Studies of Ocular Complications of AIDS

HPMPC Peripheral CMV Retinitis Trial Protocol Version 1.4

Repository:
SOCA Coordinating Center
The Johns Hopkins Center for Clinical Trials
615 North Wolfe Street
Baltimore, Maryland 21205
(410) 955-8175
(410) 955-0932 (fax)

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Contents

Summary

Objectives:

Primary

Stage 1: To assess the short-term safety of HPMPC for use in patients with AIDS and CMV-retinitis, via a comparative randomized trial of HPMPC vs observation in a study population of up to 30 patients.

Stage 2: To assess the long-term safety and efficacy of HPMPC for use in patients with AIDS and CMV-retinitis, via a comparative randomized trial of two different HPMPC maintenance dose levels vs observation in a study population of up to 70 patients.

Both stages combined: To evaluate the safety and efficacy of HPMPC for treatment of CMV retinitis in patients with AIDS.

Secondary

Stage 1: To provide preliminary data on the safety and efficacy of HPMPC.

Stage 2: To provide preliminary data on the comparative value of 3 mg/kg vs 5 mg/kg as a maintenance dose for HPMPC.

Treatments: Patients will be randomized to one of two treatment groups in Stage 1, and to one of three treatment groups in Stage 2. The treatment groups are:

Dfr: Observation, with treatment deferred until the retinitis spreads (stages 1 and 2).
H-3: HPMPC induction at 5 mg/kg, and maintenance at 3 mg/kg (stages 1 and 2).
H-5: HPMPC induction at 5 mg/kg, and maintenance at 5 mg/kg (stage 2 only).

HPMPC will be administered intravenously. The two induction doses will be given 7 days apart, and be followed by a maintenance dose given every 14 days. Oral probenecid and intravenous saline hydration will be given with the HPMPC to minimize renal toxicity. Treatments will not be masked.

Data collection schedule: Follow-up visits for all patients are scheduled at weeks 3, 5, 7, 11, 15, 19, and 23 following randomization, and every 12 weeks thereafter until study closeout. An eye examination, fundus photographs, blood and urine laboratory studies, and a brief medical history will be performed at each of these visits. Some visits will also include a general physical examination. In addition, blood and urine laboratory studies will be performed at weeks 1, 9, 13, 17, and 21. All patients receiving HPMPC will have blood and urine laboratory studies performed within the 24 hours preceding each HPMPC infusion.

HPMPC Peripheral CRT — Summary

Outcomes measures: The outcomes of primary interest are time to first retinitis progression, occurrence of nephrotoxicity, occurrence of other drug-related toxicities, and death. Other outcomes of interest are CMV shedding in urine or blood and changes in visual acuity. The evaluation of retinitis progression will be masked. The evaluation of other outcome measures will not be masked.

Implementation: The trial will be conducted in two stages. Implementation of Stage 2 is dependent on evidence from Stage 1 that HPMPC does not have life-limiting toxicity and is potentially efficacious in controlling CMV retinitis.

> **Stage 1:** Up to 30 patients will be enrolled and randomized to either the H-3 or Dfr group with a 1:1 assignment ratio. An interim analysis for safety and efficacy will be initiated once the 20th patient has been followed for one month.
>
> **Stage 2:** Up to 70 patients will be enrolled and randomized to either the H-3, H-5, or Dfr group with a 1:1:1 assignment ratio. An interim analysis for safety and efficacy will be conducted at least once every 6 months.

The recruitment goal for both stages combined is 90 patients within two years (4 patients per month). There will be a common closeout for the trial six months after enrollment of the last patient.

Analysis rules: All randomized patients will be included, regardless of their eligibility or treatment. All events occuring after randomization will be counted, regardless of how soon after randomization they occur. For primary analyses, all patients will be counted in the treatment group to which they are assigned, regardless of their course of treatment.

Oversight: The SOCA Policy and Data Monitoring Board (PDMB) will review all interim analyses and make recommendations about proceeding with the trial, with or without modifications. The voting members of the PDMB do not have any other involvement with SOCA, and are free of financial and other conflicts of interest.

1. Introduction

1.1 Cytomegalovirus infection in AIDS patients

Cytomegalovirus (CMV) infection is an important cause of morbidity in patients with the acquired immunodeficiency syndrome (AIDS) (1-3). End organ diseases include retinitis, pneumonitis, colitis, and esophagitis. Among these syndromes, retinitis accounts for 85% of CMV disease in patients with AIDS. It is the most easily diagnosed and quantified, thereby providing a target amenable to the testing of anti-CMV compounds (4).

CMV retinitis is the most common intraocular infection in patients with AIDS, occurring in 10 to 30% of AIDS patients at some time during the course of their HIV disease (5-7). Although the syndrome tends to present as a relatively late manifestation of AIDS (generally occurring in patients with CD4 cell counts < 100 cells/μL), it is occasionally the initial manifestation of AIDS (7, 8).

Over time, untreated CMV retinitis will destroy the retina. Prompt treatment of CMV retinitis involving the posterior pole is required to limit vision loss and blindness. Small peripheral lesions, however, may occur without loss of vision. While treatment will ultimately be needed, the timing of that treatment is elective within limits.

Two drugs have been licensed by the Food and Drug Administration for the treatment of CMV retinitis. Nine-(1,3-dihydroxy-2-propoxy)methylguanine (ganciclovir; also DHPG) and trisodium phosphonoformate (foscarnet) have both been shown to be effective in delaying progression of retinitis. Unfortunately, progression ultimately ensues despite use of either agent (6, 9).

Administration of each agent is associated with adverse effects. Ganciclovir therapy may be accompanied by neutropenia. While the availability of colony-stimulating factors allows the concomitant use of ganciclovir and zidovudine (AZT, which also causes neutropenia), this treatment is expensive and requires constant monitoring. Additionally, ganciclovir-resistant CMV isolates have been found in previously responsive patients (10). Foscarnet therapy, although not associated with problematic neutropenia, is often accompanied by other serious toxicities, including electrolyte and mineral imbalances and renal insufficiency (6, 11).

Both ganciclovir and foscarnet must be administered intravenously twice daily for treatment and at least once a day for maintenance, usually necessitating placement of a chronic indwelling catheter. Catheter infections are a significant source of morbidity in this population (11). Therefore, the identification of more effective, less toxic, and more convenient therapies,

particularly those which do not require placement of a chronic indwelling catheter, would be of benefit in the treatment of CMV retinitis.

1.2 The rationale for HPMPC therapy of CMV infection

Refer to the Investigator's brochure dated for October 1994 [CDV, HMPC, GS-054] injection for more details and updated information.

1.2.1 General information

HPMPC (1-(S)-(3-Hydroxy-2-phosphonylmethoxypropyl)cytosine dihydrate) is a nucleotide analog with potent activity against a broad spectrum of herpesviruses, including those which cause disease in humans. The active intracellular metabolite is HPMPC diphosphate, which inhibits DNA polymerases from herpes simplex virus types 1 and 2 at concentrations about 50-fold lower than that needed to inhibit human alpha DNA polymerase. Intracellular phosphorylation of HPMPC to HPMPC diphosphate is independent of virus infection. HPMPC diphospate persists in cells with a half-life of 30 hours after HPMPC is removed from the medium. Thus, HPMPC diphosphate in uninfected cells may prime them to resist viral replication when subsequently infected. It may also be a source of anti-cellular effects (13-16).

1.2.2 *In vitro* anti-CMV activity

HPMPC has excellent *in vitro* potency against a range of CMV isolates from humans. These isolates vary from being equally sensitive to HPMPC and ganciclovir to being 8-fold more sensitive to HPMPC than to ganciclovir. Even ganciclovir-resistant mutant viruses isolated from ganciclovir-treated patients are still sensitive to HPMPC.

HPMPC also has excellent *in vitro* potency against CMV strains from mice, guinea pigs, and rats. The ID_{50} of HPMPC for murine CMV is 0.02 μg/mL, compared to 0.3 μg/mL for ganciclovir. Activities of HPMPC against both guinea pig and rat CMV are also more potent than those of ganciclovir. In experiments to evaluate persistence of the antiviral effect, HPMPC was removed at 24 or 48 hours post-infection. The ID_{50} for HPMPC is 3-fold to 6-fold higher when it

is removed at 48 h compared to when the drug is not removed. By contrast, the ID_{50} for ganciclovir is elevated at least 45-fold under these same conditions (13-16).

1.2.3 Preclinical *in vivo* evaluations

a. Antiviral efficacy studies

The antiviral activity of HPMPC has been studied in various animal species including mice, rats, and monkeys.

In models of murine CMV infection, HPMPC treatment appears to be more potent than ganciclovir. This is in concordance with the *in vitro* results. In a lethal infection model (in which mice are infected intraperitoneally with a high viral inoculum), both HPMPC and ganciclovir improved survival significantly when initiated as late as 48 hours post-infection and continued daily for 5 days. HPMPC appeared more effective than ganciclovir when comparing equivalent non-toxic doses (1.2 mg/kg/day and 11 mg/kg/day, respectively). Importantly, reduction in the frequency of HPMPC administration to every other day or even every third day provided similar efficacy data as the daily doses (16-17).

The efficacy of HPMPC and ganciclovir has also been studied in a model of chronic murine CMV infection which employs a lower viral inoculum and measures efficacy as a reduction in target organ viral recovery. Equal doses of both agents (10 mg/kg/day) were initiated 24 hours post-infection and continued for 5 days. Ganciclovir treatment reduced viral titers in blood, lung, spleen, and kidney by 10-fold to 100-fold, while HPMPC treatment reduced these viral titers 10^5-fold to 10^6-fold. HPMPC was clearly more effective than ganciclovir in reducing the viral load of infected organs (16, 18).

Similarly, HPMPC has proven to be more effective than ganciclovir in reducing viral titers in tested organs in other murine and rat CMV models. These include studies in which therapy is delayed for 4 days post-infection, and studies in which mice are concurrently infected with the LPBM-5 retrovirus (16).

