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Medical Officer's Review of NDA 20-961
Original

NDA #20-961		Submissions:	4/6/98 & 6/29/98
M.O. Review #1		Review completed:	8/ 3/98

Generic name: fomivirsen sodium intravitreal injectable
Proposed trade name: Vitravene
Chemical name:

2′-Deoxyguanosylyl-(3′→5′ *O,O*-phosphorothioyl)- 2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)- 2′-deoxyguanosylyl-(3′→5′ *O,O*- phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxyguanosylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*- phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*- phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′*O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxyguanosylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxyguanosine, 20-sodium salt.

Sponsor: Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008

Pharmacologic Category: Oligonucleotide

Nucleotide Sequence 5'-GCG TTT GCT CTT CTT CTT GCG-3'
Molecular formula: $C_{204}H_{243}N_{63}O_{114}P_{20}S_{20}Na_{20}$
Molecular weight: 7,122

ACTIVE: Fomivirsen sodium 6.6mg
INACTIVES: Sodium bicarbonate, sodium carbonate, sodium chloride, and water for injection. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. Vitravene Injection is formulated to have an osmolality of 290mOsm/kg, and a pH of 8.7.

Proposed Indication(s):

Vitravene™ is indicated for the local treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS). The diagnosis of CMV retinitis is ophthalmologic and should be made by indirect ophthalmoscopy. Other conditions that should be considered in the differential diagnosis of CMV retinitis include ocular infections caused by syphilis, candidiasis, toxoplasmosis, histoplasmosis, herpes simplex virus and varicella-zoster virus as well as retinal scars, and cotton wool spots, any of which may produce a retinal appearance similar to CMV.

For this reason, it is essential that a physician familiar with the retinal presentation of these conditions establish the diagnosis of CMV. Vitravene™ is for intravitreal injection use only.

Dosage Form(s) and Route(s) of Administration: Intravitreal solution

NDA Drug Classification: 1 P

Related Drugs: [redacted]

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2 Table of Contents

3 Material Reviewed

Volumes 2.1, 2.19-2.139, 2.274-2.366

Fundus Photos for Studies CS 1,2,3,9, 12 Volumes 2.140-2.204

Reviewer Efficacy Results are based on independent "blinded" read of submitted fundus photographs. Reviewer comments are generally identified by text in "italics" except in the Final Review Conclusions and Recommendations.

Administrative Difficulties with the Review

1. *The electronic files where not internally linked correctly making it difficult to move from one part of the application to another.*
2. *The electronic files contained "unrecoverable errors" when converted to Corel's WordPerfect 7.*
3. *The fundus photographs of individual patients were not necessarily bundled together in the same volume.*
4. *"Electronic file space" was not immediately available at the FDA's facility to store the entire NDA.*
5. *Fundus photographs frequently did not overlap sufficient areas to permit identification of the specific location of the photograph.*
6. *Initial fundus photographs and/or follow-up photographs did not cover all areas of retinitis.*

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DETERMINED
NOT
TO BE
RELEASABLE

6.3 Foreign experience

The subject of this application, fomivirsen sodium intravitreal injectable, has never been marketed or offered for sale in any foreign country. At this time, there is no approved application for the marketing or sale of this drug, or any form of this drug, in any country.

6.6 Proposed Directions for Use

Newly Diagnosed Disease

Three consecutive, weekly intravitreal injections of 165µg (0.025mL) per eye should be administered as the Induction portion of the dosing regimen. Thereafter, one 165µg intravitreal injection every 2 weeks should be administered as the Maintenance regimen.

Previously Treated Disease

One intravitreal injection of 330µg (0.05mL) per eye every other week for two doses should be administered as the Induction portion of the dosing regimen. For Maintenance, an intravitreal injection of one 330µg dose should be administered once every 4 weeks.

7 Description of Clinical Data Sources

	Previously untreated	Previously Treated					
	CS2	CS1	CS3	CS5	CS7	CS9	CS12
Study Design	Open label	Open label	Open label	Open label Single dose PK	Open label	Open label . Dose regimen comparison	Open label Dose regimen comparison
Control Group	No treatment	Rising dose	Oral GCV control	None	None	330 monthly maintenance schedule	330 monthly maintenance schedule
Fomivirsen Doses	75 165 330	83 165 330 495	75 165 330	165 330	165 330	330	330
Location	US	US	US Europe	US	US Europe	US	Canada Europe
Planned Enroll	60	15-25	174	28	NA	100	120
Planned Evaluable	42	NA	144	NA	NA	72	90
Planned Interim	27	NA	90	NA	NA	40	40
In NDA	45	22	49	10	118	54	32
NDA Review Number	1		2			3	4

Study CS1 - *Initial Pilot Study*

Study CS5 - *Study is incomplete and no conclusions can be drawn because of the small number of patients enrolled. (See BioPharm Review).*

Study CS7 - *Open label continuation for patients previously enrolled in other studies.*

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8 Clinical Studies

8.1 Study #1

Protocol: CS2

Title: A Randomized Comparison of Immediate Versus Delayed Treatment with Intravitreal Injections of ISIS 2922 in Patients with Peripheral Cytomegalovirus (CMV) Retinitis

Investigators and Study Center(s) that enrolled patients:

Andrew Antoszyk, M.D., Charlotte, NC; David Boyer, M.D., Los Angeles, CA; Clement Chan, M.D., Palm Springs, CA; Ronald Danis, M.D., Indianapolis, IN; Debra Goldstein, M.D., Chicago, IL; David Johnson, M.D., Denver, CO; Ronni Lieberman, M.D., New York, NY; Sam Mansour, M.D., San Jose, CA; Jorge Mora-Duarte, M.D., San Jose, Costa Rica; Cristina Muccioli, M.D., Sao Paulo, Brazil; Alan G. Palestine, M.D., Washington, D.C.; Susanna Park, M.D., Dallas, TX; Julio Perez, M.D., Ft. Lauderdale, FL; Carmen Santos, M.D., San Juan, Puerto Rico; John D. Sheppard, M.D., Norfolk, VA; Brian Terry, M.D., Pasadena, CA.

Studied period (years): 20 January 1995 to ongoing patient visits through 30 November 1997

Phase of development: II/III

Objectives:

Stage 1 (Dose Escalation): To determine a clinically safe dose of intravitreally injected fomivirsen with sufficient clinical effectiveness to warrant further evaluation of the efficacy of fomivirsen as treatment for cytomegalovirus retinitis (CMVR).

Stage 2 (Immediate vs. Delayed): To compare the efficacy and safety of immediate versus delayed intravitreal injections of fomivirsen as treatment for CMVR.

Methodology:

This study began as a randomized comparison of immediate treatment with 330 μg fomivirsen or delayed treatment (2:1) to patients sequentially entering the study. Based on safety findings [*pigment changes and inflammation*] with this dose of fomivirsen, the study was modified to allow an open-label, dose escalation (Stage 1) to determine a safe dose that could be used in place of the original 330 μg dose, such that continuation of the randomized part of the study (Stage 2), with the immediate and delayed treatment groups, could proceed.

Stage 1: The first group of patients enrolled in Stage 1 received treatment with 75 μg fomivirsen (Group A). The second group of patients in Stage 1 started treatment with 150 μg fomivirsen (Group B) when the last patient in Group A had safely completed Day 29 and the safety of the Group A dose was established.

Stage 2: This stage began with randomly assigning immediate treatment with 150 μg fomivirsen or delayed treatment (2:1) to patients sequentially entering the study. Patients in the immediate treatment group entered the Induction Period, followed by a Maintenance Period. Patients in the delayed treatment group did not receive any anti-CMVR treatment and were monitored weekly for disease progression. With progression of the disease, these patients could receive fomivirsen on an identical dose and schedule as patients enrolled into immediate treatment group.

All patients were followed for time to CMVR progression determined by standard criteria. Assessments of CMVR activity and progression were based on fundus photography evaluations performed using a centralized reading center (masked) as well as clinical determinations.

Number of patients:

Original protocol, 330μg = 10 (8 immediate, 2 delayed); Stage 1 (dose escalation), 75μg=5, 150μg = 3; Stage 2 (randomized trial), 150μg = 27 (19 immediate, 8 delayed).

Diagnosis and main criteria for inclusion:

Patients with AIDS, ≥18 years of age; clinical diagnosis of previously untreated, unilateral CMVR (the leading edge of a CMVR lesion at least 750 microns from Zone 1); Karnofsky score of ≥ 70; and signed informed consent.

Doses: 330 μg (original study); 75 μg (Stage 1, Group A); 150 μg (Stage 1, Group B and Stage 2)

Mode of administration: intravitreal injection.

