the Applicant is acceptable.

1.2. Phase IV Commitments

No phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology Findings

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

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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, and 7. The clinical pharmacology findings from these studies are summarized as follows:

- 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.
- 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_{max} value of 9.46 ± 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_{max} value of 5.61 ± 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).

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Division File: NDA 22-211
HFD-520 (CSO/Gorski)
HFD-520 (MO/Lim)
HFD-520 (Chambers, Boyd)
HFD-880 (Lazor, Reynolds, Bonapace)

2. QUESTION BASED REVIEW

Since this submission is an NDA for a locally administered ophthalmic drug product, only relevant questions from the OCP question-based review (QBR) format are addressed below.

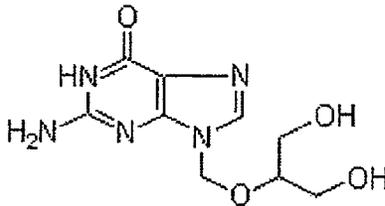
2.1. General Attributes of the Drug

2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

ST-605 is an ophthalmic gel formulation of ganciclovir 0.15% for topical instillation. The chemical structure and physical-chemical properties of ST-605 are as follows:

Structural Formula: C₉H₁₃N₃O₄

Chemical Structure:



Chemical Name: 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine

Compendial Name: Ganciclovir

International Nonproprietary Name (INN): Ganciclovir

Molecular Weight: 255.23

The qualitative and quantitative composition of the proposed ST-605 ganciclovir 0.15% ophthalmic gel drug product is shown in Table 2.2-1.

Table 2.2-1 Composition of ST-605 Ganciclovir 0.15% Ophthalmic Gel

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

Source: Section 3.2.P.1.2

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The quantitative composition of the ST-605 formulations that were used during clinical development and the current formulation marketed outside the US is presented in Table 2.2-2. Formulation A was used in the Phase 2 clinical trials (Studies 4, 5, and 6). During clinical development, the preservative used in the formulation was changed from sodium mercurothiolate at a concentration of 0.0060% (Formulation A) to benzalkonium chloride 0.0075% (Formulation B). Formulation B was then used in Studies 2 and 3 and in the Phase 3 trial (Study 7). Formulation B was the original commercially marketed formulation in Europe (first approved in 1995). A transition from Formulation B to the currently marketed formulation in Europe, Formulation C, occurred in 2001. The difference between Formulation B and Formulation C is as follows:

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Formulation B* is the proposed formulation for marketing authorization in the US. Formulation B*

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Table 2.2-2 ST-605 Ganciclovir 0.15% Ophthalmic Gel Formulation History

Parameter	Formulation/Variation			
	A	B	B*	C
Ganciclovir Concentration	0.05% and 0.15%	0.15%	0.15%	0.15%
Ganciclovir Source				

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qs, quantity sufficient

Source: Section 3.2.P.2.2 Drug Product

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Ganciclovir is a synthetic guanine derivative antiviral drug that upon phosphorylation, inhibits DNA replication by herpes simplex viruses (HSV). Ganciclovir is transformed by viral and cellular thymidine kinases (TK) to ganciclovir triphosphate, which works as an antiviral agent by inhibiting the synthesis of viral DNA in two ways: competitive inhibition of viral DNA-polymerase and direct incorporation into viral primer strand DNA, resulting in DNA chain termination and prevention of replication. ST-605 is proposed for the treatment of acute herpetic keratitis (dendritic ulcers).

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2.1.3. What is the proposed dosage and route of administration?

The proposed dosage and route of administration for ZIRGAN is as follows: 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until the corneal ulcer heals, and then 1 drop 3 times per day for 7 days.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?

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). These studies enrolled a total of 16 healthy subjects and 377 subjects with acute herpetic keratitis across multiple clinical investigative sites in Africa, Europe, and Asia. The active comparator in the Phase 2 and 3 clinical studies was topical ophthalmic acyclovir 3% ointment, the standard of care in Europe. Studies 1, 4, and 6 included both ST-605 and the development formulation ganciclovir 0.05% treatments. The dosing regimen for ganciclovir was the same in Studies 4, 5, and 7 (ie, 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 marketing. Study 6 maintained dosing at 5 times per day for 10 days. Pharmacokinetic data was obtained in Studies 1, 2, 3, and 7. Design features of the studies conducted for ST-605 are summarized in Table 2.2.1-1.

On March 27, 2009 a CDER regulatory briefing was held to discuss the findings from the Phase 3 development program for ganciclovir 0.15% gel, specifically efficacy results using topical ophthalmic acyclovir 3%, a product not approved in the US, as an active comparator. Trifluridine is the only currently marketed topical ophthalmic antiviral agent in the US. Acyclovir 3% was used as the comparator in the ganciclovir development program because placebo-controlled trials were considered unethical at the time the clinical trials were conducted and acyclovir 3% has efficacy similar to that of trifluridine. In addition, the dosing regimen for acyclovir is less frequent than that of trifluridine and identical to that of ganciclovir. The briefing focused on acceptance of trials with non-FDA active controls and reassessment of primary hypotheses from pre-planned superiority trials to post-hoc non-inferiority analysis. For additional information on the regulatory briefing, refer to the Medical Officer's and Biostatistician's review of NDA 22-211.