Antiviral activity of HPMPC has also been investigated in sub-human primates. African green monkeys infected with simian varicella virus (SVV) develop viremia and skin rash which peak between day 7 and day 11 post-infection. In some cases the animals die from the disease. In other cases they survive and neutralizing antibodies can be detected in their serum. Following the observation that intravenous (IV) administration of 5 mg/kg/day of HPMPC for 10 days

prevented the sequelae of SVV infection, various regimens employing a total dose of 50 mg/kg were studied. Regardless of the IV regimen used (5 mg/kg for 10 days, 10 mg/kg every other day for 5 doses, 25 mg/kg on days 2 and 7 post-infection, or 50 mg/kg as a single injection on day 2 or 4 post-infection), HPMPC treatment was more effective than control in preventing SVV-related rash and mortality. Importantly, no evidence of drug-related toxicity on blood counts or blood chemistry parameters was noted during the observation period of up to 2 weeks following HPMPC administration (19).

b. Pharmacokinetic studies

Preclinical studies of the pharmacokinetics of HPMPC in rodents and monkeys have been performed. In rats dosed with 5 mg/kg ^{14}C-HPMPC, the urinary recoveries of radioactivity in 0 to 24 hours were 60% for IV administration and 1.8% for oral administration. High pressure liquid chromatography analysis of urine and plasma showed that all radioactivity was present as HPMPC. No metabolites were observed (16).

Single and multiple dose pharmacokinetics of ^{14}C-HPMPC in the African green monkey showed that HPMPC has a half-life of 33 ± 4 hours after IV administration of a single dose of HPMPC (43 mg/kg). The half-life of HPMPC is 26.5 hours after multiple IV dosing (4.9 mg/kg/day x 10). After administration of a single IV dose, the clearance (207 ± 15 mL/h/kg) was comparable to the glomerular filtration rate. The clearance after administration of multiple IV doses was 275 mL/h/kg.

The results from the multiple dose study showed that the mean $AUC_{0\text{-}24\,h}$ on day 10 was about twice that determined on day 1, which is consistent with an expected accumulation factor of 2.5. Following administration of a single IV dose of ^{14}C-HPMPC, the concentration in the kidney decreased with a terminal half-life (23 hours) which approximates the plasma half-life. In the multiple dose study, the concentrations of radioactivity in the kidneys were comparable on day 1 and day 10. However, 5 days after administration of the last dose, the concentration of radioactivity in the kidney was 6% to 25% of that measured on day 10 (16).

c. Toxicology studies

In support of intravenous administration of HPMPC in humans, an extensive series of single and multiple dose toxicity studies have been conducted in several species.

Toxicity following HPMPC administration is species dependent. The order of sensitivity is guinea pig > rabbit > monkey > rodent. It is also schedule dependent. For example, single dose

administration of 50 mg/kg in African green monkeys is less toxic than 5 mg/kg/day for 10 days. The major dose limiting toxicity is nephrotoxicity, characterized by degeneration, necrosis, and/or regeneration of the proximal convoluted tubule cell. Concomitant administration of probenecid protects against nephrotoxicity in animal models.

c.1 Single dose studies

Studies in rabbits revealed no evidence for laboratory or histologic changes consistent with renal toxicity following doses of up to 25 mg/kg. A dose-related nephrosis without laboratory (BUN and creatinine) changes was observed at 50 and 100 mg/kg (16).

The minimal lethal IV single dose of HPMPC in cynomolgus monkeys is estimated to be greater than 40 mg/kg and less than 75 mg/kg. Mortality in one monkey at the 75 mg/kg dose level was preceded by evidence of nephrotoxicity (elevated BUN and creatinine) and decreased white blood cell count. In contrast, administration of 50 mg/kg as a single IV dose to African green monkeys was well-tolerated without histologic evidence of nephrotoxicity (16).

In mice and rats the minimal lethal IV single dose of HPMPC is greater than 800 mg/kg. Male rats receiving 800 mg/kg displayed only transient lack of weight gain and rough hair coat appearance (16).

c.2 Multiple dose studies

Investigation of the schedule dependency of HPMPC nephrotoxicity has been performed in guinea pigs, the species thought to be most sensitive to the renal effects of HPMPC. Animals received 25 mg/kg total dose as a single dose, two 12.5 mg/kg doses (days 1 and 4), four 6.25 mg/kg doses (days 1, 4, 8, and 12), or five 5 mg/kg doses (days 1 through 5). The latter schedule induced marked nephrotoxicity (>90% of tubules) whereas the single dose resulted in minimal toxicity (<5% of tubules). The two and four dose regimens were associated with moderate to marked nephrotoxicity. These results indicate that HPMPC renal toxicity may be reduced through less frequent dosing (16, 20).

Dose-ranging IV studies performed in cynomolgus monkeys receiving 0.1 to 50 mg/kg/day or 0.1 to 1.0 mg/kg/day for 14 or 30 days, respectively, also revealed evidence of dose-related nephrotoxicity. Significant drug-related clinical or histologic toxicity was not observed at 1 or 0.25 mg/kg/day (over 14 or 30 days, respectively) (16).

HPMPC was administered to African green monkeys to further investigate schedule dependency as well as reversibility of toxicity. As observed in guinea pig experiments, a single IV dose of 50 mg/kg was not associated with evidence of nephrotoxicity in contrast to animals receiving 10 daily IV doses of 5 mg/kg/day. Importantly, in those monkeys receiving the latter regimen who were not sacrificed until 5 days following the tenth dose, no histologic evidence of HPMPC-related nephrotoxicity was observed, suggesting that such toxicity may be reversible (16).

Dose-ranging IV studies performed in Sprague-Dawley rats receiving 10 to 250 mg/kg/day, 0.3 to 50 mg/kg/day, or 0.3 to 5.0 mg/kg/day for 5, 14, or 30 days, respectively, revealed evidence of dose-related nephrotoxicity (tubular nephrosis). Significant drug-related clinical or histologic toxicity was not observed at 10, 1, or 0.3 mg/kg/day over 5, 14, or 30 days, respectively. Bone marrow depression and thymic and splenic lymphoid depletion were noted at the higher doses, probably as a result of massive exposure subsequent to renal failure and limited clearance of the drug (16).

c.3 Amelioration of HPMPC nephrotoxicity

Preclinical investigation of HPMPC suggests a mechanism of elimination predominantly by glomerular filtration as well as that of aborted secretion, a phenomenon well known with the antibiotic cephaloridine (21).

Like HPMPC, cephaloridine is a zwitterion and is concentrated via active transport into the proximal convoluted kidney tubule cell by an anion transporter in the basolateral membrane. Export at the luminal membrane is very slow and thus high concentrations are attained in the proximal convoluted kidney tubule cell. HPMPC uptake appears to have the added feature of low capacity, saturable uptake, which would be consistent with the schedule dependency of the nephrotoxic effects.

Probenecid, a highly lipid-soluble carboxylic acid commonly used as an uricosuric agent, competes with HPMPC uptake at the proximal tubule site, thereby reducing local HPMPC concentration in the proximal tubule cell. Probenecid has been studied in rabbits and cynomolgus monkeys to investigate its potential to ameliorate HPMPC renal toxicity.

Administration of probenecid to rabbits immediately prior to an IV regimen of 25 mg/kg/day of HPMPC for 5 days was studied. Probenecid treatment (50 or 150 mg/kg/day) provided partial to complete protection against nephrotoxicity in a dose-dependent manner compared to control (HPMPC alone) animals (16). Probenecid does not affect the antiviral properties of HPMPC.

Similarly, in cynomolgus monkeys, administration of 50 mg/kg/day of probenecid 5 minutes prior to 10 mg/kg/day of HPMPC for 14 days provided almost complete protection against the severe nephrotoxicity observed in control (HPMPC alone) animals (18).

1.3 Clinical studies of HPMPC

1.3.1 Treatment plan

During the initial phase of HPMPC administration in Phase I/II studies, patients received HPMPC either weekly (GS-92-101) or twice weekly (GS-92-103) by intravenous infusion, with or without concomitant saline pre-hydration (Table 1).

Table 1. Phase I/II HPMPC regimens

Study	Dose (mg/kg)	Schedule	Hydration[1]
GS-92-103	0.5, 1.5, 5.0	Twice weekly	+/−
GS-92-101	0.5, 1.0, 3.0, 10.0	Weekly	+/−

[1]Administered as one liter of normal saline over approximately 45 minutes immediately prior to HPMPC infusion

Patients received HPMPC at a fixed dose level over four consecutive weeks. Patients enrolled on GS-92-101 completing the four week study without evidence of drug-related toxicity were offered continuing weekly HPMPC maintenance treatment.

Following the demonstration of dose-dependent HPMPC-related nephrotoxicity and prolonged anti-CMV effect, the methods for HPMPC administration were modified (Table 2).

Table 2. Phase I/II HPMPC regimens: Dose refinements

Study	Dose (mg/kg)	Schedule	Hydration[1]
GS-92-103	5.0 + Probenecid[2]	Twice weekly	+
GS-92-101	3.0 + Probenecid[3]	Weekly	+/−
GS-92-101/103	5.0 + Probenecid[3]	Weekly	+/−
GS-92-101	5.0 + Probenecid[3]	Q 2 weeks[4]	+/−
GS-92-101/103	7.5 + Probenecid[3]	Q 3 weeks	+/−

[1]Administered as one liter of normal saline over approximately 45 minutes immediately prior to HPMPC infusion
[2]Administered orally as 1 gram (3 h pre-HPMPC), 0.5 gram (2 h post-HPMPC), and 0.5 gram (8 h post-HPMPC) (total dose = 2 grams - "low dose")
[3]Administered orally as 2 grams (3 h pre-HPMPC), 1 gram (2 h post-HPMPC), and 1 gram (8 h post-HPMPC) (total dose = 4 grams - "high dose")
[4]Administered every other week following 2 consecutive weekly doses

In addition to concomitant administration of probenecid, employed in an effort to block uptake of HPMPC by the proximal tubular cell of the kidney, investigation of longer dosing intervals were pursued. Finally, information regarding the sequence of laboratory abnormalities associated with HPMPC-related nephrotoxicity (the appearance of proteinuria) was incorporated into the treatment plan, so that HPMPC administration was discontinued following the appearance of 2+ proteinuria.

1.3.2 Disposition of patients entered

The average duration of treatment on study varied according to protocol. Eighteen of 24 patients enrolled in GS-92-101 and completing the initial four week study elected to receive HPMPC maintenance treatment. In contrast, 1 of 10 patients enrolled in GS-92-103 elected to receive HPMPC beyond four weeks. Patients enrolled in these studies had asymptomatic CMV infection. They therefore had no medical indication for receipt of HPMPC. One reason for the difference between the two studies in the proportion of patients electing extended treatment may be the type of care administered at the two different institutions: primary care on a longitudinal basis at the first institution and tertiary care in a referral center at the second.