Dose Regimen:

Fomivirsen injections every 7 days (Study Days 1, 8 and 15) for 3 injections (Induction Period), followed by every 14 days dosing (Maintenance Period), starting Day 29

Duration of treatment:

In the immediate treatment group, patients were allowed to continue dosing during the Induction Period followed by the Maintenance Period (total of 22 weeks), until they experienced progression, and based on safety findings. The Maintenance Period could be extended for any patient who completed 18 weeks of maintenance therapy and had not experienced progression of CMVR.

Reference therapy, dose and mode of administration, batch number:

No reference therapies were used in this study. The delayed treatment (no treatment group) in the control arm of the study did not receive any anti-CMVR treatments until clinical determination of progression. At the time of clinical determination of progression, treatment with fomivirsen could be initiated using the same dose and schedule as the immediate arm of the study if the patient still met the eligibility criteria.

Criteria for evaluation:

Efficacy: Time to observed CMVR progression (as defined by): the appearance of any new lesion(s) 750 microns in size; the advancement of the border of existing lesion(s), including satellite lesion(s), by 750 microns along a 750 micron front; retinal detachment in an area of active CMVR; and/or CMVR involvement adjacent to the optic nerve as determined by clinical determination, concurrent with a decrease in best corrected visual acuity to worse than 20/200. A visual acuity of worse than 20/200 must represent a decrease from the baseline exam to be included as an indication of disease progression.

Safety:

Bilateral ophthalmic examination, evaluation of ocular adverse events and laboratory measurements for evaluation of systemic adverse events.

Statistical methods:

Patient population, demographic and clinical backgrounds - Descriptive statistics, frequency tabulations.

Efficacy evaluations -

The primary analysis performed was an intent-to-treat analysis. To be included in this analysis, patients in the immediate treatment group had to receive at least 1 dose of fomivirsen and at least 1 follow-up evaluation. Delayed treatment patients were required to have at least one follow-up evaluation to be included in the intention-to-treat analysis. A secondary analysis was performed for all patients with CMVR unless, in the first 29 days, they withdrew consent, did not return for follow-up visits, or received other therapy for CMVR prior to disease progression. Kaplan-Meier survival analysis of time to observed progression by fundus photography (masked) and clinical evaluations.

Applicant's Efficacy Results:

(Stage 2) The intent-to-treat analysis revealed a median time to progression of 71 days for patients in the immediate treatment (150 μg) group versus 13 days for patients assigned to the delayed treatment group ($p = 0.0001$), as determined by primary efficacy endpoints. The subset analysis revealed a median time to progression of 71 days for patients in the immediate treatment (150 μg) group versus 11.5 days for patients assigned to the delayed treatment group ($p = 0.0001$).

Applicant's Safety Results:

(Stage 2) The most frequently observed ocular adverse events were transient increased intraocular pressure and mild to moderate, reversible intraocular inflammation. No patients were discontinued from the study for fomivirsen related ocular adverse events.

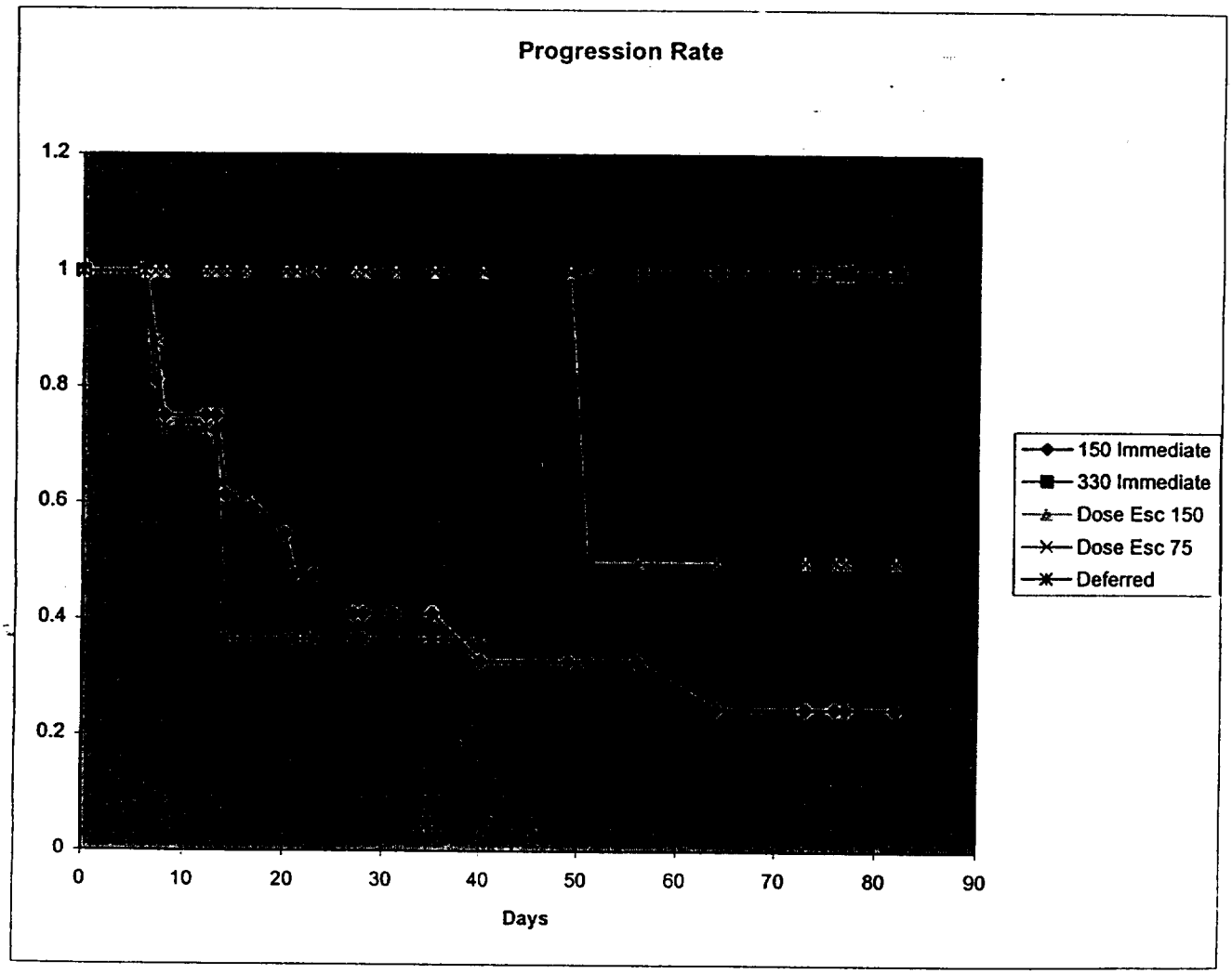
Demographics:

Site	NAME	Total Patients (Eyes)	Terminated Patients (Eyes)	Continuing Patients (Eyes)
001	Alan G. Palestine	2	2	0 (0)
004	Ronni M. Lieberman	4	4	0 (0)
005	David S. Boyer	2	2	0 (0)
006	Debra Goldstein	3	2	1
007	Sam Mansour	3	3	0 (0)
008	Susanna Park	1	1	0 (0)
009	Andrew N Antoszyk	1	1	0 (0)
010	Ronald Danis	1	1	0 (0)
011	Brian G. Terry	4	4	0 (0)
012	David W. Johnson	4	4	0 (0)
026	Julio E. Perez	2	2	0 (0)
031	Cristina Muccioli	13	10	3
033	Jorge Mora- Duarte	2	0 (0)	2
034	John D. Sheppard	2	2	0 (0)
036	Clement K. Chan	1	1	0 (0)
TOTAL		45 (52)	39 (45)	6

Patient Demographic Summary

Dose Group	Number	Age Mean	SD	Age Min	Age Max	Gender Male	Female	Race Cauc	Black	Asian	Other
75 µg DE	5	40.00	1.87	37	42	5	0	2	0	0	3
150 µg DE	3	40.33	6.81	35	48	3	0	1	1	0	1
150 µg Immed	19	38.11	8.18	23	61	18	1	12	3	1	3
330 µg Immed	8	35.00	6.19	27	43	8	0	6	0	0	2
Delayed	10	36.80	9.38	28	59	9	1	7	2	0	1
TOTAL	45	37.62	7.52	23	61	43	2	28	6	1	10

Reviewer Efficacy Results:



Number of Patients:

150 immediate	=	16
330 immediate	=	8
Dose escalation 150	=	3
Dose escalation 75	=	4
Deferred	=	8

Reviewer's Comments: *There are no progressions in the 330 group, therefore, there is some evidence of effectiveness, however, the numbers are small and the time to censoring is short.*

Significant Adverse Events (*Reviewer selection of events)*:

Number of Eyes with event

	Dose Group		
	75 (n=6)	150 (n=32)	330 (n=11)
Anterior Chamber Inflammation	1	5	1
Vitritis	0	2	2
IOP Increase	0	6	3
Peripheral Vision Decrease	0	1	2
Retinal Pigment Change	0	0	5
Desaturation Color Vision	1	1	2

Reviewer's Comments: *The events listed above are considered to represent potential threats to visual function. There were no reported significant laboratory adverse events.*

Study #2
Protocol CS3
Title of Study:

A Randomized Comparison of Intravitreal ISIS 2922 plus Ganciclovir versus Ganciclovir as Treatment for Patients with Cytomegalovirus (CMV) Retinitis

Investigators and Study Center(s) that enrolled patients:

Andrew Antoszyk, M.D., Charlotte, NC; David Boyer, M.D., Los Angeles, CA; Debra Goldstein, M.D., Chicago, IL; Jacobo Gonzalez Guijarro, M.D., Madrid, Spain; Bernard Jacob Hirschel, M.D., Geneva, Switzerland; David Johnson, M.D., Denver, CO; Ronni Lieberman, M.D., New York, NY; Sam Mansour, M.D., San Jose, CA; Alan G. Palestine, M.D., Washington, D.C.; Susanna Park, M.D., Dallas, TX; Julio Perez, M.D., Ft. Lauderdale, FL; Carla Territo, M.D., Philadelphia, PA; Brian Terry, M.D., Pasadena, CA

Studied period (years):

27 March 1995 (1st patient enrolled) to currently ongoing patients up to 31 October, 1997 (last data point entered)

Phase of development: II/III

Objectives:

Stage 1 (Dose Escalation): To determine a clinically safe dose of intravitreally injected fomivirsen with sufficient clinical effectiveness to warrant further evaluation of the efficacy of fomivirsen as treatment for cytomegalovirus retinitis (CMVR).

Stage 2 (Randomized): To evaluate the efficacy and safety of intravitreal fomivirsen plus oral ganciclovir (GCV) for treatment of CMVR.

Methodology:

This study began by randomly assigning (2:1) the combination of intravenous GCV and intravitreal fomivirsen (330 µg), followed by oral GCV and intravitreal fomivirsen (330 µg) (Regimen 1) versus intravenous GCV followed by oral GCV (Regimen 2) to patients sequentially entering the study.

Stage 1 (Dose Escalation): The first group of patients enrolled in Stage 1 received treatment with 75 µg fomivirsen (Group A) plus oral GCV. The second group of patients in Stage 1 started treatment with 150 µg fomivirsen (Group B) plus oral GCV when the last patient in Group A had safely completed Day 29.

Stage 2 (Randomized): Patients were randomly assigned (2:1) to receive either the combination of intravitreal fomivirsen (150 μg) and oral GCV, or intravenous GCV followed with oral GCV. All patients were followed for time to CMVR progression determined by standard criteria. Assessments of CMVR activity and progression were based on fundus photography evaluations performed using a centralized reading center (masked) as well as clinical determinations.

Number of patients:

Initial 330 μg randomized trial - 7 patients/9 eyes (fomivirsen + intravenous GCV to oral GCV) and 2 patients/3 eyes (intravenous GCV to oral GCV), 1 patient who was randomized (intravenous GCV to oral GCV) but never treated.

Stage 1 (Dose Escalation) - 7 patients/10 eyes (75μg + oral GCV), 5 patients/6 eyes (150μg + oral GCV).

Stage 2 (150 μg randomized trial) - 28 patients (22 patients/32 eyes on fomivirsen + oral GCV, 6 patients/9 eyes (intravenous GCV to oral GCV).

Diagnosis and main criteria for inclusion:

Patients with AIDS, ≥18 years of age; clinical diagnosis of CMVR in one or both eyes not adequately controlled by previous therapy (including uncontrolled "smoldering" or "active borders"); ≤ 1 prior progression in the eye(s) to be treated; Karnofsky score of > 60; and signed informed consent.

Original Protocol Design - Dose and Dose Regimen:

Regimen 1 - Intravitreal injections of 330 μg fomivirsen every 7 days (Study Days 1, 8 and 15) for 3 injections (Induction Period), concomitant with intravenous GCV (Cytovene, 5 mg/kg q12 hours) for 14 consecutive days, followed by 330 μg intravitreal fomivirsen injections every 14 days (Maintenance Period), concomitant with the administration of oral GCV (Cytovene, 3 grams/day).

Regimen 2 - Intravenous GCV for 14 consecutive days (5 mg/kg q12 hours, Induction Period) followed by oral GCV (3 grams/day, Maintenance Period).

Stage 1 Dose and Dose Regimen (following Amendment 2 of protocol):

Intravitreal injections of 75 μg (Group A) or 150 μg (Group B) fomivirsen every 7 days (Study Days 1, 8 and 15) for 3 injections (Induction Period), followed by intravitreal injections of 75 μg (Group A) or 150 μg (Group B) fomivirsen every 14 days dosing (Maintenance Period), concomitant with the administration of oral GCV (3 grams/day) during the Induction and Maintenance periods.

Stage 2 Dose and Dose Regimens (following Amendment 2 of protocol):

Regimen 1 - Intravitreal injections of 150 μg fomivirsen every 7 days (Study Days 1, 8 and 15) for 3 injections (Induction Period), followed by intravitreal injections every 14 days dosing (Maintenance Period), concomitant with the administration of oral GCV (3 grams/day) during the Induction and Maintenance Periods.

Regimen 2 - Intravenous GCV for 14 consecutive days (5 mg/kg q 12 hours, Induction Period) followed by oral GCV (3 grams/day, Maintenance Period).

Duration of treatment:

Each patient enrolled into this study was encouraged to comply with study requirements for a minimum of 29 days or until the progression of CMVR was determined. Patients continued to be dosed during the Maintenance Period (for a total of 20 weeks), until they experienced progression, and based on safety findings. The Maintenance Period could be extended for any patient who completed 18 weeks of maintenance therapy and had not experienced progression of CMVR.

Criteria for evaluation:

Efficacy: Time to observed CMVR progression as defined by: the appearance of any new lesion(s) 750 microns in size; the advancement of the border of an existing lesion(s), including satellite lesion(s), by 750 microns along a 750 micron front; retinal detachment in an area of active CMVR; and/or Clinical documentation of CMVR involvement adjacent to the optic nerve, concurrent with a decrease in best corrected visual acuity to worse than 20/200. A visual acuity of worse than 20/200 must represent a decrease from the baseline exam to be included as an indication of disease progression.

Safety: Complete bilateral ophthalmic examinations, evaluation of ocular adverse events and laboratory measurements for evaluation of systemic adverse events

Statistical methods:

Patient population, demographic and clinical background - Descriptive statistics and frequency tabulations.

Efficacy analysis: Time to observed CMVR progression compared between the two treatment groups. Intention-to-treat analysis of all patients who received at least 1 injection of fomivirsen or 1 dose of intravenous GCV, and had at least 1 follow-up evaluation. Kaplan-Meier survival analysis of time to progression.

Safety analysis: Incidence and prevalence of ocular and systemic adverse events; descriptive statistics and frequency tabulations.

Applicant's Efficacy Results:

Original Protocol 330 μg dose: Based on safety findings with this dose of fomivirsen, the study was modified to allow an open-label, dose escalation (Stage 1) to determine a safe dose that could be used in place of the original 330 μg dose in Regimen 1, so that continuation of the randomized part of the study (Stage 2) could proceed.

Randomized Comparison at 150 μg: By intention-to-treat analysis, the median time to progression, as determined by primary efficacy endpoint, was not definable for patients in the fomivirsen (150 μg) and oral GCV group; it was 125 days for patients assigned to the GCV control arm.

Ten patients treated with fomivirsen (150 μg) and oral GCV were censored after more than 100 days on study. One patient treated with GCV alone progressed after more than 100 days on study, with no other patients on GCV alone censored after more than 100 days.