Table 2.2.1-1 Clinical Studies Supporting the Efficacy and Safety of ST-605

Study	Study Objective	Design	Treatment/Duration	Population	# Subjects
Study 1	Evaluate the plasma concentrations of ganciclovir after repeated administration of ST-605 and ganciclovir 0.05% in subjects with herpetic keratitis	Phase 1/2, single-center (subset of Study 4)	ST-605 or ganciclovir 0.05%: 1 drop 5x/day until the ulcer healed, then 3x/day for 7 days (11-15 days)	Herpetic keratitis with dendritic or geographic ulcers (Note: This study used a subset of subjects in Study 4)	N=24 subjects ST-605: 11 subjects Ganciclovir 0.05%: 13 subjects
Study 2	To determine the concentration of ganciclovir in tears after repeated administration of ST-605	Phase 1, single-center, open-label	ST-605: 1 drop instilled into the conjunctival sac 4x in 1 day	Healthy male volunteers	N=6 subjects ST-605: 6 subjects
Study 3	To determine the plasma concentration of ganciclovir and to compare the local ocular tolerance of ST-605 with its vehicle after repeated administration	Phase 1, randomized, double-masked, within-subject (left vs. right eye) comparator of ST-605 vs. vehicle control	ST-605 in 1 eye and vehicle control in opposite eye; 1 drop instilled into the conjunctival sac 5x/day for 7 days	Healthy male volunteers	N=10 subjects ST-605: 10 subjects
Study 4	To evaluate the efficacy and safety of ST-605 and ganciclovir 0.05% vs acyclovir 3% in the treatment of herpetic keratitis	Phase 2, comparative, multicenter, randomized, stratified by center, comparison of ST-605 and ganciclovir 0.05% vs acyclovir 3%	ST-605 or ganciclovir 0.05% or acyclovir 3%: 1 drop instilled into the conjunctival sac 5x/day until the ulcer has healed, then 3x/day for 7 days	Herpetic keratitis with dendritic or geographic ulcers	N=67 subjects ST-605: 23 subjects Ganciclovir 0.05%: 22 subjects Acyclovir 3%: 22 subjects
Study 5	To evaluate the efficacy and safety of ST-605 vs acyclovir 3% in the treatment of herpetic keratitis	Phase 2, comparative multicenter, randomized, stratified by center, comparison of ST-605 vs acyclovir 3%	ST-605 or acyclovir 3%: 1 drop instilled into the conjunctival sac 5x/day until the ulcer has healed, then 3x/day for 7 days	Herpetic keratitis with dendritic or geographic ulcers	N=37 subjects ST-605: 19 subjects Acyclovir 3%: 18 subjects
Study 6	To evaluate the efficacy and safety of ST-605 and ganciclovir 0.05% vs acyclovir 3% in the treatment of herpetic keratitis	Phase 2, comparative, randomized, single-masked, comparator study of ST-605 and ganciclovir 0.05% vs acyclovir 3%	ST-605 or ganciclovir 0.05% or acyclovir 3%: 1 drop or strip instilled into the conjunctival sac 5x/day for 10 days	Herpetic keratitis with dendritic or geographic ulcers	N=109 subjects ST-605: 36 subjects Ganciclovir 0.05%: 35 subjects Acyclovir 3%: 38 subjects

Note: ST-605 refers to ganciclovir 0.15% gel formulation.

Table 2.2.1-1 Clinical Studies Supporting the Efficacy and Safety of ST-605 (continued)

Study	Study Objective	Design	Treatment/Duration	Population	# Subjects
Study 7	To evaluate the efficacy and safety of ST-605 vs acyclovir 3% in the treatment of herpetic keratitis by ulcer type	Phase 3, open-label, multicenter, randomized, stratified by center and ulcer type, comparator of ST-605 vs acyclovir 3%	ST-605 or acyclovir 3%: 1 drop instilled into the conjunctival sac 5x/day until ulcer has healed, then 3x/day for 7 days	Herpetic keratitis with dendritic or geographic ulcers	N=164 subjects total Dendritic ulcers: 138 subjects Geographic ulcers: 26 subjects ST-605: 84 subjects total Dendritic ulcers: 71 subjects Geographic ulcers: 13 subjects Acyclovir 3%: 80 subjects total Dendritic ulcers: 67 subjects Geographic ulcers: 13 subjects

Note: ST-605 refers to ganciclovir 0.15% gel formulation.

Source: 5.2 Tabular Listing of All Clinical Studies

2.2.2. *What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?*

The primary efficacy evaluation criteria for the four clinical efficacy trials were recovery rate (evaluated as the absence of fluorescein staining at the ulcer site), time until recovery of the ulcer, relapses, and withdrawals due to lack of efficacy. Recovery rate was defined as the proportion of subjects whose ulcer healed at any time point during the study.

2.2.3. *Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?*

The active moiety ganciclovir was identified and measured in plasma and urine for purposes of assessment of systemic exposure following ocular administration. Tear concentrations were also measured in one Phase 1 study. Complete bioanalytical reports were not available for submission in this NDA. Refer to Section 2.3 for further details regarding analytical methodology and performance.

2.2.4. *Exposure-Response*

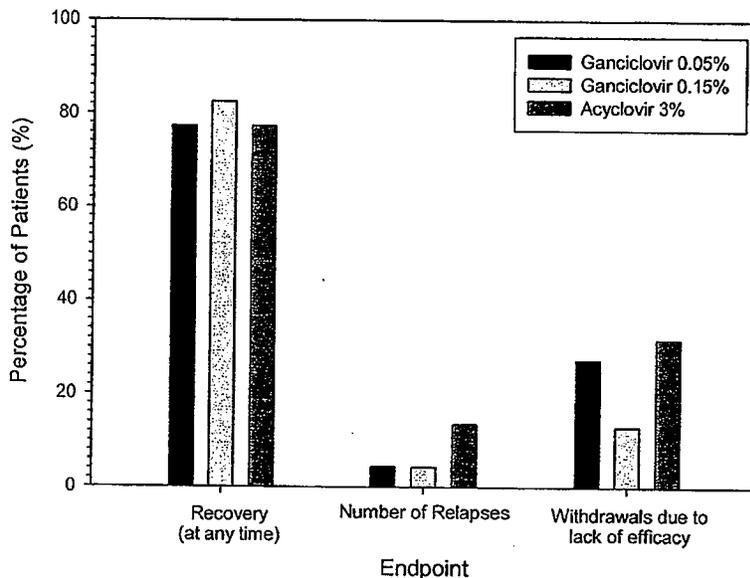
2.2.4.1. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

The integrated efficacy results of the clinical studies conducted for ganciclovir showed that ST-605 (ganciclovir 0.15%) administered 5 times a day until the healing of the herpetic ulcers, then 3 times a day for an additional 7 days, was at least as effective as acyclovir 3% for the treatment of acute herpetic keratitis. The recovery rates, which are the proportion of subjects whose ulcers were healed, were 87% for ST-605 and 82.8% for acyclovir 3% across the four efficacy studies included in the integrated analysis (three Phase 2 and one Phase 3 study). The integrated results also showed that ST-605 healed dendritic and geographic ulcers faster than acyclovir 3% (median time to healing, 6 days versus 7 days, respectively). ST-605 had fewer incidences of relapses and a higher investigator rating of efficacy than acyclovir 3%.