As of 24 September 1993, the average duration of treatment on study GS-92-101 was 20 weeks (ranging from 1 week to 68 weeks) and the average exposure to HPMPC was 28 mg/kg (ranging from 3 to 67 mg/kg). The average duration of treatment on study GS-92-103 was 3 weeks (ranging from 0.5 to 6 weeks) and the average exposure to HPMPC was 12 mg/kg (ranging from 4 to 40 mg/kg). Data regarding the number of patients treated, HPMPC exposure by treatment regimen, and patient status are presented in Tables 3 and 4. As shown in Table 4, 11 of 45 patients did not complete the intended four week course of treatment.

Table 3. HPMPC exposure

HPMPC dose (mg/kg)	Schedule	n	Mean exposure (mg/kg)	Range of exposure (mg/kg)
0.5	Twice weekly	4	4	4
1.5	Twice weekly	4	12	11-12
5.0	Twice weekly	2	10	10
0.5	Weekly	5	4	3-5
1.0	Weekly	5	4	4
3.0	Weekly	5	27	12-51
10.0	Weekly	5	25	20-43
5.0 + P[1]	Twice weekly	2	10	10
3.0 + P[2]	Weekly	8[3]	45	28-60
5.0 + P[2]	Weekly	8	29	10-67
5.0 + P[2]	Q 2 weeks[4]	10	29	13-45

[1]Probenecid administered according to "low dose" regimen (2 grams total)
[2]Probenecid administered according to "high dose" regimen (4 grams total)
[3]Patients enrolled on the 3 mg/kg + probenecid regimen had previously received HPMPC without probenecid. Mean exposure includes both periods of treatment
[4]Administered every other week following 2 consecutive weekly doses

Table 4. Patient status[1]

	GS-92-101	GS-92-103	Total
Patients entered in study	29	16	45
Patients completing initial phase	24	10	34
Patients removed early[1]	5	6	11
• Nephrotoxicity	4	5	9[2]
• Neutropenia	1	0	1
• Probenecid reaction	0	1	1
Patients enrolled on maintenance	18	1	19
Patients removed from maintenance	10		10
• Patient request	3		3
• Nephrotoxicity	3		3[3]
• Kaposi's sarcoma (chemotherapy)	2		2
• Seizure disorder	1		1
• Mycobacterium infection	1		1

[1]Patients recently enrolled on the 5.0 mg/kg q 2 week regimen and the 7.5 mg/kg q 3 week regimen are not included in this analysis

[2]3 of 9 patients had a serum Cr > 2 mg/dL; 2 of the 3 elevations were persistent. The remaining 6 patients were removed following the appearance of proteinuria

[3]1 of 3 patients had persistent serum Cr > 2 mg/dL. The remaining 2 patients were removed following the appearance of proteinuria and mild creatinine elevation, respectively

1.3.3 Results

Dose-dependent nephrotoxicity appears to the major dose-limiting toxicity of HPMPC administration, as predicted by animal models. The relationship of HPMPC-induced nephrotoxicity and drug exposure, hydration status, and probenecid are discussed below.

a. Dose relationship of nephrotoxicity

Examination of renal function tests, including serum creatinine and urinary protein, in patients receiving HPMPC without concomitant probenecid provide evidence for dose-dependent nephrotoxicity related to HPMPC administration. Patients receiving weekly intravenous HPMPC on study GS-92-101 at doses of 0.5 and 1.0 mg/kg did not have evidence of significant drug-related laboratory toxicity (serum creatinine ≥ 2.0 mg/dL). Patients treated at higher dose levels of 3.0 and 10.0 mg/kg developed evidence of HPMPC-related nephrotoxicity, consistent with the animal models (Table 5).

Table 5. HPMPC: Nephrotoxicity dose-dependency

HPMPC dose (mg/kg)	n	Mean exposure (mg/kg)	Range of exposure (mg/kg)	Proteinuria ≥ 2+	Glycosuria	Serum Cr ≥ 2 (mg/dL)
0.5	5	4	3-5	0/5	0/5	0/5
1.0	5	4	4	1/5	0/5	0/5
3.0	5	27	12-51	2/5	3/5	1/5
10.0	5	25	20-43	4/5	4/5	3/5

Proteinuria, as measured by urinalysis, appears to be an early and sensitive indicator of HPMPC toxicity. Continued administration of HPMPC by weekly intravenous infusion without probenecid in this initial cohort following the development of proteinuria was accompanied by evidence of proximal tubular cell injury, including glycosuria, decreases in serum phosphate, serum uric acid, and serum bicarbonate, and finally elevations in serum creatinine.

Two of five patients (001-11 and 001-12) receiving 3.0 mg/kg of HPMPC once weekly developed grade 2 nephrotoxicity (serum creatinine ≥ 2.0 mg/dL or 2+ proteinuria) following six and fourteen consecutive weekly doses of HPMPC, respectively. The first patient (001-11) developed a creatinine of 2.2 mg/dL. Following discontinuation of HPMPC his creatinine fell to 1.6 mg/dL. However, over the next three months his creatinine gradually rose to 5.4 mg/dL. Development of severe diarrheal illness complicated his volume and renal status, necessitating 2 days of dialysis 3.5 months after discontinuing HPMPC. At last follow-up 6.5 months off HPMPC, the patient continues off dialysis with a serum creatinine of 4.7 mg/dL.

Two of five patients (001-18 and 001-19) receiving 10.0 mg/kg of HPMPC once weekly developed evidence of persistent grade 4 nephrotoxicity following two consecutive weekly doses. Both patients had evidence of non-oliguric renal insufficiency consistent with proximal tubular cell injury. In patient 001-18, complications regarding volume status in association with pneumonia and congestive heart failure led to intermittent courses of dialysis over a four month period, six months after discontinuing HPMPC.

Both patients treated at 3.0 mg/kg noted above, as well as one of the two patients (001-18) treated at 10.0 mg/kg, underwent diagnostic renal biopsy. Examination of these specimens by light and electron microscopy provide evidence of injury primarily involving proximal tubular cells, consistent with the preclinical toxicology studies.

Results of urinalysis in patients enrolled in GS-92-103 also provide evidence of the dose-dependent nephrotoxic effects of HPMPC. Proteinuria ($\geq$ 2+) developed in two of four patients receiving 5 mg/kg twice weekly after one week of HPMPC, compared with two of four patients receiving 1.5 mg/kg twice weekly after four weeks of HPMPC, and zero of four patients receiving 0.5 mg/kg twice weekly after four weeks of HPMPC. Given (a) the short course of HPMPC treatment administered in GS-92-103, $\leq$ 4 weeks for all cases, and (b) the identification of the sequence of urinalysis and serum chemistry abnormalities associated with HPMPC-related nephrotoxicity observed in GS-92-101, the lack of progression to significant nephrotoxicity (serum creatinine $\geq$ 2 mg/dL) in any patients in GS-92-103 was presumably due to interruption of HPMPC treatment for proteinuria and modification of the dosing interval.

Various refinements in the administration of HPMPC, including concomitant probenecid administration and extension of the dosing interval, were made in subsequent cohorts of both studies. These have substantially reduced the incidence of significant HPMPC-related nephrotoxicity (Table 6).

Table 6. HPMPC: Nephrotoxicity and probenecid administration[1]

HPMPC dose (mg/kg)	n	Mean exposure (mg/kg)	Range of exposure (mg/kg)	Proteinuria ≥ 2+	Glycosuria	Serum Cr ≥ 2 (mg/dL)
3.0[2]	8	45	28-60	1/8	0/8	0/8
5.0[2]	8	29	10-67	2/8	0/8	0/8
5.0[3]	10	29	13-45	2/10	0/10	0/10

[1]Administered orally as 2 grams (3 h pre-HPMPC), 1 gram (2 h post-HPMPC), and 1 gram (8 h post-HPMPC) (total dose = 4 grams - "high dose")
[2]Administered weekly
[3]Administered weekly × 2, then q 2 weeks

b. Nephrotoxicity and probenecid administration

The concomitant administration of probenecid has been associated with a reduction in HPMPC-related nephrotoxicity (Table 6). Sampling of blood and urine from patients receiving HPMPC and concomitant probenecid for pharmacokinetic studies has provided evidence of significant reduction in tubular secretion of HPMPC. This apparently allows administration of higher cumulative doses of HPMPC without development of significant nephrotoxicity (serum creatinine ≥ 2.0 mg/dL). Patients treated with HPMPC and concomitant probenecid have not had evidence of proximal tubular cell injury extending beyond proteinuria. Glycosuria and decreases in serum phosphorus and serum bicarbonate have not been observed.

To date, 41 patients have received HPMPC with concomitant probenecid (8 patients at 3 mg/kg [range 2-11 doses]; 27 patients at 5 mg/kg [range 1-9 doses]; and 6 patients at 7.5 mg/kg [range 1-8 doses]). None of these patients have developed a serum creatinine >1.7 mg/dL. Seven of 41 patients have developed evidence of allergic symptoms temporally related to probenecid administration. Each occurred after 3 to 4 consecutive weeks of treatment. Three developed pruritic maculopapular rashes responsive to antihistamine therapy, permitting continued administration. Four patients developed evidence of a systemic reaction including fever, rash, nausea and headache. An oral desensitization program with low dose probenecid has been successfully employed to permit continued HPMPC administration in 2 of these patients. The contribution of other medications interacting with probenecid is uncertain at this time; however, as zidovudine (AZT) levels have been demonstrated to increase significantly when administered with

probenecid, patients have been cautioned to withhold or reduce (e.g., 50 percent reduction) their AZT doses on days of probenecid administration.

c. Nephrotoxicity and hydration status

Within each dose level cohort of four to five patients on GS-92-101 and GS-92-103, the first two patients received saline pre-hydration (1 liter normal saline infused over approximately 1 hour immediately before HPMPC infusion) during the first four weeks of HPMPC administration. Patients receiving ongoing maintenance HPMPC treatment on study GS-92-101 were encouraged to continue such pre-hydration. However, in some cases they did not. Examination of the hydration status of patients developing ≥ grade 2 nephrotoxicity (serum creatinine ≥ 2.0 mg/dL or ≥ 2+ proteinuria) provides some evidence for a relationship between hydration status and HPMPC-related nephrotoxicity.

Two patients receiving 3.0 mg/kg HPMPC once weekly developed grade 2 nephrotoxicity following six and fourteen doses of HPMPC, respectively. One patient (001-12) had no evidence of HPMPC-related nephrotoxicity following 9 doses received with concurrent hydration, However, pre-hydration was not administered with his next 3 doses, with the development of proteinuria and serum creatinine elevation from 1.2 to 1.7 mg/dL.

