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STATISTICAL REVIEW AND EVALUATION

AUG 6 1998

NDA #: 20-961/Drug Class 1P

APPLICANT: Isis Pharmaceuticals Inc.

NAME OF DRUG: Vitravene™ (fomivirsen sodium) Intravitreal Injection

INDICATION: Cytomegalovirus Retinitis (CMVR) in AIDS Patients

DOCUMENTS REVIEWED: Vol. 2.1, 2.205-2.273 dated April 10, 1998

MEDICAL REVIEWER: Wiley Chambers, MD (HFD-550).

This review is organized in four sections. Section I provides Background and Summary of this submission. Section II gives Sponsor's Analyses and Results for CS2 and CS9. Section III contains FDA's Analyses and Results for CS2 and CS9 as well as Statistical Reviewer's Comments on Sponsor's Adjusted Analyses. Finally, Section IV summarizes Statistical Reviewer's Conclusions that may be conveyed to the sponsor.

I. Background & Summary

In this NDA, the sponsor has submitted results from seven clinical trials: CS1, CS2, CS3, CS5, CS7, CS9 and CS12. Among these seven trials, 91 patients (118 eyes) received 165 μg/injection and 239 patients (315 eyes) received 330 μg/injection. These 330 patients (433 eyes) were evaluated by 43 investigators at different centers in nine countries. On the average, the number of patients (eyes) per investigator is really very small.

Controlled clinical trials in this NDA include two different study designs (CS2 and CS3) for *newly diagnosed* CMVR patients and two almost identical study designs (CS9 and CS12) for *previously treated* CMVR patients. Sponsor's planned interim analysis was completed for only two controlled studies (CS2 and CS9). Both CS3 and CS12 were originally designed as well-controlled studies, but neither has reached the protocol-specified threshold of patients needed for an interim analysis. The sponsor called CS2 – Pivotal Study and CS9 – Key Supportive Study. Thus, this statistical review is focused on the evaluation of these two trials, CS2 and CS9, only.

For descriptive details of other trials, please see the medical officer's review.

II. Sponsor's Analyses and Results for CS2 and CS9

CS2 (Immediate vs. Delayed Treatment): Pivotal Study

This study began as a randomized comparison of immediate treatment with 330 µg/injection fomivirsen or delayed treatment (randomized 2:1) to patients sequentially entering the study. 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/injection dose, such that the 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/injection fomivirsen (Group A). The second group of patients in Stage 1 started treatment with 150 µg/injection 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/injection or delayed treatment (randomized 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.

The primary endpoint for evaluation of efficacy was time to observed progression of CMVR in the primary eye. 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. There were several secondary endpoints.

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 one dose of fomivirsen and at least one follow-up evaluation. Delayed treatment patients were required to have at least one follow-up evaluation to be included in the intent-to-treat analysis. Kaplan-Meier survival analysis of time to observed CMVR progression by fundus photography (masked) and clinical evaluations were performed.

Patient characteristics at the Baseline are provided in the following Table.

Table: Patient Characteristics at Baseline

Summary Statistics		Treatment Groups	
		Immediate (n=19)	Delayed (n=10)
Age:	Median	36	32.5
	Range	23 – 61	28 - 59
Gender:	Male	18 (94.7%)	9 (90%)
	Female	1 (5.3%)	1 (10%)
Race:	Caucasian	12 (63.1%)	7 (70%)
	Black	3 (15.8%)	2 (20%)
	Asian	1 (5.3%)	0 (0%)
	Other	3 (15.8%)	1 (10%)

Results on the primary endpoint of time to observed CMVR progression for intent-to-treat dataset are provided in the following Table.

Table: Time to Observed CMVR Progression (ITT)

	Treatment Groups	
	Immediate (n=18)	Delayed (n=10)
Median (Days)	71	13
95% Confidence Interval	(28, ND)	(9, 15)
25th Percentile	28	9
Number of Patients With CMVR Progression	8 (44%)	7 (70%)

ND=Not Determinable

The intent-to-treat analysis showed a median time to progression of 71 days for patients in the immediate treatment group versus 13 days for the delayed treatment group (logrank p=0.0002, Wilcoxon p=0.0001), as determined by the primary efficacy endpoint.

The sponsor concluded that this study demonstrated the efficacy and safety of fomivirsen at 150 µg/injection for the treatment of previously untreated CMVR in patients with AIDS.

CS9 (Schedule Comparison): Key Supportive Study

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 for patients who completed the 22 weeks of dosing.

The primary endpoint for evaluation of efficacy was time to observed progression of CMVR. 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. There were several secondary endpoints.

The primary analysis performed was an intent-to-treat analysis (all patients who received at least one dose of fomivirsen and had at least one follow-up evaluation) comparing time to CMVR progression in Regimen A versus Regimen B. Kaplan-Meier survival analysis was utilized.

Patient characteristics at the Baseline are provided in the following Table.