In the two clinical studies that compared ST-605 and ganciclovir 0.05% (Studies 4 and 6), the higher concentration of ST-605 (0.15%) was more effective than ganciclovir 0.05%. Study 4 was a Phase 2, multicenter, randomized, comparative study conducted in Africa and stratified by center, evaluating ST-605 (ganciclovir 0.15%), ganciclovir 0.05%, and topical ophthalmic acyclovir 3%. Sixty-seven (67) subjects with herpetic keratitis received one of the three study drugs as 1 drop 5 times daily until the ulcer recovered, and then 3 times daily for an additional 7 days. The efficacy evaluation criteria was the time until the ulcer recovered (evaluated by the absence of fluorescein staining at the ulcer site), recovery rates, the number of relapses, withdrawals due to lack of efficacy, and the investigator's assessment of efficacy. Evaluations were performed on Days 2, 7, 10, and 14, with a follow-up visit at Day 21 if the ulcer recovered at Day 14. All results relating to recovery rates, number of relapses, and withdrawals due to lack of efficacy showed a trend towards the superiority of ST-605 in comparison with ganciclovir 0.05% and better efficacy of ST-605 compared with acyclovir 3%, as displayed in Figure 2.2.4.1-1. The recovery rates at any time were 82.6% (19/23) in the ST-605 group, 77.3% (17/22) in the acyclovir 3% group, and 77.3% (17/22) for the ganciclovir 0.05% group. Only one relapse was found in each of the ganciclovir groups (ST-605, 4.3% [1/23]; ganciclovir 0.05%, 4.5% [1/22]); three relapses were found in the acyclovir 3% group (13.6% [3/22]). The

percentage of subjects who withdrew due to lack of efficacy in the acyclovir 3% group (31.8% [7/22]) was significantly higher than that of the ST-605 group (13% [3/23]). The median time to recovery was 7 days across the three groups.

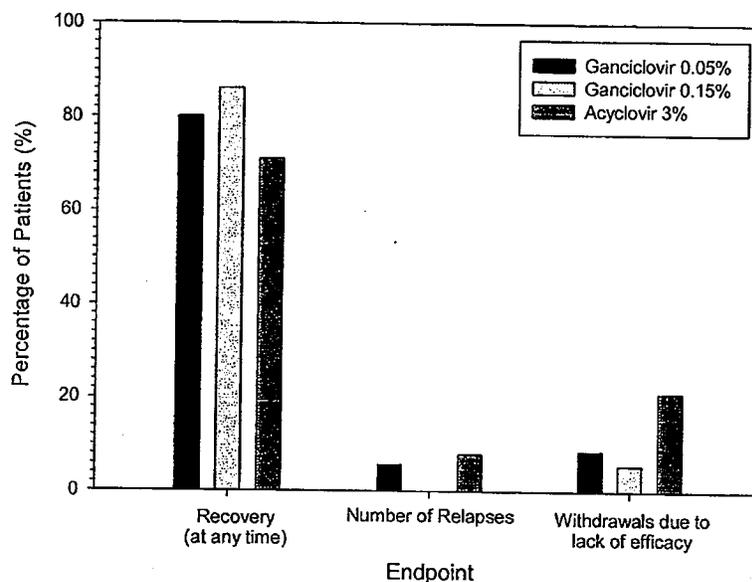
Figure 2.2.4.1-1. Summary of Efficacy Results – Study 4 (ITT Population)



Source: 2.7.3 Summary of Clinical Efficacy

Study 6 was a Phase 2, multicenter, randomized, comparative study conducted in Pakistan evaluating ST-605 (ganciclovir 0.15%), ganciclovir 0.05%, and topical ophthalmic acyclovir 3%. There were 109 subjects with herpetic keratitis, randomized to one of the treatment groups, who received their study drug as 1 drop 5 times daily for 10 days and were evaluated on Days 3, 7, 10, and 14. The efficacy evaluation criteria were time until the ulcer recovered (evaluated by the absence of fluorescein staining at the ulcer site), recovery rate, the number of relapses, and withdrawals due to lack of efficacy. In this study, ST-605 and ganciclovir 0.05% were as effective as acyclovir 3%, although there were no significant differences between the three treatment groups in recovery rate at any time (ST-605, 86.1% [31/36]; acyclovir 3%, 71.1% [27/38]; ganciclovir 0.05%, 80% [28/35]) or time to recovery of the ulcer (ST-605, 6 days; acyclovir 3%, 7 days; ganciclovir 0.05%, 4 days). Subjects treated with ST-605 had a lower rate of withdrawals for lack of efficacy than those treated with either ganciclovir 0.05% or acyclovir 3% (ST-605, 5.6% [2/36]; acyclovir 3%, 21.1% [8/38]; ganciclovir 0.05%, 8.6% [3/35]), as displayed in Figure 2.2.4.1-2.

Figure 2.2.4.1-2. Summary of Efficacy Results – Study 6 (ITT Population)



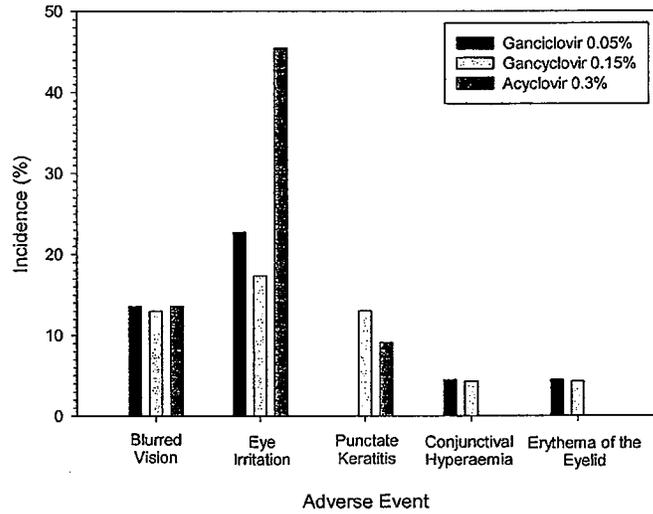
Source: 2.7.3 Summary of Clinical Efficacy

In summary, a dose-response relationship for efficacy was suggested in both the phase 2 studies which compared ganciclovir 0.05% and 0.15% (Studies 4 and 6). 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. For further discussion of the efficacy comparison of the two ganciclovir doses, refer to the Medical Officer's review of NDA 22-211.