Applicant's Safety Results:

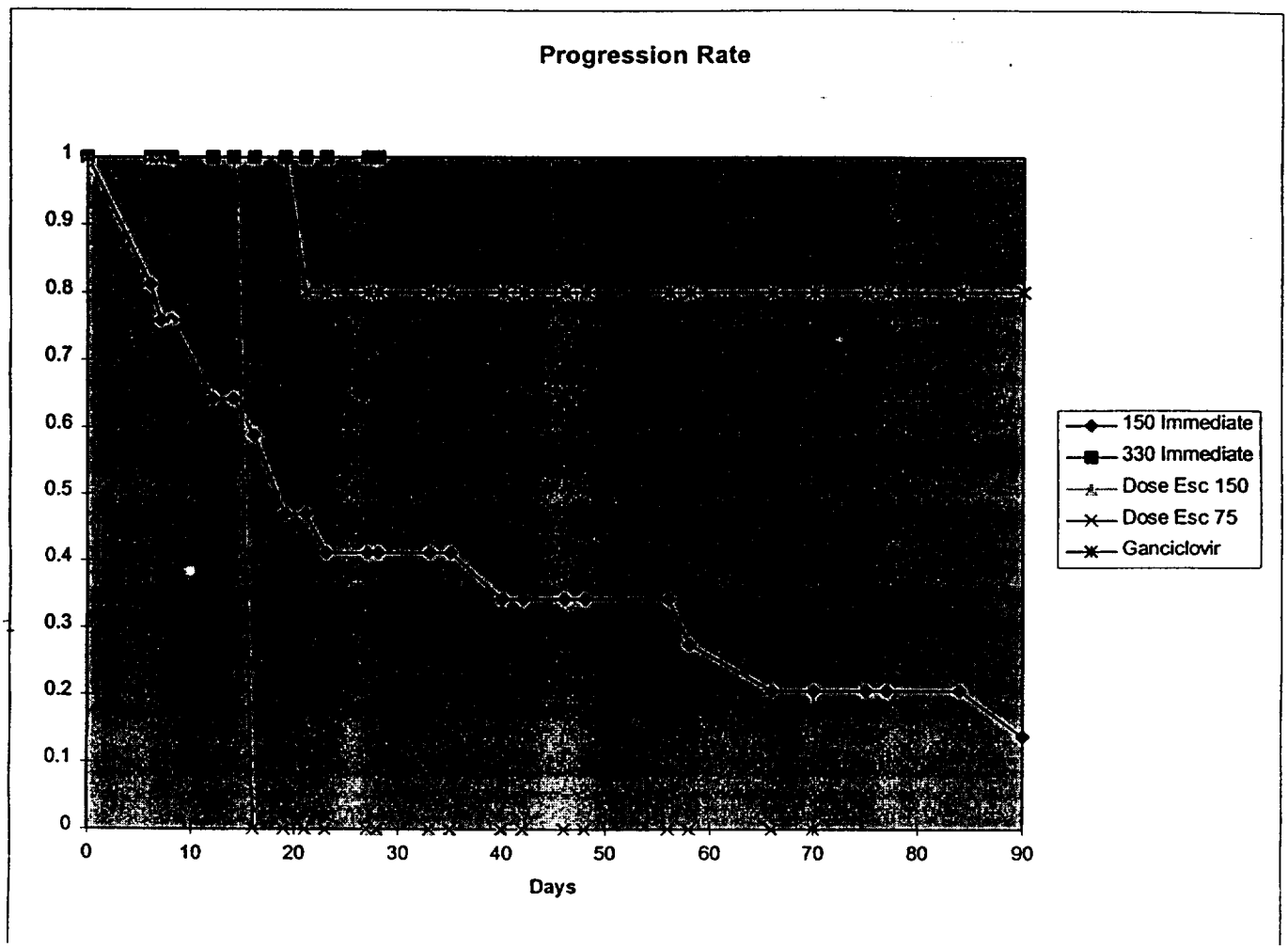
The most frequently observed ocular adverse events were abnormalities of retinal pigment epithelium (6 eyes/10% overall, 2 eyes/5% at 150 μg), transient increased intraocular pressure (2 eyes/5% at 150 μg), and mild to moderate, reversible anterior chamber inflammation (3 eyes/8% at 150 μg). Five patients were discontinued from the study for fomivirsen-related ocular adverse events; three in the original protocol (fomivirsen at 330 μg) and two in the randomized trial using fomivirsen at 150 μg. No patients were discontinued from the study for GCV-related ocular adverse events.

Site (Eyes)	NAME	Total Patients (Eyes)	Discontinued Patients (Eyes)	Continuing Patients
001	Alan G. Palestine	1 (1)	1 (1)	0 (0)
004	Ronni M. Lieberman	13 (21)	12 (19)	1 (2)
005	David S. Boyer	3 (3)	3 (3)	0 (0)
006	Debra Goldstein	2 (3)	2 (3)	0 (0)
007	Sam Mansour	1 (2)	1 (2)	0 (0)
008	Susanna Park	4 (7)	4 (7)	0 (0)
009	Andrew N Antoszyk	9 (14)	9 (14)	0 (0)
011	Brian G. Terry	3 (3)	3 (3)	0 (0)
012	David W. Johnson	3 (4)	3 (4)	0 (0)
014	Carla Territo	2 (2)	2 (2)	0 (0)
026	Julio E. Perez	5 (7)	5 (7)	0 (0
064	B Hirschel	1 (1)	1 (1)	0 (0)
067	J Gonzalez Guijarro	2 (3)	2 (3)	0 (0)
TOTAL		49 (71)	48 (69)	1 (2)

Demographic Summary

Dose Group		Mean	SD	Min	Max	Gender		Race			
						Male	Female	Cauc	Black	Asian	Other
75 µg DE	7	36.57	7.85	28	50	7	0	6	1	0	0
150 µg DE	5	31.40	3.51	26	35	4	1	4	0	0	1
150 µg Combo	22	37.36	8.22	25	56	18	4	11	5	0	6
330 µg Combo	7	34.86	4.74	29	44	7	0	6	0	0	1
GCV Only	8	43.50	9.38	30	56	7	1	6	1	0	1
TOTAL	49	37.29	8.06	25	56	43	6	33	7	0	9

Reviewer Efficacy Results



Number of Patients:

150 immediate	=	29
330 immediate	=	6
Dose escalation 150	=	6
Dose escalation 75	=	4
Ganciclovir	=	8

Reviewer's Comments: *There are no progressions in the 330 group, therefore, there is some evidence of effectiveness, however, the numbers are small and the time to censoring is short.*

Significant Adverse Events (*Reviewer selection of events)*:

Number of Eyes with event

	Dose Group		
	75 (n=10)	150 (n=40)	330 (n=9)
Cataract	0	4	0
Anterior Chamber Inflammation	0	3	0
Uveitis	0	2	0
Photophobia	0	0	4
IOP Increase	0	2	1
Peripheral Vision Decrease	0	0	2
Retinal Pigment Change	1	2	3
Blurred Vision	0	3	2

Reviewer's Comments: *The events listed above are considered to represent potential threats to visual function.*

Study #3
Protocol 9
Title of Study:

A Randomized Comparison of Two Dosage Schedules of Intravitreal Fomivirsen for Patients with Advanced Cytomegalovirus Retinitis (CMVR)

Investigators and Study Center(s) that enrolled patients:

David S. Boyer, M.D., Los Angeles, CA; Sheldon J. Cowen, M.D., Seattle WA; Ronald P. Danis, M.D., Indianapolis, IN; James G. Diamond, M.D., New Orleans, LA; Richard Fish, M.D., Houston, TX; Debra Goldstein, M.D., Chicago, IL; Glenn Jaffe, M.D., Durham, NC; Jacob Lalezari, M.D., San Francisco, CA; Ronni Lieberman, M.D., New York, NY; Cristina Muccioli, M.D., Sao Paulo, Brazil; Alan G. Palestine, M.D., Washington, D.C.; Julio Perez, M.D., Ft. Lauderdale, FL; Carla Territo, M.D., Philadelphia, PA

Studied period (years): 29 December 1995 to 30 November 1997 for all ongoing patients

Phase of development: III

Objectives:

The study objective was to determine if a less intense dosing schedule (Regimen B) of 330 μg intravitreal injections of fomivirsen elicited the same response as a more intense dosing schedule (Regimen A) in the treatment of advanced CMVR.

Methodology:

The study began by randomly assigning one of two treatment regimens using 330 μg fomivirsen in a 2:1 ratio (Regimen A:Regimen B) to patients as they entered the study. Patients with bilateral disease, where both eyes met inclusion and exclusion criteria, received the same Regimen of fomivirsen in both eyes. Treatment with fomivirsen consisted of an Induction Period followed by a Maintenance Period which could be extended (Extended Maintenance Period) for patients who completed the 22 weeks of dosing. All patients were followed for time to CMVR progression determined by standard criteria. Assessment of CMVR activity and progression were based on a central reading center evaluation (masked) of fundus photographs as well as clinical determinations. After completing the Induction Period, patients in Regimen A and Regimen B who experienced progression in one or both eyes treated with fomivirsen, could have been re-treated according to Regimen A (reinduction and maintenance) and allowed to continue in the study.