Examination of the five patients receiving HPMPC at 10.0 mg/kg once weekly on GS-92-101 provide further support for a potential nephro-protective effect of hydration. Both patients receiving concomitant pre-hydration (001-16 and 001-17) developed evidence of transient nephrotoxicity following administration of four and two doses of HPMPC, respectively. In contrast, of the three remaining patients in the cohort who did not receive pre-hydration, two developed evidence of persistent nephrotoxicity (serum creatinine ≥ 2.0 mg/dL) following two doses of HPMPC.

d. Anti-CMV effect

Dose-dependent anti-CMV effects have been observed at the 3.0 mg/kg and 10.0 mg/kg weekly dose levels. Semen CMV titer reductions of greater than 100-fold and conversion of positive urine CMV cultures to negative have occurred in a majority of patients treated at these dose levels. These effects have been seen as early as one week following the administration of 10.0 mg/kg of HPMPC as a single dose. Additionally, serial semen cultures have documented persistent anti-CMV effect following discontinuation of HPMPC. Culture negativity persisted for approximately 30 days following cessation of treatment at the 10 mg/kg dose level.

Dose-dependent anti-CMV effects have also been observed in patients receiving HPMPC in combination with probenecid. Conversion of positive urine CMV cultures to negative has occurred in 22 of 24 patients treated at doses ≥ 3 mg/kg/dose. Serial urine cultures have provided evidence of persistent anti-CMV effect for as long as four weeks following cessation of treatment at the 5 mg/kg/dose level. Comparison of decreases in semen CMV titers after four consecutive 3 mg/kg weekly doses of HPMPC +/- probenecid is suggestive of enhanced anti-CMV effect in patients receiving concomitant probenecid.

e. Summary of clinical studies

Administration of systemic HPMPC to HIV-infected patients with asymptomatic CMV infection of urine and semen is associated with dose-dependent nephrotoxicity and dose-dependent prolonged anti-CMV effect, as predicted by preclinical animal models. Concomitant administration of probenecid and saline hydration, extended HPMPC treatment intervals (one to two weeks), and adherence to a strict monitoring schedule (pre-dose urinalysis and serum creatinine) appear to permit the administration of systemic HPMPC without significant drug-related toxicity while preserving its potent anti-CMV effects. Pharmacokinetic data on HPMPC are summarized in the Investigator's Brochure for cidofovir dated October 1994 (12).

2. Objectives and design summary

The primary objective of the trial is to evaluate the safety and efficacy of intravenous HPMPC for treatment of small peripheral CMV retinitis lesions. A secondary objective, if the trial proceeds to Stage 2, is to obtain data on the relative safety and efficacy of the 3 mg/kg vs 5 mg/kg HPMPC maintenance dosage regimens. The outcomes of primary interest are time to progression of retinitis and occurrence of drug-related toxicity. Additional outcome measures of interest include mortality, viral shedding in urine and blood, and changes in visual acuity.

There are three treatment groups evaluated in the trial. These are:

- Dfr: Observation with deferral of treatment for CMV retinitis until the retinitis progresses. At the time of progression, patients will be treated according to best medical judgement. This includes the option of treatment with HPMPC.
- H-3: HPMPC at 5 mg/kg/dose for two consecutive weekly induction doses, followed by 3 mg/kg/dose every other week for maintenance.
- H-5: HPMPC at 5 mg/kg/dose for two consecutive weekly induction doses, followed by 5 mg/kg/dose every other week for maintenance.

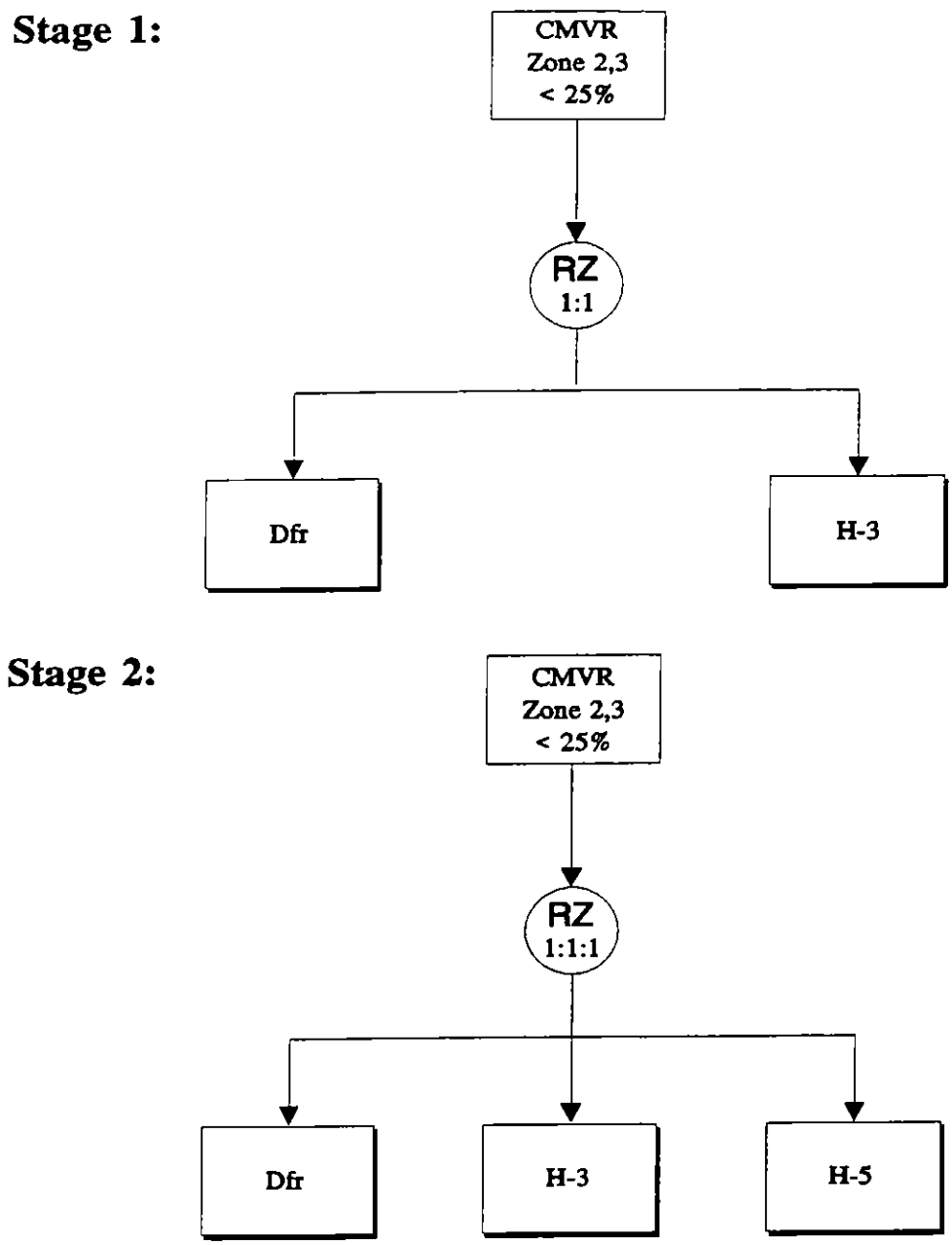
The overall recruitment goal for the two stages combined is 90 patients within a two year period. The procedures for treatment, data collection, and data monitoring are detailed in later sections of this protocol. There will be a common closeout for the trial at six months following enrollment of the last patient.

The trial will be conducted in two stages (Figure 1). In Stage 1, up to 30 patients will be enrolled and randomized to either the Dfr or H-3 group with a 1:1 assignment ratio. In Stage 2, up to 70 patients will be randomized to either the Dfr, H-3, or H-5 group with a 1:1:1 assignment ratio. The implementation of Stage 2 will depend on the results of Stage 1.

Interim analyses of safety and efficacy will be performed using the data from Stage 1. These will be reviewed by the SOCA Policy and Data Monitoring Board (PDMB). On the basis of these data, the PDMB will recommend whether to proceed to Stage 2 as planned, modify the trial, or terminate the trial.

The interim analyses will be started once there is one month of follow-up on the 20th patient enrolled. Although up to 10 more patients may be enrolled while the interim analyses are being done, no more than a total of 30 patients will be enrolled in the trial until the PDMB has completed its review of the data and made its recommendation.

Figure 1. Trial design



3. Patient enrollment

Recruitment, assessment of eligibility, and enrollment will be performed at participating SOCA clinics (Appendix A).

Once it has been determined that a patient is eligible for the trial, the specifics of the trial will be explained and discussed. Patients considering participating in the trial will be given the consent statement and other informational materials and will be allowed at least 24 hours to think about enrolling in the trial. All baseline evaluations will be conducted prior to randomization and within the 5 days up to and including randomization. Patients unable to complete the baseline evaluations will not be eligible for participation in the trial.

3.1 Inclusion criteria

Patients must fulfill all of the following criteria to be eligible for enrollment:

- The diagnosis of AIDS according to the current Centers for Disease Control and Prevention (CDC) definition.
- 13 years or older at entry.
- Diagnosis of CMV retinitis as determined by a SOCA-certified ophthalmologist. Retinitis lesion(s) must be small, involving less than 25% of the total area of the retina. The lesion(s) must also be confined to the periphery of the retina, located at least 1,500 μ from the margin of the optic disc and 3,000 μ from the center of the fovea (entirely in zones 2 or 3). Diagnoses are based on the presence of characteristic necrotizing retinitis consisting of white, fluffy, or granular retinal infiltrates with or without hemorrhage.
- At least one lesion whose size is one-quarter disc area or more that can be photographed.
- Visual acuity in an affected eye of 3 or more lines on the ETDRS chart at 1 meter distance (Snellen equivalent 8/200).
- An ambulatory performance status of 60 or more on the Karnofsky scale.
- Serum creatinine of 1.5 mg/dL or less.
- Less than 1+ proteinuria on urinalysis.
- Total bilirubin of 3.0 mg/dL or less.
- Hepatic transaminase levels that do not exceed 5 times the normal levels.
- Absolute neutrophil count of 750 cells/μL or greater.

- Platelet count of 50,000 cells/μL or greater.
- Hemoglobin of 7.5 g/dL or greater.
- Negative serum pregnancy test (females of childbearing potential).
- All men and women of childbearing potential should be willing to practice adequate birth control to prevent pregnancies while on study and for three months afterwards.
- Willingness and ability, with the assistance of a caregiver if necessary, to comply with treatment and follow-up procedures.
- Signed consent statement.