2.2.4.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

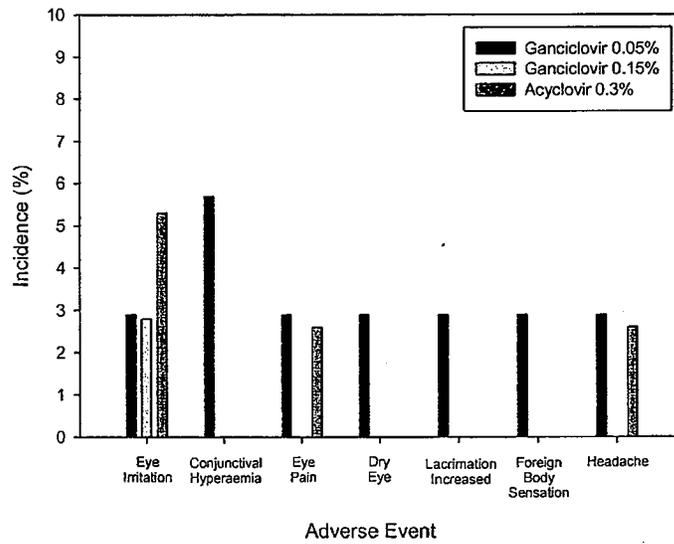
In general, subjects in the ganciclovir treatment groups had similar frequency and severity of adverse events in the two phase 2 clinical studies that compared ganciclovir 0.05% and 0.15% (Studies 4 and 6). Adverse events reported in Studies 4 and 6 are presented in Figures 2.2.4.2-1 and 2.2.4.2-2, respectively. In Study 4, the two formulations of ganciclovir had similar adverse event profiles except for punctate keratitis; the incidence of punctate keratitis was higher in the 0.15% treatment group versus the 0.05% group (incidences of 13% and 0%, respectively) but comparable to acyclovir 0.3% (incidence of 9.1%). In study 6, ganciclovir 0.05% had more ocular adverse events versus ganciclovir 0.15%. The two ganciclovir formulations are similar in composition (see Table 2.2-2), therefore any differences in adverse events could not be attributed to differences in formulation (e.g. excipients).

Figure 2.2.4.2-1. Adverse Events Reported in Study 4 (Safety Population – Pooled Dendritic and Geographic Populations)



Source: 2.5 Clinical Overview

Figure 2.2.4.2-2. Adverse Events Reported in Study 6 (Safety Population)



Source: 2.5 Clinical Overview

In summary, no dose-response relationship for safety was observed in the Phase 2 studies which compared ganciclovir 0.05% and 0.15% (Studies 4 and 6). For further discussion of the safety comparison of the two ganciclovir doses, refer to the Medical Officer's review of NDA 22-211.

2.2.5. *What are the PK characteristics of the drug and its major metabolite?*

2.2.5.1. *Systemic Exposure Following Ocular Administration*

The extent of local and systemic exposure to ganciclovir from topical ophthalmic administration of ST-605, ganciclovir 0.15% gel, was evaluated in four clinical studies: two multiple dose pharmacokinetic studies in healthy volunteers (Studies 2 and 3) and studies in subjects with acute herpetic keratitis as part of the Phase 2 and Phase 3 clinical studies (Studies 1 [a subset of patients in Study 4] and 7).

In Study 3, ten healthy male volunteers received ganciclovir 0.15% administered as 1 drop 5 times per day for 7 days, and blood was collected to measure the plasma concentrations of ganciclovir after 7 days of treatment. In healthy volunteers, the mean \pm SD plasma concentration was 11.5 ± 11.8 ng/mL (range: 0 to 30 ng/ml) at an average of 3.5 hours following instillation (range: 2.25 to 4 hours). In four subjects (Subjects 4, 5, 6 and 10), ganciclovir concentrations were lower than the quantification threshold of the method (5 ng/mL). The highest concentration observed was 30 ng/mL. Plasma concentrations of ganciclovir were also determined in herpetic keratitis patients enrolled in Study 1 (a subset of patients enrolled in Study 4). Plasma samples were obtained on the 14th day of treatment with ganciclovir 0.15% and 0.05% administered 5 times a day until cicatrization of the ulcer, then 3 times a day for one week. The mean \pm SD plasma concentration measured in patients receiving ganciclovir 0.15% in Study 4 was 12.7 ± 12.2 ng/ml (range: 0 to 37 ng/ml) at an average of 42 minutes following instillation (range: 30 to 70 minutes). Ganciclovir concentrations obtained in healthy subjects and in herpetic keratitis patients in Studies 3 and 4 following multiple administration of 0.15% ganciclovir gel were much lower in magnitude compared to concentrations achieved via IV and oral administration of approved ganciclovir products. In comparison to systemic concentrations following IV administration of ganciclovir, concentrations ranged between 0 to 37 ng/mL with ganciclovir gel versus a reported mean C_{max} value of 9.46 ± 2.02 μ g/mL with the intravenous formulation. Similarly, systemic concentrations following instillation of ganciclovir gel are much lower than the reported mean ganciclovir C_{max} value of 5.61 ± 1.52 μ g/mL following oral administration of valganciclovir tablets.

In Study 2, tear concentrations were measured in six healthy volunteers, who received 0.15% ganciclovir ophthalmic gel in both eyes as 4 instillations over 1 day, separated by 3-hour intervals. For the 48 samples taken two hours forty-five minutes after each instillation of ganciclovir 0.15%, the concentrations of ganciclovir were below the detection threshold in 16 cases (33%). For the 31 remaining samples (65%), a high variability in the ganciclovir concentrations was found within and between individuals (concentration range: 0.06 μ g/g to 46.10 μ g/g of tears). The clinical relevance of ganciclovir tear concentrations or their variability is unknown.