Table: Patient Characteristics at Baseline

Summary Statistics		Treatment Groups	
		Regimen A (n=34)	Regimen B (n=20)
Age:	Median	35.5	39.5
	Range	25 – 51	25 - 50
Gender:	Male	28 (82.4%)	19 (95%)
	Female	6 (17.6%)	1 (5%)
Race:	Caucasian	26 (76.5%)	14 (70%)
	Black	3 (8.8%)	0 (0%)
	Asian	1 (2.9%)	2 (10%)
	Other	4 (11.8%)	4 (20%)

Results on the primary endpoint of time to observed CMVR progression for intent-to-treat dataset are provided in the following Table. There was no statistically significant difference in time to progression for Regimen A compared to Regimen B for patients included in the intent-to-treat analysis (p=0.4847).

Table: Time to Observed CMVR Progression (ITT)

	Treatment Groups	
	Regimen A (n=34)	Regimen B (n=20)
Median (Days)	106	267
95% Confidence Interval	(71, ND)	(42, ND)
25th Percentile	42	42
Number of Patients With CMVR Progression	16 (47%)	6 (30%)

ND=Not Determinable

The sponsor concluded that in terms of efficacy, Regimen A and Regimen B are comparable; but in terms of safety, Regimen B appears to be better tolerated.

III. FDA's Analyses and Results for CS2 and CS9 & Statistical Reviewer's Comments on Adjusted Analyses

FDA's analyses and results are based on an independent blinded read of fundus photographs by the Medical Officer.

CS2 (Immediate vs. Delayed Treatment)

The number of patients included in FDA's analysis are:

150 Immediate	=	16
330 Immediate	=	8
Dose Escalation 150	=	3
Dose Escalation 75	=	4
Deferred	=	8.

Results on the primary endpoint of time to observed CMVR progression for intent-to-treat dataset are provided in the following Table for the 150 Immediate and 330 Immediate groups only.

Table: Time to Observed CMVR Progression (ITT)

	Treatment Groups	
	150 Immediate (n=16)	330 Immediate (n=8)
Median (Days)	27	ND
95% Confidence Interval	(14, 70)	ND
25th Percentile	14	ND
Number of Patients With CMVR Progression	12 (75%)	0 (0%)

ND=Not Determinable

The comparison of the two survival curves yielded statistically significant p-values (logrank test p=0.0102, Wilcoxon test p=0.0157). There are no observed CMVR progressions in 330 Immediate group whereas in 150 Immediate group 75% of the patients progressed to CMVR.

There appears to be some efficacy with 330 immediate group but the sample size is really very small to make a definite conclusion.

Please see Medical Officer's review for the graphs of progression rates for various treatment groups.

CS9 (Schedule Comparison)

The number of patients included in FDA's analysis are:

Regimen A = 29
Regimen B = 10.

Results on the primary endpoint of time to observed CMVR progression for intent-to-treat dataset are provided in the following Table.

Table: Time to Observed CMVR Progression (ITT)

	Treatment Groups	
	Regimen A (n=29)	Regimen B (n=10)
Median (Days)	70	125
95% Confidence Interval	(27, 121)	(28, 294)
25th Percentile	22	35
Number of Patients With CMVR Progression	19 (66%)	5 (50%)

Regimen B appears to be better than Regimen A numerically but there was no statistically significant difference in time to progression for Regimen A compared to Regimen B for patients included in the intent-to-treat analysis (logrank p=0.2981, Wilcoxon p=0.1830).

Please see Medical Officer's review for the graphs of progression rates for various treatment groups.

Statistical Reviewer's Comments on Sponsor's Adjusted Analyses

The sponsor has performed survival analyses adjusting for Baseline Protease Inhibitor Use and Baseline CD4 Counts.

In CS2, the baseline protease inhibitor use and CD4 counts were not significantly predictive for time to CMVR progression but time to observed CMVR progression remained highly significant when adjusted for the presence of protease inhibitors and baseline CD4 counts.

Usually, covariates are used in Analysis of Covariance (ANCOVA) to reduce noise but in survival analysis (Cox Regression Model), using covariates brings p-values down without reducing noise. So, (unadjusted) statistically significant results remain statistically significant (after adjusting for covariates) and (unadjusted) non-significant results sometimes become statistically significant (after adjusting for covariates). This statistical dilemma is currently under research by David Hoberman, Ph.D. (FDA/CDER/OEB) under Dr. Woodcock's Review Science Research Project No. RSR-96-009A.

IV. Statistical Reviewer's Conclusions (That may be conveyed to the sponsor)

In this NDA, some studies were submitted prior to their completion. In some cases, they were submitted prior to their scheduled interim analysis. This caused sample sizes to be really very small to make any definite statistical conclusions.

In study CS2 (Sponsor's Pivotal Study), there appears to be some efficacy with fomivirsen 330 immediate group but the sample size is small to make a definite conclusion.

In study CS9 (Sponsor's Key Supportive Study), Regimen B appears to be (numerically) better than Regimen A, but there is no statistically significant difference in time to CMVR progression for Regimen A compared to Regimen B for patients included in the intent-to-treat analysis.

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cc:
NDA 20-961
HFD-550/Div Files
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HFD-725/Stat/Huque
HFD-725/Stat/Lin
HFD-725/Stat/Taneja
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This review contains 7 pages of text.