3.2 Exclusion criteria

Patients with any of the following will be excluded from enrollment in the trial:

- Evidence of a CMV retinitis lesion within zone 1. A lesion less than 1,500 μ from the margin of the optic disc or less than 3,000 μ from the center of the fovea in either eye excludes a patient.
- Evidence of a CMV retinitis lesion(s) that involves 25% or more of the retinal area regardless of location.
- Previous or ongoing therapy for CMV disease with ganciclovir, foscarnet, CMV hyperimmune immunoglobulin, or other investigational agents with anti-CMV activity. However, patients who have received anti-CMV agents solely as prophylaxis are eligible for enrollment.
- Retinal detachment(s) in the affected eye(s).
- Media opacity that precludes visualization of the fundus of both eyes.
- Patients with a diagnosis of extraocular CMV disease.
- Patients with history of clinically significant renal disease or renal dialysis.
- Patients with history of clinically significant cardiac disease, including symptoms of ischemia, congestive heart failure, or arrhythmia.

- Pregnant or lactating patients.
- Patients with active medical problems including drug or alcohol abuse which are considered sufficient to hinder compliance with treatment or follow-up procedures.
- Patients receiving therapy within the previous 7 days with nephrotoxic drugs, including:
    - Amphotericin B
    - Vidarabine®
    - Aminoglycoside antibiotics
    - Intravenous pentamidine

  Patients receiving any of these drugs must discontinue the drug(s) at least one week prior to the time of enrollment, and for the duration of the trial period.
- A history of clinically significant probenecid allergy.

3.3 Randomization

Randomization will be stratified by clinic. The randomization schedules will be written and controlled by the SOCA Coordinating Center and will be designed to yield an expected assignment ratio of 1:1 for Stage 1 and 1:1:1 for Stage 2. Assignments will be generated in permuted blocks of varying lengths.

Clinic personnel will obtain assignments as needed from the Coordinating Center. Before an assignment is revealed, eligibility must be established, all baseline data must be collected and recorded, and signed consent must be obtained. Once an assignment is revealed to clinic personnel, the patient is counted in the assigned treatment group for the primary analysis, regardless of subsequent treatment or compliance. If a patient withdraws their consent or is otherwise determined ineligible before the assignment is revealed, the unopened treatment assignment will be returned to the Coordinating Center.

4. Outcome measures

4.1 Design outcome measure

The outcome measure used for sample size analysis is time to first progression of retinitis after randomization. Retinitis progression will be measured by masked readings of fundus photographs by the Fundus Photography Reading Center (FPRC). For purposes of this protocol, the criteria the FPRC will use to define retinitis progression are:

(1) Advancement of the edge of an existing lesion by one-half the diameter of the optic disc (0.5 disc diameters = 750 μ[1]) perpendicularly from the edge and along $\geq$ 750 μ of it; or

(2) Occurrence of a new lesion $\geq$ one-quarter disc area in size (a circle, $\geq$ 750μ in diameter), separate from the previous lesion in the same eye or in a previously uninvolved eye.

The edge of a CMV lesion is often difficult to determine. This is because of the presence of small (100 to 400 μ diameter) white foci of active retinitis ("satellites") surrounded by normal appearing retina in a zone of variable width adjacent to the solid white marginal zone of the lesion. In the assessment of progression, the junction of the satellite zone and the normal retina, designated the "satellite margin," will be used. The satellite zone is often observed to fill in and become solidly involved during the first 2 to 4 weeks of treatment, and this may lead to a false impression of progression, unless care is taken to measure progression from the satellite margin.

The border of a CMV lesion is defined as a zone that is about 1,000 μ in width extending into the lesion from its junction with normal retina. Lesion borders will be classified as active or inactive. Active lesions are composed of diffuse, white, opaque retinitis which may have a solid or granular appearance. Lesion borders containing multiple satellites with intervening normal

1 For convenience, the long-standing clinical convention of considering the diameter of the average optic disc to be 1,500 μ will be followed, even though 1,800 to 1,900 μ is probably a more accurate estimate.

retina will also be classified as active. Inactive borders are composed of retinal and retinal pigment epithelium (RPE) atrophy, with or without white deposits or areas of gliosis.

4.2 Other outcome measures

Outcome measures other than retinitis progression will be assessed by clinic personnel who are not masked to treatment.

4.2.1 Mortality

Time to death will be measured from the date of randomization to date of death, or censored at study closeout.

4.2.2 Visual acuity

Changes in visual acuity are defined as changes from baseline in the number of letters read on an Early Treatment for Diabetic Retinopathy Study (ETDRS) chart. Changes in visual acuity will be measured both in the involved eye(s) and in the better eye. Time to visual acuity worse than 20/40 (cutpoint for driving), visual acuity worse than 20/200 (cutpoint for blindness), and visual acuity decreasing 3 lines (doubling of the visual angle) will be analyzed.

4.2.3 Viral shedding

Based on data from the Foscarnet-Ganciclovir CMV Retinitis Trial, it is anticipated that about 75% of patients will have positive CMV blood or urine cultures at baseline. Culture conversion rates will be assessed.

5. Treatment plan

5.1 Deferral of treatment

Following documentation of retinitis progression or development of biopsy-confirmed extraocular CMV disease patients assigned to Dfr will receive treatment according to the best medical judgement of study physicians. Fundus photographs must be taken within the seven days before treatment is started. During the first stage of the trial, patients who still meet all trial eligibility criteria may receive HPMPC according to the H-3 schedule. During the second stage, patients who still meet all trial eligibility criteria may receive either HPMPC regimen.

5.2 HPMPC

The first induction dose of HPMPC (5 mg/kg) will be started as soon as possible after randomization, ideally within 24 hours. The second induction dose will be administered 7 days later. Maintenance doses (3 mg/kg for H-3 or 5 mg/kg for H-5) will be given every 14 days thereafter, as long as the drug is well tolerated and CMV disease has not progressed. Patients assigned to immediate treatment groups (H-3 and H-5) will receive HPMPC by intravenous (IV) infusion. Treatment with HPMPC will continue until retinitis progression, as assessed by a study ophthalmologist, or dose-limiting toxicity occurs. Treatment after the documentation of retinitis progression is according to the best medical judgment of study physicians. Patients may receive a second course of induction and maintenance treatment with HPMPC according to their assigned dose following retinitis progression as long as retinitis does not involve zone 1.

5.2.1 Administration of HPMPC

HPMPC should be administered according to the treatment schedule. The second induction treatment must be administered on the seventh day after the first treatment. Maintenance treatments should be administered every 14 days, but the dosing interval may vary from 13 to 15 days. Prior to each infusion of HPMPC, serum creatinine and urine protein levels will be checked on specimens obtained within the 24 hours prior to the infusion. Other laboratory measures will be checked on specimens obtained within the 72 hours prior to the infusion. The criteria for modification or termination of the treatment regimen are described in sections 5.5 and 5.6, respectively.

The volume of HPMPC dose should be measured to the nearest tenth of a milliter. Doses should be diluted in 100 mL saline infusion bags for administration. HPMPC is administered by intravenous infusion over a 1 hour period. Use of a standard infusion pump for administration is recommended. The infusion will be supervised by a physician or nurse, and may be done on either an inpatient or outpatient basis.

HPMPC will be supplied by the Sponsor as a sterile liquid for parenteral administration in 5 mL vials at a concentration of 75 mg/mL.

HPMPC will be administered on a milligram per kilogram basis. Each HPMPC administration will be based on the patient's initial weight **unless** a weight change of ≥ 5% has occurred. Assuming a 65 kg patient (143 lbs), the following HPMPC doses and corresponding volume should be extracted from the vial:

HPMPC (mg/kg)	HPMPC (mg/65 kg)	Volume* (mL) (75 mg/mL)
5	325	4.33
3	195	2.6

* Doses and volumes provided assume a 65 kg patient. Please adjust according to the patient's specific weight.

Following extraction, the appropriate volume of HPMPC should be transferred to an infusion bag containing 100 mL 0.9% (normal) saline solution.

5.2.2 Concomitant saline hydration

All patients receiving HPMPC will receive a total of 2 liters of normal saline solution (0.9 percent NaCl) intravenously with each infusion of HPMPC. The first liter of saline will be infused over a 1 to 2 hour period immediately before the HPMPC infusion. The second liter of saline will be infused over a 1 to 3 hour period, and may be started either during the HPMPC infusion or immediately afterward. The second liter can be piggybacked with the HPMPC infusion. For patients weighing less than 50 kg, hydration volume should be based on 3% of body weight. For example, a patient weighing 45 kg should receive a total of 1.3 liters of saline, 0.65 L before HPMPC administration and 0.65 L with HPMPC.

5.2.3 Concomitant probenecid

All patients receiving HPMPC will take a total of 4 grams of probenecid (8 tablets, 500 mg/tablet) orally with each infusion of HPMPC. Two grams (4 tablets) will be taken 3 hours before the HPMPC infusion. One gram (2 tablets) will be taken 2 hours after completion of the HPMPC infusion, and the remaining 1 gram (2 tablets) will be taken 8 hours after completion of the infusion. For patients weighing less than 50 kg, probenecid doses should be halved. The first of the three doses of probenecid should be administered at the clinic.

Patients in the earlier HPMPC studies experienced mild dyspepsia after the initial dose of probenecid (2 grams, 4 tablets). Patients in this study will therefore be encouraged to eat before

taking each dose of probenecid. Additionally, prochlorperazine (Compazine®) may be given to reduce the incidence of nausea associated with probenecid ingestion.

Administration of probenecid with AZT results in a roughly 50% decrease in the clearance of AZT as well as decreased formation of the glucuronidated AZT metabolite. Patients taking AZT should therefore temporarily discontinue their AZT on days when HPMPC and probenecid are administered.

Additionally, given the potential for allergic reactions to probenecid, the use of prophylactic or therapeutic antihistamines such as diphenhydramine (Benadryl®) will be allowed. Patients with significant allergic reactions to probenecid may receive probenecid according to the following oral desensitization regimen:

- One 500 mg tablet of probenecid daily for the first 3 to 5 days.
- Two 500 mg tablets (1 gram) of probenecid daily for the duration of the desensitization period, except on the days when HPMPC is received.
- Eight 500 mg tablets (4 grams) of probenecid as described above on the days when HPMPC is received.

The desensitization program should continue until the patient tolerates the full dose of probenecid given on the days HPMPC is administered

AZT should be discontinued during the probenecid desensitization period.

HPMPC may not be administered without concomitant probenecid. Therefore, HPMPC will be stopped for patients who develop severe probenecid intolerance.