Urine concentrations of ganciclovir were determined in Studies 4 and 7. In Study 4, a 24-hour urine sample was taken on the first day of treatment from one patient who had received five instillations of 0.15% ganciclovir gel. In Study 7, urine was collected from herpetic keratitis patients over the 24 hours following the initial instillation of ganciclovir 0.15%. A single urine sample was also collected on Day 10 (in the case of recovery on Day 3) or on Day 14 (in the case

of no recovery on Day 3). Urine samples from Studies 4 and 7 yielded no detectable ganciclovir concentrations (LLOQ = 0.1 µg/mL).

In summary, systemic exposure of ganciclovir is minimal following multiple administration of ganciclovir 0.15% gel, as evidenced by plasma and urine concentrations following multiple administration.

2.3. Intrinsic Factors

Not applicable.

2.4. Extrinsic Factors

Not applicable.

2.5. General Biopharmaceutics

Not applicable.

2.6. Analytical Section

2.6.1. How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Plasma, urine, and tear concentrations of ganciclovir were determined by high performance liquid chromatography (HPLC) with reverse phase polarity and spectrophotometric detection.

2.6.2. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total ganciclovir concentrations were measured in plasma of subjects and patients in the ganciclovir clinical trials. The measurement of total concentrations of ganciclovir for purposes of determining systemic exposure following ophthalmic administration is appropriate.

2.6.3. What bioanalytical methods are used to assess concentrations?

Plasma, urine, and tear concentrations of ganciclovir were assessed by high performance liquid chromatography (HPLC) with reverse phase polarity and spectrophotometric detection.

2.6.3.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

For plasma, the standard curve ranged from 5 to 2000 ng/mL and was linear between 0 and 25 µg/mL. For urine, the calibration range was 0.1 to 20 µg/mL and was linear over the range of 0 and 100 µg/mL. Although the linear ranges seem appropriate for determining systemic exposure of ganciclovir following ophthalmic administration, complete bioanalytical reports were not submitted in the NDA and are not available. Thus, the suitability of the standard curve could not be assessed.

For measurement of ganciclovir in tears, the standard curve ranged from 10 to 500 µg/mL and was linear over this range. This method was appropriate for purposes of determining ganciclovir concentrations in tears.

2.6.3.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The lower limit of quantitation (LLOQ) of ganciclovir in plasma was 5 ng/mL; an upper limit of quantitation (ULOQ) was not specified. The lower limit for the urine assay method was 0.1 µg/mL. In tears, the lower and upper limits were 4 ng/Schirmer strip and 200 ng/Schirmer strip, respectively.

2.6.3.3. What are the accuracy, precision, and selectivity at these limits?

Complete validation reports were not submitted and are not available. Thus, the accuracy, precision and selectivity of the bioanalytical method are not known, and data obtained using these unvalidated analytical methods should be used for informational purposes and not to support regulatory decisions.

2.6.3.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Information on ganciclovir sample stability was not submitted or reported.

2.6.3.5. What is the QC sample plan?

Quality control information for these bioanalytical methods were not submitted or reported.

**APPEARS THIS WAY
ON ORIGINAL**

2 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

4. APPENDICES

4.1. Individual Study Reviews

4.1.1. Study 1

TITLE

Evaluation of systemic passage of ganciclovir administered as an eye gel (0.05 and 0.15%) in patients treated for herpetic keratitis (Protocol Number 64.GV550/04.92)

Study Initiation: 14APR1990

Study Completion: 22MAY1992

OBJECTIVES

To evaluate the systemic passage of Virgan and 0.05% GV 550 (ganciclovir gel) after repeated administration to the eye

STUDY DESIGN

Study 1 is a pharmacokinetic analysis of samples collected in Study 4, a comparative, multicenter study evaluating the efficacy of Virgan, 0.15% ganciclovir gel, and GV 550, 0.05% ganciclovir gel, in the treatment of geographic or dendritic herpetic corneal ulcers versus acyclovir, 3% ophthalmic ointment. The dosage of the three products was 5 times a day until cicatrisation of the ulcer, then 3 times a day for one week. The systemic passage of ganciclovir administered ophthalmically was evaluated in 24 patients, of whom 11 were treated with the 0.15% ganciclovir gel and 13 were treated with the 0.05% ganciclovir gel. Plasma concentrations of acyclovir were also determined in 2 patients treated with 3% acyclovir ophthalmic ointment. One patient affected bilaterally was treated with 0.15% ganciclovir on one side and 3% acyclovir on the other.

FORMULATIONS

Test Product: Virgan eye gel 0.15% (batch number 233) and GV 550 eye gel 0.05% (batch number 232)

Reference Product: Acyclovir 3% ophthalmic ointment (lot/batch information unspecified)

PHARMACOKINETIC ASSESSMENTS

Blood samples were obtained from all patients on the 14th day of treatment on average, approximately 30 minutes to 1 hour after the instillation of a drop of ganciclovir gel in the affected eye. In 3 patients, a sample was also taken on the first day of treatment (Day 0): 2 samples for 0.05% gel and 1 sample for the 0.15% gel.

A 24-hour urine collection was also obtained on the first day of treatment from one patient who had received five instillations of 0.15% ganciclovir gel, to evaluate the elimination of ganciclovir in the urine.

BIOANALYTICAL METHODOLOGY

Plasma and urine concentrations of ganciclovir were determined by high performance liquid chromatography with reverse phase polarity and spectrophotometric detection. The calibration scale ranged from 0 to 2000 ng/ml (0, 10, 20, 50, 100, 500, 1000 and 2000 ng/mL) and was linear between 0 and 25 µg/ml. The quantification threshold for the quantitative plasma analyses is 5 ng/ml. The quantification threshold for the quantitative urine analysis method is 500 ng/ml.

Reviewer Comments: Complete validation reports were not submitted and are not available. Therefore, data obtained using this analytical method should not be used to support regulatory decisions. Samples were also obtained from patients in the active comparator arm for measurement of acyclovir plasma concentrations. No information on the bioanalytical method used to determine acyclovir concentrations was submitted in the current NDA.

PHARMACOKINETIC/STATISTICAL ANALYSIS:

Actual ganciclovir plasma and urine concentrations were reported and average \pm SEM values were calculated.