Number of patients: Regimen A = 34; Regimen B = 20

Diagnosis and main criteria for inclusion:

Patients with AIDS, ≥ 18 years of age; clinical diagnosis of active advanced CMVR which had been previously treated and had reactivated, or CMVR that was not controlled despite antiviral therapy; Karnofsky score of > 60; and signed informed consent were included in this study.

Dose and mode of administration: 330 μg and 150 μg* intravitreal injection.

- Regimen A: Days 1, 8 and 15 (Induction Period), and every second week thereafter (Maintenance Period).

- Regimen B: Days 1 and 15 (Induction Period), and every fourth week thereafter (Maintenance Period).

*A deviation was granted to patient 031-955 to continue on study with a dose reduction (150 μg fomivirsen) due to an adverse event.

Duration of treatment:

Patients continued dosing during the Induction Period followed by the Maintenance Period for a minimum of 22 weeks, or until they experienced progression or a treatment terminating adverse event. The Maintenance Period could have been extended for any patient who completed 22 weeks of dosing.

Criteria for evaluation:

Efficacy: Time from initiation of fomivirsen treatment to CMVR progression was defined by 1) the appearance of any new lesion(s) 750 microns in size; 2) the advancement of the border of existing lesion(s), including satellite lesion(s), by 750 microns along a 750 micron front; 3) retinal detachment in an area of active CMVR; and/or 4) CMVR involvement adjacent to the optic nerve concurrent with a decrease in best corrected visual acuity to worse than 20/200.

Safety: Complete bilateral ophthalmic examinations, evaluation of ocular adverse events and laboratory measurements for evaluation of systemic adverse events were performed.

Statistical methods:

Patient population, demographic and clinical background - Descriptive statistics and frequency tabulations.

Primary Efficacy Analysis - Time to progression in Regimen A versus Regimen B was compared in an intention-to-treat analysis (all patients who received at least 1 dose of fomivirsen and had at least 1 follow-up evaluation); Kaplan-Meier survival analysis of time to observed progression by fundus photography (masked) and clinical evaluations; and logrank and Wilcoxon survival analysis tests for comparison of the two distributions in Regimen A and Regimen B.

Safety Analysis - Descriptive statistics; Incidence of ocular and systemic adverse events; and comparison of Regimen A to Regimen B using descriptive statistics.

Applicant's Efficacy Results:

There was no difference in time to progression for Regimen A compared to Regimen B for patients included in the intention to treat analysis (p=0.4847). The interpolated median time to progression was 90.65 days (Regimen A) compared to 90.34 days (Regimen B), as determined by primary efficacy endpoint. Subset analyses yielded similar results. There was no difference in time to progression for patients on concomitant oral ganciclovir compared to those not on ganciclovir.

Applicant's Safety Results:

There was no significant difference in the safety profile of Regimen B compared to the more frequent dosing schedule in Regimen A, although the incidence of some events relative to intraocular inflammation was less frequent in Regimen B. The most frequently observed ocular adverse event were intraocular inflammation and elevations in intraocular pressure. Few patients were discontinued from study because of ocular adverse events.

Site (Eyes)	NAME	Total Patients (Eyes)	Discontinued Patients (Eyes)	Continuing Patients
001	Alan G. Palestine	1 (2)	1 (2)	0 (0)
004	Ronni M. Lieberman	6 (8)	5 (7)	1 (1)
005	David S. Boyer	2 (2)	1 (1)	1 (1)
006	Debra Goldstein	3 (3)	3 (3)	0 (0)
010	Ronald Danis	2 (3)	2 (3)	0 (0)
014	Carla Territo	2 (3)	2 (3)	0 (0)
019	Richard Fish	1 (1)	1 (1)	0 (0)
023	Sheldon Cowen	1 (1)	1 (1)	0 (0)
024	Jacob P. Lalezari	8 (8)	8 (8)	0 (0)
026	Julio E. Perez	1 (1)	1 (1)	0 (0)
028	Glenn Jaffe	1 (1)	0 (0)	1 (1)
030	James Diamond	1 (1)	1 (1)	0 (0)
031	Cristina Muccioli	25 (29)	12 (13)	13 (16)
TOTAL		54 (63)	38 (44)	16 (19)

Demographic Summary

						Gender		Race			
Dose Group		Mean	SD	Min	Max	Male	Female	Cauc	Black	Asian	Other
Regimen A	34	36.62	6.41	25	51	28	6	26	3	1	4
Regimen B	20	38.60	7.04	25	50	19	1	14	0	2	4
TOTAL	54	37.35	6.65	25	51	47	7	40	3	3	8

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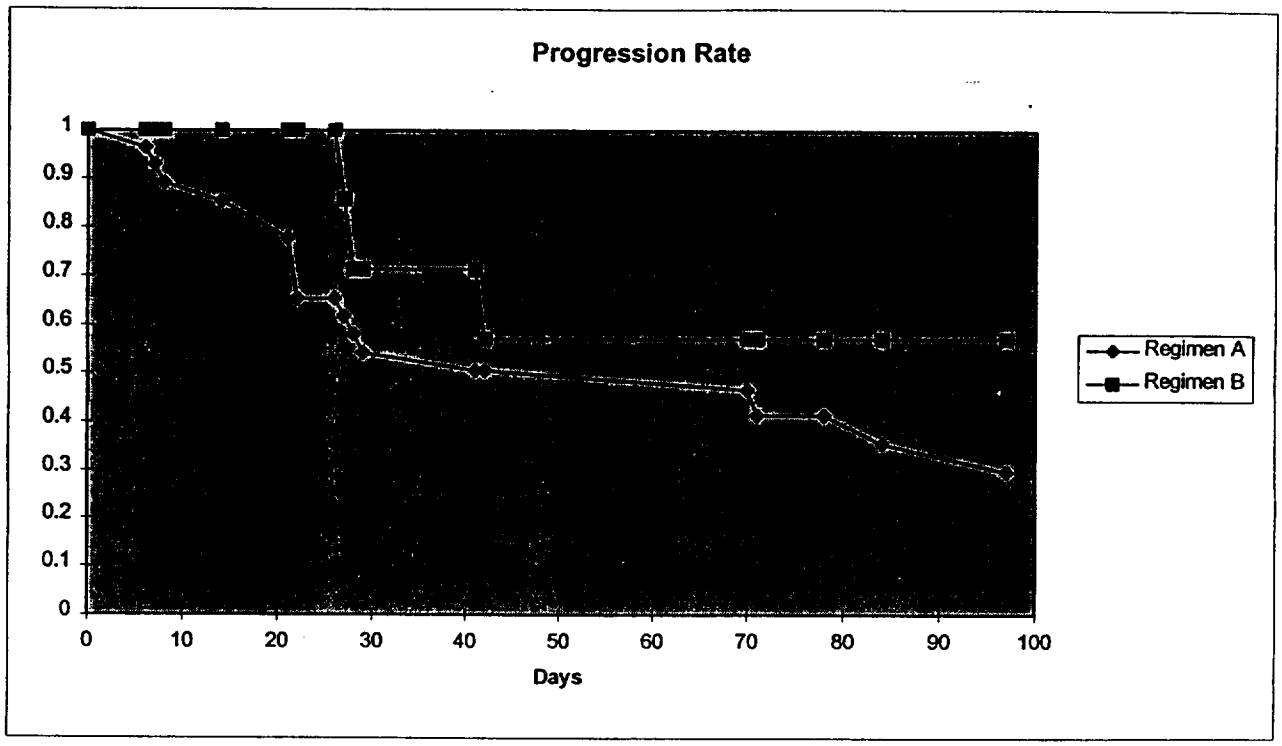
ON ORIGINAL

Reviewer Efficacy Results:



Patients on Regimen A	=	29	Weekly initially then every other week
Patients on Regimen B	=	10	Every other week initially then every month

Reviewer's Comments:

1. *Numerically, Regimen B appears better than Regimen A. However, the number of patients is small and therefore unlikely to be statistically significant.*

2. *The efficacy demonstrated is not consistent with the "no progressions" demonstrated for the 330 treatment group in Studies CS2 and CS3 of this review.*

Visual Acuity - 3 line change from Baseline

	Patients Evaluated (Eyes)	Incidence	
Regimen A	34 (39)	25 (27)	(74%)
Regimen B	20 (24)	9 (9)	(45%)

APPEARS THIS WAY
ON ORIGINAL

Significant Adverse Events (*Reviewer selection of events)*:

Number of Eyes with event

	Dose Group		
	150 (n=1)	330 A (n=43)	330 B (n=24)
Cataract	1	5	4
Corneal Edema	1	4	0
Anterior Chamber Inflammation	0	10	2
Vitritis	0	7	4
IOP Increase	1	10	3
Peripheral Vision Decrease	0	2	0
Retinal Pigment Change	0	4	0
Retinal Detachment	0	8	1