5.3 Other concomitant medications

Patients may be treated with any of the following medications while enrolled in the trial:

- Oral trimethoprim/sulfamethoxazole
- Aerosolized pentamidine
- Dapsone
- Fluconazole, ketoconazole, itraconazole
- Rifabutin
- Filgrastim (G-CSF)

The following medications are restricted both for patients receiving HPMPC and for those in the deferred treatment group whose retinitis has not yet progressed:

- Ganciclovir
- Foscarnet
- CMV hyperimmune immunoglobulin
- Amphotericin B
- Diuretics
- Aminoglycoside antibiotics
- Intravenous pentamidine
- Other nephrotoxic agents
- Investigational drugs with potential anti-CMV activity or potential nephrotoxicity

Acyclovir must be discontinued at baseline for patients assigned to the H-3 or H-5 groups. If herpetic lesions develop acyclovir may be started. Patients assigned to Dfr may continue acyclovir therapy at doses less than or equal to 1,200 mg/day.

Maintaining or initiating anti-retroviral therapy (licensed or available through expanded access programs or research studies) is considered an integral part of optimal medical care for people enrolled in this trial. Anti-retroviral therapy with zidovudine (AZT) has been shown to delay progression of complications associated with HIV-induced immunosuppression. Other anti-retroviral medications such as didanosine (ddI) and dideoxycytidine (ddC) may have similar effects.

5.4 Management of neutropenia

If a patient develops grade 3 or 4 neutropenia (ie ≤ 500 cells/μl), HPMPC therapy should be held until the ANC > 500 cells/μl and filgrastin (G-CSF) therapy should be instituted. The recommended initial dose of filgrastim is 300 μg (1 vial) three times per week. After 1 week, the ANC level should be checked; the recommended dose modifications are as follows:

- If the ANC level remains ≤ 500 cells/μl, the dose of filgrastim should be increased to 300 μg (1 vial) daily. If after 7 days of therapy, the ANC remains ≤ 500 cells/μl, the filgrastim dose should be increased to 600 μg (2 vials) daily (maximum dose).

- When the ANC level is > 500 cells/μl, HPMPC therapy may be reinstituted and the frequency of filgrastim administration should be reduced on a weekly basis as follows:

  - 600 μg (2 vials) daily, reduce dosage to 1 vial daily
  - 300 μg (1 vial) daily, reduce to 1 vial 3 times per week
  - 300 μg (1 vial) 3 times per week, reduce to 1 vial twice a week
  - 300 μg (1 vial) twice a week, reduce to 1 vial once a week
  - 300 μg (1 vial) once a week, discontinue filgrastim

If ANC falls ≤ 500 cells/μl after dosage reduction, resume the dosage that previously maintained ANC > 500 cells/μl and recheck ANC after 1 week. Escalate or reduce doses as described above.

- Filgrastim may be administered to patients in the deferred arm who develop an ANC ≤ 500 cells/μl according to the same dosage schedule described above.

5.5 Criteria for treatment modification

Treatment with HPMPC may be modified or stopped if CMV disease progresses. Progression of the CMV disease refers to either retinitis progression (as defined in section 4.1) or development of biopsy-documented extraocular CMV disease. Patients may undergo a second course of induction with HPMPC if retinitis does not involve zone 1. Patients for whom HPMPC is discontinued due to progression will be treated according to the best medical judgment of study physicians. Patients will still be seen for scheduled followup visits.

5.6 Criteria for treatment termination

Treatment with HPMPC will be stopped if CMV retinitis progresses into zone 1 of the retina, if a serious drug-related toxicity develops, if the patient is unable to tolerate probenecid, if the patient so requests, or if the patient becomes pregnant. HPMPC treatment also may be discontinued if an intercurrent illness requires treatment with other nephrotoxic drugs, or at the request of the sponsor or SOCA, following consultation with the center director. Patients for whom HPMPC is stopped will be treated according to the best medical treatment of study physicians.

HPMPC treatment will be stopped if there is evidence of renal toxicity. The following criteria will be used: 1+ proteinuria accompanied by an increase in serum creatinine of ≥ 0.5 mg/dL from baseline, proteinuria ≥ 2+, serum creatinine ≥ 2.0 mg/dL, calculated creatinine clearance ≤40 mL/min. All measurements should be confirmed by repeat measurements before stopping treatment. If the urinalysis performed prior to treatment indicates ≥2+ proteinuria, the second measurement should be performed after the patient has received the first liter of hydration.

For other types of toxicity, treatment with HPMPC will be continued (unless thought to be contraindicated by study physicians) if a mild (grade 1) or moderate (grade 2) toxicity is noted. If a severe (grade 3) or life-threatening (grade 4) toxicity is either noted for the first time or is thought to be related to HPMPC, related laboratory tests will be repeated. Patients who experience a confirmed grade 3 or 4 toxicity that is thought to be related to HPMPC will have their HPMPC treatment discontinued. However, grade 3 or 4 neutropenia may be managed as outlined in section 5.4. Patients who experience a grade 3 or 4 toxicity that is not thought to be related to HPMPC

may continue HPMPC treatment at the discretion of study physicians. A scale for grading toxicities is included as Appendix D.

6. Data collection plan

6.1 Data collection schedule

Data will be collected from all patients enrolled in the trial according to the schedule presented in Table 7. This represents a data collection schedule, not a patient care schedule. More frequent visits for patient care may be scheduled based on the judgment of the treating physicians.

All baseline evaluations for eligibility must be completed within the five days up to and including randomization. A patient will not be randomized until these evaluations are completed. Some laboratory evaluations may need to be repeated before the initial administration of HPMPC, since renal function must be evaluated within the 24 hours prior to an infusion, and the other laboratory assessments must be done within the 72 hours prior to an infusion.

Follow-up evaluations will be conducted at weeks 1, 3, 5, 7, 9 and 11 following randomization, then every 2 weeks until week 23, then every 12 weeks thereafter. At weeks 13, 17, and 21 only data on selected laboratory evaluations will be collected. Laboratory studies will be conducted in the 24 hours before each HPMPC treatment. Patients not receiving HPMPC will have the same data collection schedule as those receiving HPMPC, i.e., selected laboratory studies will be conducted at weeks 13, 17, and 21. All patients will be followed until death or a common study closeout. Study closeout will occur six months after randomization of the last patient.

6.1.1 Ophthalmologic evaluations

An ophthalmic history interview, assessment of best corrected visual acuity, intraocular pressure and dilated indirect ophthalmoscopy will be performed at baseline and at weeks 1, 3, 5, 7, 9 and 11 following randomization, then every 4 weeks until week 23, then every 12 weeks thereafter. However, patients who are assigned to deferral of treatment who have not started treatment by week 11 of followup will continue to have ophthalmologic exams every two weeks until treatment is started. Intraocular pressure may be measured with applanation tonometer or pneumatonometer, however, applanation tonometry is preferred. Pressures should be measured before dilation. Slit lamp exams should be performed when clinically indicated due to level of IOP; data from these exams will not be collected on study forms. Best corrected visual acuity will

be assessed using the refraction and acuity assessment procedures described in the SOCA handbook.

6.1.2 Fundus photography

Photographs of the fundus of each eye will be taken on the same schedule as ophthalmologic exams, however, photographs are not required every two weeks after week 11. Photographs will be taken with a Canon 60° wide angle camera; procedures for fundus photography are described in the SOCA handbook for patients whose treatment continues to be deferred after week 11. In addition, a set of fundus photographs should be taken within the seven days before starting treatment for a patient assigned to the Dfr group.

6.1.3 Medical history

A medical history will be taken on the same schedule as fundus photographs. The history includes health history prior to the onset of AIDS, date of AIDS diagnosis, index disease for AIDS diagnosis, occurrence of other opportunistic infections and manifestations of AIDS, and treatment history for HIV and CMV. The patient's current level of functioning will be assessed using the Karnofsky performance scale, which is described in the SOCA handbook.

6.1.4 Physical examination

A physical examination will be performed at baseline, at weeks 3, 11, 19, and 35 after randomization, and every 12 weeks thereafter. Data obtained will include weight, height, and status of major body systems.

6.1.5 Laboratory studies

Laboratory assessments will be done at every data collection visit and before each administration of HPMPC. Tests to be performed are:

- Serum chemistry profile: Creatinine, blood urea nitrogen, total bilirubin, sodium, potassium, chloride, bicarbonate, glucose, albumin, globulin, cholesterol, triglycerides, uric acid, phosphate, calcium, magnesium, alkaline phosphatase, SGOT (AST), SGPT (ALT), lactate dehydrogenase (LDH) and amylase

- Hematology profile: CBC with differential and platelet count
- Urinalysis: Specific gravity, pH, glucose, blood/hemoglobin and protein
- CMV cultures of urine and blood (at baseline, week 3, and week 15)
- Lymphocyte T-cell subsets: CD4 and CD8 cell counts (at baseline only)
- Serum pregnancy test for females of childbearing potential (at baseline, as necessary during follow-up and following discontinuation of HPMPC)

6.2 Monitoring adverse reactions

The terms *adverse event* and *adverse drug event* mean any adverse experience whether or not considered drug related. This includes any side effect, injury, toxicity, or sensitivity reaction. An adverse event is considered serious or severe if it: (1) is fatal or life-threatening, (2) is permanently disabling, or (3) requires or prolongs a hospitalization. Death, congenital anomalies, cancer, anaphylaxis, shock or overdose are always considered "serious" or "severe". A graded toxicity scale for some adverse events is included in Appendix C.

All serious (grade 3) or severe (grade 4) adverse events must be reported on the appropriate data forms. For adverse events related to renal function or intraocular pressure, all adverse events from mild (grade 1) through severe (grade 4) must be reported. However, trace proteinuria should not be reported.

Laboratory tests must be repeated for confirmation of all occurrences of a serious or severe event related to renal function. Laboratory tests must also be repeated at the first occurrence of any other serious or severe event which is assessed by a laboratory measure.

As there are requirements for reporting adverse events to the FDA, clinical personnel are responsible for notifying the SOCA Coordinating Center (410/955-8175) within 24 hours of learning about a serious or severe event. The Coordinating Center will then notify the Sponsor.

Treatment with HPMPC may continue at the discretion of the Investigator if a mild (grade 1) or moderate (grade 2) adverse event occurs. If a patient experiences a serious or severe adverse event considered not to be HPMPC-related, the patient may continue HPMPC treatment at the discretion of study physicians. If a patient experiences a serious or severe event considered likely to be HPMPC-related, HPMPC treatment of that patient will be terminated. However, if a patient experiences neutropenia, HPMPC treatment may continue and treatment with G-CSF should be instituted as described in section 5.4.