RESULTS:

Plasma

For the 0.15% ganciclovir gel, 11 pharmacokinetic blood samples were collected between the 11th and 15th days of treatment at an average of 42 minutes after instillation (range of 30 to 70 minutes post-instillation). The average \pm SEM plasma concentration measured in these circumstances was 12.7 ± 3.7 ng/ml (range: 0 to 37 ng/ml). In the case of 0.05% ganciclovir gel, 13 blood samples were obtained between the 13th and 14th days of treatment, at an average of 45 minutes after instillation (range of 30 to 115 minutes post-instillation). The average \pm SEM plasma concentration measured in these circumstances was 22.6 ± 10.4 ng/ml (range: 0 to 135 ng/mL).

For the 3% acyclovir ophthalmic ointment, 3 blood samples were taken on the 14th day of treatment, at an average of 43 minutes after instillation (range of 40 to 45 minutes post-instillation). The average \pm SEM plasma concentration measured in these circumstances was 10 ± 2.9 ng/ml (range: 5 to 15 ng/mL).

Urine

The urinary concentration of ganciclovir as measured in one patient after one day of treatment with 5 instillations of 0.15% ganciclovir was not detectable.

APPLICANT'S CONCLUSIONS:

The determination of the plasma concentrations of ganciclovir and acyclovir administered ophthalmically demonstrated a very low level of systemic passage, even after repeated topical applications on an ulcerated cornea. The average concentration of ganciclovir in the plasma found 45 minutes after instillation, for repeated administration to the eye over 2 weeks (5 times a day until the cicatrisation of the ulcer, then 3 times daily for 1 week) is approximately 100 times less than the residual plasma concentrations normally determined in patients treated intravenously, which are regarded as effective and non-toxic. When administered parenterally, at the usual dose of 5 mg/kg every 12 hours, the plasma concentrations of ganciclovir are between 0.6 and 1.2 ng/ml for residual concentrations, and between 6 and 8 ug/ml for maximum concentrations, in patients. The administration of ganciclovir in the form of an eye gel (0.15%) in patients suffering from superficial herpetic keratitis is therefore not likely to lead to any systemic adverse events of ganciclovir.

REVIEWER ASSESSMENT:

In general, the systemic exposure to ganciclovir following repeated administration in healthy subjects is very low. Ganciclovir concentrations obtained in patients with herpetic keratitis in Study 4 following administration of 0.15% and 0.05% ganciclovir gel 5 times a day until cicatrisation of the ulcer, then 3 times a day for one week were much lower in magnitude compared to concentrations achieved via IV and oral administration of approved ganciclovir products. In comparison to systemic concentrations following IV administration of ganciclovir,

concentrations following ophthalmic administration are much lower; concentrations ranged between 0 to 37 ng/mL with ganciclovir gel versus a reported mean C_{max} value of 9.46 ± 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_{max} value of 5.61 ± 1.52 µg/mL following oral administration of valganciclovir tablets.

The Applicant's conclusion regarding very low systemic *absorption* (passage) is questionable. The estimated maximum daily dose of ganciclovir in the current study is 0.375 mg, compared to maintenance doses for systemically administered ganciclovir of 900 mg (oral valganciclovir) and 5 mg/kg (IV ganciclovir). Thus, the ophthalmically administered dose is approximately 0.04% and 0.1% of the oral and IV doses, respectively. The mean C_{max} of 11.5 ng/mL following ganciclovir gel is approximately 0.2% and 0.1% of the reported C_{max} values for oral and IV administration, respectively; this indicates systemic absorption of ophthalmically administered ganciclovir may be relatively high.

**APPEARS THIS WAY
ON ORIGINAL**

4.1.2. Study 2

TITLE:

Kinetics of ganciclovir in tears following repeated instillation of 0.15% ganciclovir eye gel, VIRGAN®, in healthy volunteers (Protocol Number F-94-02)

Study Initiation: 20OCT2004

Study Completion: 20OCT2004

OBJECTIVES:

To determination the concentration of ganciclovir in tears after repeated administration of VIRGAN® at a therapeutic rate, every 3 hours just before each new application, in healthy volunteers

STUDY DESIGN:

This was an open trial conducted on six healthy volunteers, who received VIRGAN® (0.15% ganciclovir ophthalmic gel) in both eyes. The dosage was 4 instillations over 1 day, separated by 3-hour intervals. The objective of this trial was to measure the residual concentration of ganciclovir in the tears at the end of each interval of time separating 2 instillations (the 4 evaluated intervals of time, corresponding to a rate of 5 instillations a day). Before the first instillation and two hours forty-five minutes after each instillation, the tears from each eye were collected by means of a Schirmer strip. The Schirmer strip was removed as soon as the tears had impregnated a 10 mm length of paper.

FORMULATIONS:

VIRGAN®, ophthalmic gel containing 0.15% ganciclovir (Lot Number: 352; Expiry Date: May 1995).

PHARMACOKINETIC ASSESSMENTS:

Tear samples for determination of ganciclovir concentrations were obtained from each eye by means of a Schirmer strip half an hour before the first instillation (first sample before instillation serving as control) and 2 hours 45 minutes after each instillation (4 samples from each eye after instillation).

BIOANALYTICAL METHODOLOGY

The concentrations of ganciclovir from the Schirmer paper strips were determined by reversed-phase high performance liquid chromatography (HPLC) with spectrophotometric detection after liquid extraction. The ganciclovir calibration range with increasing quantities of ganciclovir ranged from 0 to 500 ug/ml (0, 10, 25, 50, 62.5, 100, 250 and 500 ug/ml). The relationship between concentrations and areas under the peaks (calibration range) was linear over this range: coefficient of variation = 3.3% (n = 40). The detection limit was therefore 0.5 ng per injection and the upper quantification limit was 25 ng per injection (25 µl injected), i.e.: 4 ng/strip and 200 ng/strip respectively. The extraction yield from the Schirmer paper strips (calculated by comparison with the areas under the peaks obtained after overloading Schirmer paper or from aqueous solution) was 100 ± 10.1% (n = 40). The repeatability was determined by means of 4 injections for each calibration point. The coefficient of variation varied from 0.67% to 9.39% (n = 2). The reproducibility was determined by means of 4 injections for each calibration point. The coefficient of variation varied from 1.95% to 9.43% (n = 32). The quantification threshold

(10 µg/mL) was determined by means of 6 injections of 50 µL of a solution of ganciclovir after extraction. The coefficient of variation is less than 7.5% (n = 6).