Reviewer's Comments: *The events listed above are considered to represent potential threats to visual function. Regimen A has considerably more events than Regimen B.*

APPEARS THIS WAY
ON ORIGINAL

Study #4
Protocol CS-12
Title of Study:

A Randomized, Controlled Comparison Of The Efficacy And Safety Of Two Different Dosing Regimens Of Intravitreal ISIS 2922 In The Treatment Of Active, Advanced Cytomegalovirus Retinitis (CMVR) In AIDS Patients

Investigators and Study Center(s) that enrolled patients:

David Andreu, M.D., Barcelona, Spain; Jean Deschenes, M.D., Montreal, Canada; Martin Fisher, M.D., Brighton, UK; Jean-Albert Gastaut, M.D., Marseille, France; Brian Gazzard, M.D., London, UK; Hermann Gümbel, M.D., Frankfurt, Germany; Margaret A. Johnson, M.D., London, UK; Volker Klauss, M.D., Munich, Germany; Volker Knospe, M.D., Hamburg, Germany; Jose Mallolas-Masferrer, M.D., Barcelona, Spain; Marc D. de Smet, M.D., The Netherlands

Studied period (years): 12 June 1996 to ongoing patient visits through 19 November 1997

Phase of development: III

Objectives:

To determine if a less intense dosing schedule (Regimen B) with intravitreal injections of 330 μg fomivirsen elicited the same response as a more intense dosing schedule (Regimen A) in the treatment of advanced CMVR.

Methodology:

The study began by randomly assigning one of two regimens using 330 μg fomivirsen in a 2:1 ratio (Regimen A: Regimen B) to patients as they entered the study. Patients with bilateral disease, where both eyes met inclusion and exclusion criteria, received the same regimen of fomivirsen in both eyes. Treatment consisted of an Induction Period followed by a Maintenance Period which could be extended (Extended Maintenance Period) for patients who completed 22 weeks of dosing. All patients were followed for time to CMVR progression determined by standard criteria. Assessments of CMVR activity and progression were based on a central reading center evaluation (masked) of fundus photographs as well as clinical determinations. In addition, the safety profile of Regimen A was to be compared with the safety profile of Regimen B.

Number of patients:

A total of 32 patients were enrolled and treated; Regimen A = 21, Regimen B =11.

Diagnosis and main criteria for inclusion:

Patients with AIDS; ≥18 years of age; active advanced CMVR in one or both eyes which have been previously treated and had reactivated, or was not controlled despite antiviral therapy and had >25% retinal involvement of CMVR or Zone 1 disease with a leading edge > 1000 μ from the center of the macula or optic disc; Karnofsky score of > 60; signed informed consent; and, if female, agreed to use a reliable form of contraception for the duration of the trial.

Dose Regimen A:

Days one, eight and 15 (Induction Period) and every second week thereafter (Maintenance Period).

Dose Regimen B:

Days one and 15 (Induction Period) and every fourth week thereafter (Maintenance Period).

Duration of treatment:

Patients continued dosing during the Induction Period followed by the Maintenance Period for a minimum of 22 weeks, or until they experienced progression and based on safety findings. The Maintenance Period could have been extended for any patient who completed 22 weeks of dosing.

Criteria for Evaluation:

Efficacy: Time from initiation of fomivirsen treatment to CMVR progression was defined by: the appearance of any new lesion(s) 750 microns in size; the advancement of the border of existing lesion(s), including satellite lesion(s), by 750 microns along a 750 micron front; retinal detachment in an area of active CMVR; and/or CMVR involvement adjacent to the optic nerve as determined by clinical determination concurrent with a decrease in best corrected visual acuity to worse than 20/200 (6/60). A visual acuity of worse than 20/200 (6/60) must represent a decrease from the baseline exam to be included as an indication of progression.

Safety: Complete bilateral ophthalmic examination, evaluation of ocular adverse events and laboratory measurements for evaluation of systemic adverse events were performed.

Statistical methods:

Patient population, demographic and clinical background: Descriptive statistics; frequency tabulations.

Primary Efficacy Analysis: Time to CMVR progression in Regimen A and Regimen B was compared in an intention-to-treat analysis of all patients who received at least 1 dose of fomivirsen and had at least 1 follow-up evaluation; Kaplan-Meier survival analysis of time to observed progression by fundus photography (masked) and clinical determination.

Safety Analysis: Complete bilateral ophthalmic examination, evaluation of ocular adverse events and laboratory measurements for incidence of local and systemic adverse events.

Applicant's Efficacy Results:

Intention-to-treat analysis revealed an interpolated median time to progression that was not definable for patients treated in Regimen A compared to 181.67 days for patients treated in Regimen B, as determined by fundus photography. This analysis also revealed a 25^{th} percentile time to observed CMVR progression of 91 days for patients treated in Regimen A compared to 71 days for patients treated in Regimen B.

Applicant's Safety Results:

The most frequently observed ocular adverse events were increased intraocular pressure and intraocular inflammation. Nine patients were terminated from the study ocular adverse events (seven patients in Regimen A and two patients in Regimen B).

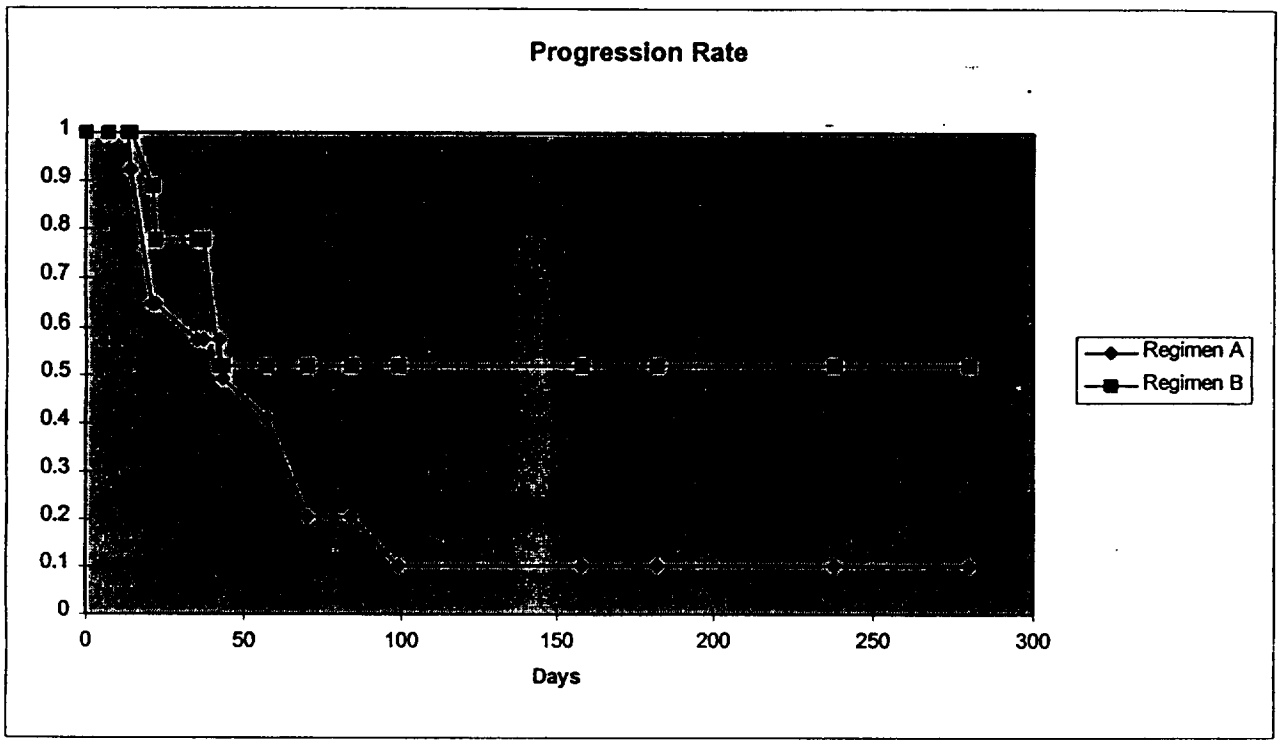
Site (Eyes)	NAME	Continuing Patients (Eyes)	Patients (Eyes)	Patients
029	Jean Deschnes	1 (1)	0 (0)	1 (1)
040	Susan Lightman	9 (12)	9 (12)	0 (0)
041	M A Johnson	2 (2)	2 (2)	0 (0)
042	M Fisher	1 (2)	1 (2)	0 (0)
045	J Mallolas	1 (1)	1 (1)	0 (0)
046	D Andreu	7 (11)	6 (10)	1 (1)
048	V Knospe	2 (3)	0 (0)	2 (3)
049	H Gumbel	4 (7)	2 (4)	2 (3)
050	V Klauss	2 (4)	2 (4)	0 (0)
051	J A Gastaut	1 (1)	1 (1)	0 (0)
055	M D de Smett	2 (2)	2 (2)	0 (0)
TOTAL		32 (46)	26 (38)	6 (8)