7. Biostatistics

7.1 Staged approach

Because of the limited amount of data available on the safety and efficacy of HPMPC for the treatment of patients with CMV retinitis, a two-stage approach will be implemented. An interim analysis will be initiated once the 20th patient has been enrolled in the study for one month. Data from the first 20 patients enrolled in Stage 1 will be used to compare the short-term relative safety and efficacy of Dfr vs H-3. If Stage 2 is implemented as currently planned, the final analyses will combine data from Stage 1 and Stage 2, emphasizing the long-term relative safety and efficacy of Dfr vs H-3 vs H-5.

7.2 Sample size

The power to detect significant differences in adverse events between the treatment groups at the end of Stage 1 is uniformly low. Incidence and severity of adverse events will be monitored on a frequent basis.

The following calculations of minimum detectable differences at the end of Stage 2 in median time-to-progression assume a median of 16 days in the Dfr treatment group (unpublished data from the SOCA FGCRT), a 10% loss to followup, a two-sided Type I error probability of 5% and a power level of 80% and are based on the logrank test.

The estimated minimum detectable differences are: a 100% increase in median time-to-progression (16 to 32 days) between the Dfr group (n=35) and the H-3 group (n=35); a 144% increase in median time-to-progression (16 to 39 days) between the Dfr group (n=35) and the H-5 group (n=20); and assuming a homogeneous treatment effect across the H-3 and H-5 groups and therefore pooling the patients assigned to HPMPC treatment, a 81% increase in median time-to-progression (16 to 29 days) between the Dfr group (n=35) and the combined HPMPC groups (n=55).

7.3 Treatment effects monitoring

The SOCA Policy and Data Monitoring Board (PDMB) will be responsible for reviewing the accumulating data related to safety and efficacy. In reviewing those data, the PDMB will not be masked to treatment assignment. The voting members of the PDMB are not involved in the conduct of SOCA trials and have no affiliation with the drug sponsor. The members of the PDMB are listed in Appendix B.

The PDMB will meet to review the short-term safety and efficacy data collected in Stage 1 on the first 20 (10 H-3, 10 Dfr) patients randomized into the trial. Recommendations by the PDMB for continuing, modifying or stopping the trial will be based upon safety issues (including mortality and drug toxicities) and efficacy issues (including rates of retinitis progression). The PDMB recommendations will be submitted for approval to both the SOCA Steering Committee and the drug sponsor.

In addition to the scheduled meeting at the end of Stage 1, the PDMB will meet and review interim data every 6 months, or more often if necessary, throughout the course of the trial.

7.4 Data analysis

General analysis principles include analysis by original treatment assignment (intention-to-treat analysis), counting all patients, including ineligible patients, into their assigned treatment once the treatment assignment is revealed, and counting all events after randomization.

Comparisons to be made among the treatment groups will be both unadjusted and adjusted for baseline covariates including history of anti-retroviral use. P-values will be presented as descriptive statistics without adjusting for multiple looks, multiple outcomes or multiple comparisons. Other analyses will include comparisons by treatment administered (as a time-dependent covariate) when appropriate.

Test statistics for treatment group comparisons will include likelihood ratio tests from Cox regression models and repeated measures analyses using Generalized Estimating Equations, and logrank tests from Kaplan-Meier procedures. Retinitis progression, adverse events, visual loss and CMV shedding will be compared among the three (two during the first stage) treatment groups.

Additionally, the outcomes in the two actively treated groups, H-3 and H-5, will be compared. Depending on the results of tests of homogeneity of effects, the H-3 and H-5 treatment groups will either be analyzed separately, pooled, or analyzed in a dose-response fashion.

8. Patient rights and responsibilities

8.1 IRB approvals

This protocol will be submitted to the Institutional Review Board (IRB) of participating centers for review and approval. Clinics may not start recruiting patients into the trial prior to approval of this protocol by their local IRB. All trial patients must sign a consent statement and medical record release form.

8.2 Confidentiality of patient data

All patient data will be kept in a secure place. Name, social security number, address and other such personal data will not be used by the Coordinating Center. Data collected from trial evaluations and interviews will be identified by trial ID codes only; a patient ID number and name code will be assigned at registration. Data may also be released to the pharmaceutical sponsor, the FDA, or other regulatory concerns for monitoring purposes without written consent of the patient. Clinically relevant information may be placed in the patient's medical record. Release of data to any other persons or organizations will require the written consent of the patient.

9. Biohazards

It is probable that blood and urine specimens collected during the trial will be contaminated with CMV, HIV, and other pathogens. All personnel involved in collecting and handling biologic specimens should follow appropriate precautionary procedures as currently recommended by the Centers for Disease Control and Prevention.

10. HPMPC product information

10.1 Dose form and strength

HPMPC will be supplied by the Sponsor as a sterile liquid for parenteral administration in 5 mL vials. Each vial contains 5 mL of liquid at a concentration of 75 mg/mL, formulated in Water for Injection and pH-adjusted to 7.5. The formulation does not contain a preservative and is suitable for single dose use only. Unused or expired vials should be returned to the source pharmaceutical repository, Ogden BioServices, Inc., Attention: Bob Hughes, 625-C Lofstrand Lane, Rockville, Maryland, 20850. Partially used vials can be destroyed on site by crushing or incineration (according to institutional protocol).

10.2 Shipping, storage, and handling

Drug will be shipped to the Investigator by a registered courier service following specified Standard Operating Procedures. Drug product will be stored at room temperature (15° to 30°C) until required for administration.

As HPMPC is an investigational drug and limited information is available on the mutagenic and carcinogenic potential of this compound, appropriate precautions should be followed to avoid direct contact with skin, mucous membranes, or exposure through inhalation when handling HPMPC. Although there is no general agreement on which measures are necessary or appropriate, consideration should be given to handling, preparation, and disposal through measures that minimize contact. If skin or eye contact does occur, these areas should be washed with copious amounts of water.

Table 7. Treatment and data collection schedule (baseline to 8 months)

		Weeks													
Data	Bl	0	1	3	5	7	9	11	13	15	17	19	21	23	35
HPMPC Treatment (mg/kg/dose)															
H-3		5	5	3	3	3	3	3	3	3	3	3	3	3	3
H-5		5	5	5	5	5	5	5	5	5	5	5	5	5	5
Data collection															
Registration	x														
Ophthalmologic	x		x	x	x	x	x	x	x‡	x	x‡	x	x‡	x	x
Fundus photos	x		x	x	x	x	x	x		x		x		x	x
Visual acuity	x*			x	x	x		x*		x		x		x*	x*
*refraction															
Renal tests	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
BUN															
Creatinine															
Urinalysis															
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CBC															
Differential															
Platelet															
Chemistries	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Electrolytes															
Enzymes															
Proteins															
Fats															
CMV cultures	x			x						x					
Blood															
Urine															
T-cell subsets	x														
Pregnancy test†	x														
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Health history	x			x	x	x		x		x		x		x	x
AIDS history															
Other Rx															
Physical exam	x			x				x				x			x

†At the discontinuation of HPMPC treatment and as necessary during followup
‡For patients assigned to deferral of treatment who have not started treatment.

Table 8. HPMPC administration

General information

- HPMPC is provided in 5 mL vials at a concentration of 75 mg/mL
- AZT should be discontinued on the day of HPMPC administration.
- A total of 2 liters of 0.9% saline will be administered with each HPMPC infusion. For patients weighing less than 50 kg, hydration volume should be 3% of body weight.
- A total of 4 grams of probenecid will be administered with each HPMPC infusion, patients should eat before each dose of probenecid. For patients weighing less than 50 kg, probenecid dosage should be halved.
- Base dosage on baseline weight unless a weight change ≥ 5% occurs
- Transfer HPMPC dose to infusion bag containing 100 mL 0.9% saline

Dosage for H-3 treatment group

- Induction: 5 mg/kg/week for 2 weeks
- Maintenance: 3 mg/kg every 2 weeks

Dosage for H-5 treatment group

- Induction: 5 mg/kg/week for 2 weeks
- Maintenance: 5 mg/kg every 2 weeks

HPMPC administration

- Obtain blood and urine specimens and results for serum creatinine and urinalysis ≤ 24 hours before HPMPC infusion; obtain serum chemistry results ≤ 72 hours before infusion
- Administer 4 tablets of probenecid (500 mg/tablet) 3 hours before HPMPC infusion
- Hydrate via IV infusion with 1 liter 0.9% saline, 1 to 2 hour infusion, just before administering HPMPC
- Administer HPMPC in 100 mL of 0.9% saline via IV infusion over a 1 hour period
- Hydrate via IV infusion with a second liter of 0.9% saline over 1 to 3 hours; the second liter of saline may be piggy backed with the HPMPC infusion
- Administer 2 tablets of probenecid (500 mg/tablet) 2 hours after HPMPC infusion is completed
- Administer 2 tablets of probenecid (500 mg/tablet) 8 hours after HPMPC infusion is completed

Treatment termination criteria

- CMV retinitis progression
- Development of biopsy-documented extraocular disease
- Unacceptable drug toxicity thought to be related to HPMPC (if it is the first occurrence of a toxicity, confirm immediately by repeating laboratory test on a new specimen)
- Unacceptable probenecid toxicity
- Patient request
- Need to use nephrotoxic drugs to treat intercurrent illness

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Appendix A: SOCA centers

SOCA ID	Institution	Director
Clinical centers		
BCM	Cullen Eye Institute Baylor College of Medicine Houston, TX	Richard A. Lewis, MD
JHU	Wilmer Ophthalmological Institute Johns Hopkins University Baltimore, MD	James P. Dunn, MD
LSU	LSU Eye Center Louisiana State University New Orleans, LA	Bruce Barron, MD
MSK	Memorial Sloan Kettering Cancer Center Cornell Medical Center New York, NY	Murk-Hein Heinemann, MD
MSMC	Mount Sinai Medical Center New York, NY	Alan H. Friedman, MD
NYU	Department of Ophthalmology New York University Medical Center New York, NY	Dorothy Friedberg, MD
NU	Northwestern University Chicago, IL	David Weinberg, MD
UCLA	Jules Stein Eye Institute University of California Los Angeles, CA	Gary Holland, MD
UCSD	Department of Ophthalmology University of California San Diego, CA	William Freeman, MD