Reviewer Comments: Complete validation reports were not submitted and are not available. Therefore, data obtained using this analytical method should not be used to support regulatory decisions.

PHARMACOKINETIC/STATISTICAL ANALYSIS:

The quantity of tears in each strip was determined gravimetrically (weighing before and just after sampling). Knowing the amount of ganciclovir and the weight (and hence the volume) of tears for each strip, the concentration of ganciclovir in the tears could be calculated for each sample taken. The weight of tears was converted to a volume (1 g = 1 mL) in order to calculate the concentration of ganciclovir in the tears, expressed in µg/ml.

Actual ganciclovir tear concentrations were reported and mean ± SD values were calculated for each of the 5 instillations.

RESULTS:

Tear samples were obtained from the six (6) healthy male volunteers that were enrolled and completed the trial. The concentrations of ganciclovir in the first sampling time point (before the first instillation) were below the quantifiable limit. For Subject 4, none of the samples collected exhibited measurable concentrations of ganciclovir. For the 48 samples taken after instillations of VIRGAN®, the concentrations of ganciclovir were below the detection threshold in 16 cases (33%) and above the upper quantification threshold in 1 case (2%). For the 31 remaining samples (65%), a high variability in the ganciclovir concentrations was found within and between individuals (ranging from a minimum of —µg/g to a maximum of —µg/g of tears.) The means of the ganciclovir concentrations in the different samples, taking the values below the detection threshold as equal to 0 µg/g and the value above the quantification threshold as equal to 200 µg/g, are presented in Table 4.1.2-1.

b(4)

Table 4.1.2-1. Mean Ganciclovir Concentrations in Tears Following Multiple Administration

Sample Number	Mean ± SD Ganciclovir Concentration (µg/g of tears)
1	ND
2	0.92 ± 1.26
3	3.05 ± 3.60
4	6.86 ± 13.41
5	3.31 ± 2.98

ND, not detectable in all samples for that time point
Source: Study 2 pharmacokinetic study report (VIRGAN/F-94-02)

APPLICANT'S CONCLUSIONS:

The aim of this study was to quantify ganciclovir in tears. This was done by administering VIRGAN® to healthy volunteers 4 times in 1 day and collecting the tears just before each instillation (interval of 2 hours 45 minutes since the previous instillation) by means of a Schirmer strip. The results show that in 67% of cases, the active substance of VIRGAN® is found in the tears and that there is a high variability within and between individuals. These results were obtained using a sampling process which remains open to criticism (i.e. the induction of reflex lacrimation is very difficult to quantify and can reduce the concentration of ganciclovir by dilution, etc.). This simple and well-tolerated method was chosen in the absence of other tear sampling techniques which have been properly validated in man.

In the samples in which ganciclovir is detected, all of the concentrations were greater than the inhibitory concentration (ED_{50}) for the HSV-1 strain (0.05 - 0.12 g/ml) and 91% of the concentrations were greater than the inhibitory concentration for the HSV-2 strain (0.10-0.46 µg/ml). Although determination of the concentration of ganciclovir in tears is a valuable parameter in the evaluation of its efficacy, it remains only a surrogate since the virus develops essentially in the cornea and the concentrations of active substance in this tissue, which cannot be removed from human subjects, is unknown in man.

REVIEWER ASSESSMENT:

In general, the Applicant's conclusions regarding qualitative tear pharmacokinetics of ganciclovir following repeated administration are acceptable from a clinical pharmacology perspective. The clinical relevance of ganciclovir tear concentrations cannot be determined due to the high variability observed within and between subjects.

4.1.3. Study 3

TITLE:

Evaluation of local tolerance in healthy volunteers following repeated instillation of 0.15 % ganciclovir eye gel, VIRGAN® (Protocol Number F-94-01)

OBJECTIVES:

To compare the local ocular tolerance of Virgan® with that of its vehicle after repeated administration in healthy subjects.

STUDY DESIGN:

Ten healthy volunteers were enrolled in this randomized, double-blind trial. In one eye each subject received Virgan® and in the other its vehicle. For each, a dose of one single drop of test drug or vehicle to be administered in the randomized eyes 5 times a day for 7 days at 8 hr, 11 hr, 14 hr, 17 hr and 20 hr. Duration of treatment was limited to the 7 days of the trial.

FORMULATIONS:

Virgan®, ophthalmic gel containing 0.15% ganciclovir (lot information unspecified). The vehicle had the same composition except for the active substance ganciclovir.

PHARMACOKINETIC ASSESSMENTS:

A blood sample for determination of plasma ganciclovir concentrations was taken from all the healthy volunteers on the 7th day of treatment (last day of the study), approximately 2 to 4 hours after instillation of one drop of Virgan® gel.

BIOANALYTICAL METHODOLOGY

Ganciclovir plasma concentrations were determined by reverse-phase HPLC and spectrophotometric detection. The calibration range was 0 to 2000 ng/ml (0, 10, 20, 50, 100, 500, 1000 and 2000 ng/ml). The linearity range for the analytical method was between 0 and 25 µg/ml. The quantification threshold of the method for the plasma assay was 5 ng/ml.

Reviewer Comments: Complete validation reports were not submitted and are not available. Therefore, data obtained using this analytical method should not be used to support regulatory decisions.

PHARMACOKINETIC/STATISTICAL ANALYSIS:

Actual ganciclovir plasma concentrations were reported and a mean ± SEM value was calculated.