Demographic Summary

						Gender		Race			
Dose Group		Mean	SD	Min	Max	Male	Female	Cauc	Black	Asian	Other
Regimen A	21	37.24	8.22	24	54	20	1	18	0	3	0
Regimen B	11	35.91	5.58	29	45	9	2	11	0	0	0
TOTAL	32	36.78	7.35	24	54	29	3	29	0	3	0

MOR_2

Reviewer Efficacy Results:



Patients on Regimen A	=	14	Weekly initially then every other week
Patients on Regimen B	=	13	Every other week initially then every month

Reviewer's Comments:

1. *Numerically, Regimen B appears better than Regimen A. However, the number of patients is small and therefore unlikely to be statistically significant.*

2. *The efficacy demonstrated is not consistent with the "no progressions" demonstrated for the 330 treatment group in Studies CS2 and CS3 of this review.*

Visual Acuity - 3 line change from Baseline

	Patients Evaluated (Eyes)	Incidence	
Regimen A	21 (29)	11 (14)	52%
Regimen B	11 (17)	6 (7)	55%

Significant Adverse Events (*Reviewer selection of events*):

Number of Eyes with event

	Dose Group 330 A (n=29)	330 B (n=21)
Cataract	3	1
Corneal Edema	3	0
Anterior Chamber Inflammation	4	1
Vitritis	5	0
Uveitis	13	6
IOP Increase	8	1
Retinal Pigment Change	2	0
Retinal Detachment	4	4
Pain	6	1

Reviewer's Comments: *The events listed above are considered to represent potential threats to visual function. Regimen A has considerably more events than Regimen B.*

APPEARS THIS WAY
ON ORIGINAL

9 Overview of Efficacy

While some efficacy appears to have been demonstrated, the number of patients treated is small precluding accurate assessments of efficacy. The median time to progression for the 330 dose in Studies 2, 3, 9 and 12 together (80 eyes) was approximately 80 days recognizing that this time may be biased due to the use of additional anti-viral therapies. The median time for the untreated group from Study 2 was 14 days.

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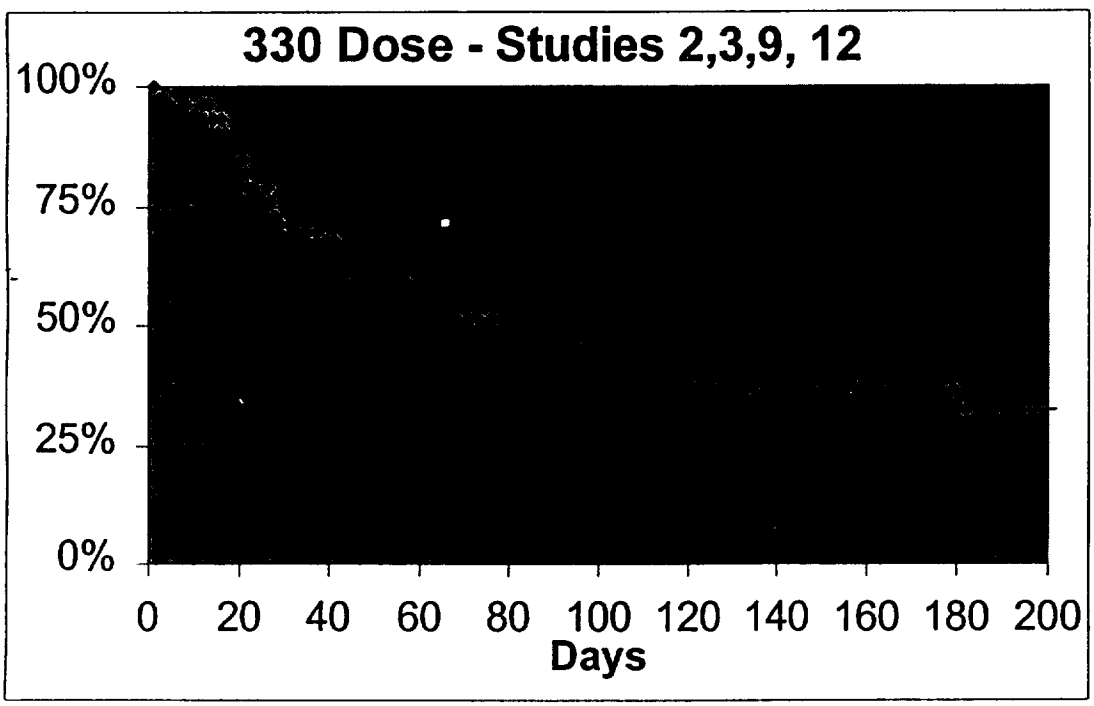

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10 Overview of Safety

1. *There is an inadequate sized safety data base to adequately evaluate safety.*
2. *Systemic effects observed to date have been minimal.*
3. *The mechanism and the potential adverse effects on vision of retinal pigment changes observed in the clinical trials have not been fully clarified.*
4. *Ocular inflammation appears to be correlated with increasing administered doses.*

10.1 Significant/Potentially Significant Events

10.1.1 Deaths - *None beyond those expected in this patient population.*

10.1.3 Overdose Experience- *Only 1 reported event and that event resolved after flushing of the anterior chamber.*

10.2.1 ADR Incidence Tables - Systemic events ≥3 (>1%) – 330 dose (n=221)

Studies 1, 2, 3, 7, 9, 12

Event	Number
Fever	33
Pneumonia	27
Headache	26
Asthenia	24
Diarrhea	21
Nausea	20
HIV Syndrome	17
Infection	15
Sinusitis	14
Vomiting	14
Sepsis	13
Anemia	12
Pain, abdominal	11
CMV Systemic	10
Monilia, oral	10
Rash	10
Cough increased	9
Infected cath	9
Dehydration	8
Dyspnea	8
Flu Syndrome	8
Neutropenia	8
Dizziness	7
Anorexia	6
Neuropathy	6
Weight decreased	6
Abnormal thinking	5
Cachexia	5
Nausea/vomiting	5
Pain, chest	5
Sweating	5
Bronchitis	4
Depression	4
GGTP increased	4
Kidney failure	4
Liver function abnormality	4

Event	Number
Lymphoma like reaction	4
Pancreatitis	4
Skin disease	4
Allergic reaction	3
Chills	3
Confusion	3
GI Hem	3
Heart failure, right	3
Herpes simplex	3
Hypertension	3
Infection, fungal	3
Kidney calculus	3
Lipase increased	3
Malaise	3
Neuritis, peripheral	3
Pain	3
Pain, back	3
Peripheral edema	3
Sarcoma	3
Thrombocytopenia	3

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Ocular Events

Event	165 Dose (n=90)	330 Dose (n=221)
Anterior chamber inflammation	13	55
IOP increase	13	41
Vision abnormal	9	38
Eye pain	7	34
Vitritis	5	33
Eye irritation	3	32
Vision blurred	7	32
Retinal detachment	4	29
Retinal edema	5	29
Cataract	8	25
Conjunctival hemorrhage	7	22
Floaters	3	19
Uveitis	3	17
Retinal disease	10	15
Retinal hemorrhage	5	15
Color vision desaturation	1	14
Corneal edema	1	11
Photophobia	5	11
Visual acuity decreased	2	11
Photopsia	1	10
Retinal pigment	3	10
Peripheral vision decrease	3	8
Conjunctivitis	3	7
Vitreous disease	6	7
Application site reaction	1	6
Conjunctival hyperemia	1	6
Visual field defect	0	6
Eye Disease	1	5
Hypotony	1	5
Corneal opacity	0	4
Keratic precipitates	0	4
Eye pallor	0	4
Night blind	1	3
Dry eye	0	3
Optic neuritis	0	3
Blepharitis	1	2
Eye implant complication	0	2
Corneal lesion	1	2
Cystoid macular edema	2	2

Event	165 Dose (n=90)	330 Dose (n=221)
Eye fatigue	0	2
Sclera hemorrhage	0	2
Keratitis	0	2
Lens pigment	0	2
Macular degeneration	2	2
Retinal artery occlusion	1	2
Retinal tear	3	2
Scleritis	0	2
Accommodation abnormal	0	1
Optic atrophy	0	1
Orbital cellulitis	0	1
Corneal pigment	0	1
Diplopia	0	1
Periorbital edema	0	1
Endophthalmitis	1	1
Glaucoma	0	1
Optic Nerve disease	0	1
Retinal vascular disease	4	1
Tearing	1	1
Vasculitis	0	1
Color blind	1	0
Chromatopsia	1	0
HIV eye	2	0
Hyphema	1	0
Retinal vein occlusion	1	0
Pupillary disorder	1	0
Refractive disorder	1	0
Vitreous opacity	1	0