Appendix A: SOCA centers

SOCA ID	Institution	Director
UCSF	Beckman Vision Center University of California San Francisco San Francisco General Hospital San Francisco, CA	James O'Donnell, MD
UM	Bascom Palmer Eye Institute University of Miami Miami, FL	Janet Davis, MD
Resource Centers		
CO	Chairman's Office Wilmer Ophthalmological Institute Johns Hopkins University Baltimore, MD	Douglas Jabs, MD
CC	Coordinating Center Center for Clinical Trials Johns Hopkins University Baltimore, MD	Curtis Meinert, PhD
FPRC	Fundus Photography Reading Center Department of Ophthalmology University of Wisconsin Madison, WI	Matthew Davis, MD
NEI	Project Office National Eye Institute Bethesda, MD	Richard Mowery, PhD

Appendix A: SOCA centers

SOCA ID	Institution	Director
NIAID	ACTG Operations Office National Institute of Allergy and Infectious Disease Rockville, MD	Beverly Alston, MD
Support centers		
Ogden	Drug Distribution Center Ogden BioServices Corporation Rockville, MD	Gary A. Stewart, MS, RPh

Appendix B: Policy and Data Monitoring Board

Name	Institution/study position
Voting	
Byron W. Brown, PhD (Chairman)	Biostatistician Stanford University Department of Biostatistics
Brian Conway, MD	Ophthalmologist University of Virginia Department of Ophthalmology
James Grizzle, PhD	Biostatistician University of Washington Department of Biostatistics
Robert Nussenblatt, MD	Ophthalmologist National Eye Institute
John Phair, MD	Infectious Disease Specialist Northwestern University Department of Medicine
Harmon Smith, PhD	Theologian Duke University Department of Theology
Richard Whitley, MD	Infectious Disease Specialist University of Alabama Department of Pediatrics, Microbiology and Medicine
Non-voting	
Matthew Davis, MD	Ophthalmologist FPRC Director
Mary Foulkes, PhD	Biostatistician NIAID
Beverly Alston, MD	Infectious Disease Specialist NIAID

Appendix B: Policy and Data Monitoring Board

Name	Institution/study position
Non-voting (cont'd)	
Douglas Jabs, MD	Ophthalmologist Study Chairman
Curtis Meinert, PhD	Biostatiscian CC Director
Richard Mowery, PhD	Project Officer NEI
James Tonascia, PhD	Biostatiscian CC Deputy Director

Appendix D: Graded Toxicity Scale

	Category			
	Grade 1 (Mild)	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Life-threatening)**
A. **Hematologic**				
1) Neutrophils	626-749/μL	501-625/μL	250-500/μL	< 250/μL
2) Platelets	35,000-49,999/μL	20,000-34,999μL	10,000-19,999/μL	< 10,000/μL
3) Hgb	7.0-8.5g/dL	6.0-6.9g/dL	5.0-5.9g/dL	< 5.0g/dL
B. **Metabolic**				
1) Hyperglycemia	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	> 500 mg/dL or ketoacidosis
2) Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	< 30 mg/dL
3) Hypercalcemia	10.6-11.5 mg/dL	11.6-12.5 mg/dL	12.6-13.5 mg/dL	> 13.5 mg/dL
4) Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.1-6.9 mg/dL	≤ 6.0 mg/dL
5) Hypomagnesemia	1.2-1.4 mg/dL	0.9-1.1 mg/dL	0.6-0.8 mg/dL	≤ 0.5 mg/dL
C. **Coagulation**				
1) Prothrombin time	14-16 sec	17-18 sec	≥ 19 sec without bleeding	≥ 19 sec with bleeding
2) Partial thrombo-plastim time	40-45 sec	46-50 sec	≥ 51 sec without bleeding	≥ 51 sec with bleeding
D. **Hepatic**				
1) Total bilirubin	2.0-3.0 x BL/ULN*	3.1-5.0 x BL/ULN*	5.1-10.0 x BL/ULN*	> 10.0 x BL/ULN*
2) SGOT or SGPT	2.0-3.0 x BL/ULN*	3.1-5.0 x BL/ULN*	5.1-10.0 x BL/ULN*	> 10.0 x BL/ULN*
3) Alkaline phosphatase	2.0-3.0 x BL/ULN*	3.1-5.0 x BL/ULN*	5.1-10.0 x BL/ULN*	> 10.0 x BL/ULN*
E. **Renal**				
1) BUN	20-50mg/dL	51-75 mg/dL	76-100 mg/dL	> 100 mg/dL
2) Creatinine	1.5-1.6 mg/dL	1.7-1.9 mg/dL	2.0-3.0 mg/dL	> 3.0 mg/dL
3) Proteinuria	Trace or < 0.3 g % or < 3 g/l	1+ or 0.3-1.0 g % or 3-10 g/l	2+ to 4+ or > 1.0 g % or > 10 g/l	nephrotic syndrome
4) Creatinine clearance	51-55 ml/min	41-50 mL/min	26-40 mL/min	≤ 25 ml/min

*BL/ULN = baseline or upper limit of normal, whichever is higher

HPMPC Peripheral CRT

Appendix D: Graded Toxicity Scale

	Category			
	Grade 1 (Mild)	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Life-threatening)**
F. **Gastrointestinal**				
1) Nausea	Mild or transient; maintains reasonable food intake	Moderate discomfort; some limitation of food intake	Severe discomfort; minimal food intake for 3 or more days OR 2.5-5.0 kg weight loss resulting from nausea	Life threatening; unable to ingest any food or fluid in 24 hours OR > 5.0 kg weight loss resulting from persistent nausea
2) Vomiting	Mild or transient; 2-3 episodes in 24 hours OR 1-2 episodes per day lasting less than 1 week	Moderate or persistent; 4-5 episodes in 24 hours OR 1-2 episodes per day for more than one week	Severe; vomiting all food or fluids in 24 hours OR orthostatic hypotension OR 2.5-5.0 kg weight loss resulting from vomiting	Life threatening; hypotensive shock OR > 5.0 kg weight loss resulting from persistent vomiting
3) Diarrhea	Mild or transient; 3-4 loose stools in 24 hours OR mild diarrhea lasting less than one week	Moderate or persistent; 5-7 loose stools in 24 hours OR 3-4 loose stools per day for more than one week	Severe; bloody diarrhea OR 8-9 loose stools in 24 hours OR orthostatic hypotension OR 2.5-5.0 kg weight loss resulting from diarrhea	Life threatening; hypotensive shock OR hospitalization for IV fluids OR > 5.0 kg weight loss resulting from diarrhea
4) Stomatitis	Mild discomfort; no difficulty swallowing	Difficulty swallowing, but able to eat and drink fluids	Unable to swallow solids	Unable to drink fluids; requires IV fluids
G. **Pulmonary**	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea at rest	requires ventilatory support
H. **Neurologic**				
1) Muscle strength	Subjective weakness; no objective symptoms	Mild objective weakness; no decrease in function	Objective weakness; function limited	Paralysis
2) Neuro-cerebellar	Slight incoordination; dysdiadochokinesia	Intention tremor; dysmetria; slurred speech; nystagmus	Locomotor ataxia	Incapacitated

*BL/ULN = baseline or upper limit of normal, whichever is higher

HPMPC Peripheral CRT

Appendix D: Graded Toxicity Scale

	Category			
	Grade 1 (Mild)	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Life-threatening)**
3) Mood	Mild anxiety or mild depression	Therapy required for moderate depression	Needs assistance for severe anxiety or severe depression or severe mania	Acute psychosis or incapacitated or hospitalization
4) Peripheral Neuropathy	Mild discomfort; no therapy required	Moderate discomfort persisting for > 72 hours; requiring non-narcotic analgesia OR mild discomfort persisting for > 72 hours accompanied by loss of deep tendon reflex previously present	Severe discomfort; marked antalgic; gait; narcotic analgesia required with symptomatic improvement	Incapacitating; intolerable discomfort; not improved OR unable to walk despite narcotic analgesia
5) Headache	Mild; no therapy required	Moderate; non-narcotic analgesic therapy required	Severe; responds to initial narcotic therapy	Intractable; requiring repeated narcotic therapy
I. **Fatigue**	No decrease in daily activities	Normal activity reduced 25-50%	Normal activity reduced > 50%; cannot work	Unable to care for self
J. **Fever** (in absence of infection) > 12 hours	37.7-38.5°C or 100.0-101.5°F	38.6-39.5°C or 101.6-102.9°F	39.6-40.5°C or 103-105°F	> 40.5°C or > 105°F
K. **Cardiac**				
1) Cardiac function		mild CHF	moderate CHF	severe or refractory CHF
2) Hypotension	20-25 percent decrease from baseline systolic	26-30 percent decrease from baseline systolic	31-40 percent decrease from baseline systolic	> 40 percent decrease from baseline systolic
3) Hypertension	20-25 percent increase from baseline systolic	26-30 percent increase from baseline systolic	31-40 percent increase from baseline systolic	> 40 percent decrease from baseline systolic

*BL/ULN = baseline or upper limit of normal, whichever is higher

HPMPC Peripheral CRT

Appendix D: Graded Toxicity Scale

	Category			
	Grade 1 (Mild)	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Life-threatening)**
L. **Skin or allergy**				
1) Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema	Anaphylaxis
2) Local reaction	Tenderness or erythema	Induration < 10 mm or phlebitis or inflammation	Induration > 10 mm or ulceration	Necrosis
3) Cutaneous	Erythema or pruritus	Diffuse maculopapular rash, dry desquamation	Vesiculation, moist desquamation, ulceration	Exfoliative dermatitis; mucous membrane involvement, OR Stevens-Johnson Syndrome, OR erythema multiforme, OR necrosis requiring surgery
M. **Other toxicity**				
1) Seizure				
2) Overdose				
3) Ocular hypotony		≥50% reduction from baseline IOP† to an IOP between 5 and 10 mm Hg	≥ 50% reduction from baseline IOP to an IOP < 5 mm Hg with no structural changes	Occurrence of ocular changes indicative of hypotony such as retinal or choroidal folds, elevation of optic nerve head, suprachoroidal effusions or hemorrhage, or corneal striae associated with an IOP ≤ 5 mm Hg

†IOP = intraocular pressure

HPMPC Peripheral CRT

Appendix D: Graded Toxicity Scale

	Category			
	Grade 1 (Mild)	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Life-threatening)**
Other	Transient or mild discomfort; requiring no limitation in activity; no therapy	Moderate impact on activity; may require some assistance or medical intervention	Marked impact on activity; requiring some assistance and medical intervention	Complete disability; requiring significant assistance and medical intervention and/or hospitalization