RESULTS:

Ten (10) blood samples were taken on the 7th day of treatment at on average 3.5 ± 0.4 hrs [mean ± SEM] in average post-instillation. Plasma concentrations of ganciclovir were low, with a mean ± SEM concentration of 11.5 ± 3.7 ng/mL. In four subjects (Subjects 4, 5, 6 and 10), ganciclovir concentrations were lower than the quantification threshold of the method (5 ng/mL). The highest concentration observed was 7 ng/mL.

b(4)

APPLICANT'S CONCLUSIONS:

The determination of plasma ganciclovir concentrations following ocular administration in Study 3 shows very low systemic absorption of ganciclovir. Following repeated ocular administration in healthy volunteers at a dosage of 5 instillations per day for one week, the mean plasma ganciclovir concentration measured 2 to 4 hours after instillation is approximately

100 times lower than the residual plasma concentrations usually obtained in patients treated intravenously. These residual plasma concentrations are regarded as both effective and nontoxic. Ganciclovir plasma concentrations, following parenteral administration at the usual dose of 5 mg/kg every 12 hours, are between 0.6 and 2 µg/ml for residual concentrations and 6 to 8 µg/ml for maximum concentrations in patients. Results from Study 3 are consistent with results from Study 1 where 0.05% and 0.15% ganciclovir eye gel (old formulation) was administered to patients being treated for herpetic keratitis. Average plasma concentrations were 12.7 ± 3.7 ng/mL and 22.6 ± 10.4 ng/mL for the 0.15% and 0.05% gels, respectively.

REVIEWER ASSESSMENT:

In general, the systemic exposure to ganciclovir following repeated administration in healthy subjects is very low. Ganciclovir concentrations obtained in healthy subjects and in herpetic keratitis patients following multiple administration of 0.15% ganciclovir gel were much lower in magnitude compared to concentrations achieved via IV and oral administration of approved ganciclovir products. In comparison to systemic concentrations following IV administration of ganciclovir, concentrations following ophthalmic administration are much lower; concentrations ranged between ng/mL with ganciclovir gel versus a reported mean C_{max} value of 9.46 ± 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_{max} value of 5.61 ± 1.52 µg/mL following oral administration of valganciclovir tablets.

b(4)

The Applicant's conclusion regarding very low systemic *absorption* (passage) is questionable. The estimated daily dose of ganciclovir in the current study is 0.375 mg, compared to maintenance doses for systemically administered ganciclovir of 900 mg (oral valganciclovir) and 5 mg/kg (IV ganciclovir). Thus, the ophthalmically administered dose is approximately 0.04% and 0.1% of the oral and IV doses, respectively. The mean C_{max} of 11.5 ng/mL following ganciclovir gel is approximately 0.2% and 0.1% of the reported C_{max} values for oral and IV administration, respectively; this indicates systemic absorption of ophthalmically administered ganciclovir may be relatively high.

**APPEARS THIS WAY
ON ORIGINAL**

4.1.4. Study 7

TITLE

Detection and assay of ganciclovir in the urine after administration in the form of 0.15% ophthalmic gel in patients being treated for herpetic keratitis

Study Initiation: 12SEP1992

Study Completion: 17SEP1994

OBJECTIVES

Primary: To measure on Day 0 (the first day of the study) the elimination of ganciclovir in the urine over 24 hours.

Secondary: To detect at the end of treatment (Day 10 or Day 14) the presence of ganciclovir in urine collected during a single urination.

STUDY DESIGN

The aim of this comparative, parallel, multicenter, randomised study, stratified according to center and type of ulcer (dendritic versus geographic) was to evaluate the efficacy of VIRGAN®, 0.15% ganciclovir gel (formulation containing benzalkonium chloride as preservative agent) versus ZOVIRAX®, 3% acyclovir ophthalmic ointment, in the treatment of acute herpetic corneal ulcers. The patients are treated at a rate of 5 instillations a day until recovery of the ulcer, then 3 instillations a day for one week. The principal assessment criterion was the period of cicatrisation of the ulcer. Assessments were performed on Days 0, 3, 7 and 10.

FORMULATIONS

Test Product: Virgan eye gel containing ganciclovir 0.15% (batch number 352)

Reference Product: Acyclovir 3% ophthalmic ointment (no lot/batch information specified)

PHARMACOKINETIC ASSESSMENTS

Urine was collected over the 24 hours following the initial instillation of Virgan eye gel 0.15%. A single urine sample was also collected on Day 10 (in the case of recovery on Day 3) or on Day 14 (in the case of no recovery on Day 3).

BIOANALYTICAL METHODOLOGY

Urine concentrations of ganciclovir were determined by high performance liquid chromatography with spectrophotometric detection following liquid-liquid extraction. The calibration range was 0 to 20 µg/ml (0, 0.1, 0.2, 0.5, 1, 2, 5, 10 and 20 µg/ml). The analytical method was linear over the range of 0 and 100 µg/ml. The quantification threshold of the assay method is 0.1 µg/ml.

Reviewer Comments: Complete validation reports were not submitted and are not available. Therefore, data obtained using this unvalidated analytical method should not be used to support regulatory decisions.

PHARMACOKINETIC/STATISTICAL ANALYSIS:

Actual ganciclovir plasma and urine concentrations were reported.

RESULTS:

Concentrations of ganciclovir in urine on Day 1 (first day of study following initial instillation on Day 0) and at end of treatment (Day 10 or 14) were below the quantification threshold of the method (< 0.1 µg/ml) in all samples from acute herpetic keratitis patients.

APPLICANT'S CONCLUSIONS:

Following intravenous administration of ganciclovir, more than 90% of ganciclovir is eliminated unchanged in the urine. In the current study, concentrations of ganciclovir in the urine were used to confirm the absence or presence of a very low systemic passage of ganciclovir after administration by ophthalmic means. In Study 7, urine concentrations were below the detection threshold for the analytical method (0.1 µg/ml) and confirm the results obtained from previous studies with plasma sampling, which showed a very low systemic passage of ganciclovir after administration of a 0.15% ganciclovir eye gel in patients being treated for herpetic keratitis. The ganciclovir concentration values measured at the end of treatment were also very low (< 0.1 µg/ml) and do not reveal any marked accumulation of ganciclovir over the course of the treatment.

REVIEWER ASSESSMENT:

The Applicant's conclusions regarding systemic absorption of ganciclovir following repeated administration in patients with herpetic keratitis are based on an assessment of urine concentrations. Although ganciclovir concentrations in urine were below quantifiable limits following single and multiple instillation of ganciclovir gel, the lack of sensitivity of the urine assay (LLOQ of 100 ng/mL) limits interpretation of urine PK results. Conclusions regarding systemic absorption following ophthalmic administration of ganciclovir gel cannot be made from these study findings.

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