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

13 pages

12 Conclusions

1. While some efficacy appears to have been demonstrated, the number of patients treated is small precluding accurate assessments of efficacy.
2. Most of the studies were submitted prior to their scheduled completion and in several cases prior to their scheduled first interim analysis.
3. The small number of patients treated, the questionable efficacy and the potential safety issues suggest that there is not sufficient support for an indication of first line therapy. Since patients who were failures on prior therapies were studied, consideration may be given to an indication in patients who have failed (or who have demonstrated intolerance to) at least one other CMV retinitis therapy or to those who have failed (or who have demonstrated intolerance to) at least two other CMV retinitis therapies.
4. Treatment on Days 1 and 15, followed by monthly injections appears to be safer and no less effective than dosing weekly, followed by fortnightly treatments.
5. The mechanism and the potential adverse effects on vision of retinal pigment changes observed in the clinical trials have not been fully clarified.
6. [redacted]
7. There are an insufficient number of patients studied to evaluate mean visual acuity effects either from an efficacy or safety prospective.
8. [redacted]
9. The pH of the product should be more tightly controlled.
10. The particulate matter specifications should be more tightly controlled.

Additional Comments:

The Ophthalmologic Sub-committee of the Dermatology and Ophthalmology Advisory Committee met on July 22, 1998, to discuss this application. By a 5-2 vote, it was recommended that the product be considered to have sufficient safety and efficacy to support an indication for CMV retinitis. Serious concerns remained with respect to the small numbers of patients studied and the consequential lack of information about the product.

[redacted]

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Medical Officer's Review of NDA 20-961
Amendment

NDA #20-961		Submission date:	8/7/98
M.O. Review #2		Receive date:	8/10/98
		Review completed:	8/11/98

Generic name: fomivirsen sodium intravitreal injectable
Proposed trade name: Vitravene

Sponsor: Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008
(760) 603-2378

Pharmacologic Category: Oligonucleotide

Nucleotide Sequence 5'-GCG TTT GCT CTT CTT CTT GCG-3'

Submitted: Response to Initial Review Deficiencies 1-9 and request for meeting.

1. Revised labeling has been submitted. The applicant has requested a meeting based on their belief that the NDA supports a broader indication than suggested by the Division.

Reviewer's Comments: *See labeling review below. The applicant has declined to meet with the Division and requested a meeting with the Office Director. The Division will recommend that the Office meet with the applicant although action on the package may proceed.*

Reviewer's Comments: *Acceptable.*

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

16 pages

Conclusions

1. While some efficacy appears to have been demonstrated, the number of patients treated is small precluding accurate assessments of efficacy.
2. Most of the studies were submitted prior to their scheduled completion and in several cases prior to their scheduled first interim analysis.
3. The small number of patients treated, the questionable efficacy and the potential safety issues suggest that there is not sufficient support for an indication of first line therapy. Since patients who were failures on prior therapies were studied, consideration may be given to an indication in patients who have failed (or who have demonstrated intolerance to) at least one other CMV retinitis therapy or to those who have failed (or who have demonstrated intolerance to) at least two other CMV retinitis therapies.
4. Treatment on Days 1 and 15, followed by monthly injections appears to be safer and no less effective than dosing weekly, followed by fortnightly treatments.
5. The mechanism and the potential adverse effects on vision of retinal pigment changes observed in the clinical trials have not been fully clarified.
6. [redacted]
7. There are an insufficient number of patients studied to evaluate mean visual acuity effects either from an efficacy or safety prospective.
8. [redacted]
9. The submitted labeling is potentially misleading.

Recommendations

NDA 20-961, Vitravene (fomivirsen sodium intravitreal injectable) **is not recommended for approval** for the proposed indication. It may be considered for approval with revised labeling identified in this review which limits the indication to the treatment of CMV retinitis in patients who are intolerant of another treatment for CMV retinitis or who were insufficiently responsive to another treatment for CMV retinitis provided the applicant commits to completing the clinical information by:

[redacted]

APPEARS THIS WAY
ON ORIGINAL

/S/

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: Orig NDA 20-961
HFD-550/DivFiles
HFD-340/Carreras
HFD-550/PM/Gorski
HFD-550/CHEM/Tso
HFD-805/MICRO/Hughes
HFD-550/PHARM/Yang
HFD-725/STAT/Taneja
HFD-880/BIOPHARM/Tandon
HFD-550/MO/Chambers

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 20-961
Amendment

NDA #20-961
M.O. Review #3

Submission dates: 8/25 & 26/98
Receive date: 8/26/98
Review completed: 8/26/98

Generic name: fomivirsen sodium intravitreal injectable
Proposed trade name: Vitravene Injection

Sponsor: Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008
(760) 603-2378

Pharmacologic Category: Oligonucleotide

Nucleotide Sequence 5'-GCG TTT GCT CTT CTT CTT GCG-3'

Submitted: Response to items discussed at August 24, 1998 meeting.

1. Revised labeling has been submitted.

Reviewer's Comments: *See labeling review below. The August 26, 1998, labeling contained minor revisions and is acceptable. Changes between the August 25th and August 26th versions are identified in this review.*

[redacted]

Reviewer's Comments: *Acceptable.*

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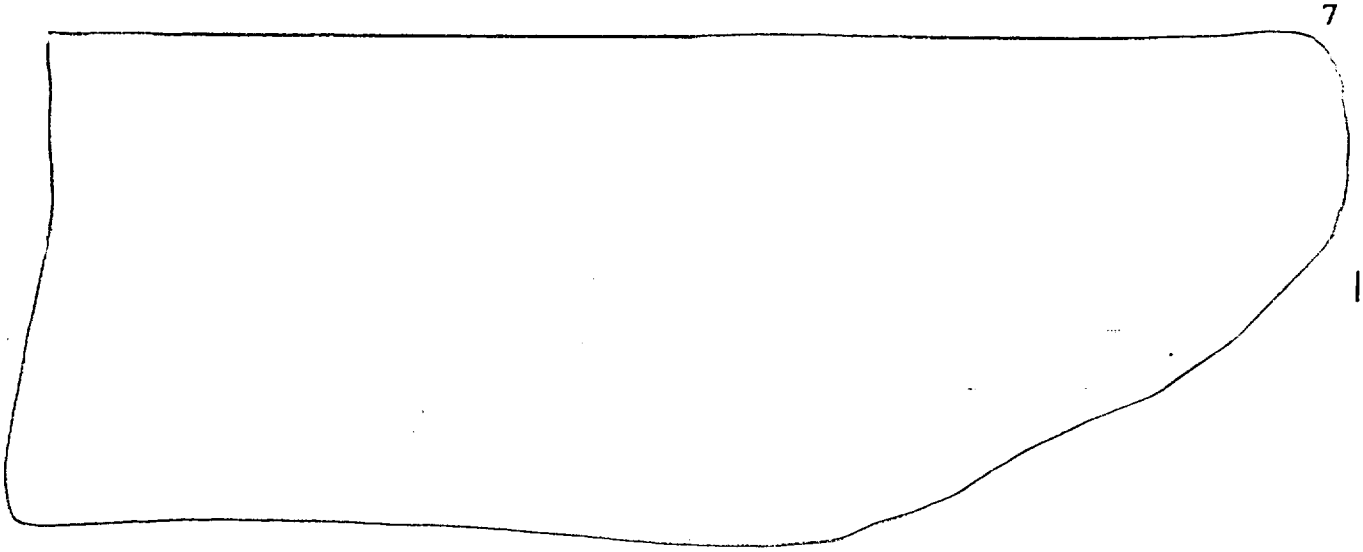
5 pages



Recommendations

NDA 20-961, Vitravene (fomivirsen sodium intravitreal injectable) **is recommended for approval** for the treatment of CMV retinitis in patients who are intolerant of or have a contraindication to other treatment(s) for CMV retinitis or who were insufficiently responsive to other treatment(s) for CMV retinitis.

APPEARS THIS WAY
ON ORIGINAL

/S/

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: Orig NDA 20-961
HFD-550/DivFiles
HFD-340/Carreras
HFD-550/PM/Gorski
HFD-550/CHEM/Tso
HFD-805/MICRO/Hughes
HFD-550/PHARM/Yang
HFD-725/STAT/Taneja
HFD-880/BIOPHARM/Tandon
HFD-550/MO/Chambers

APPEARS THIS WAY
ON ORIGINAL