Studies of Ocular Complications of AIDS

SOCA

Ganciclovir-Cidofovir CMV Retinitis Trial (GCCRT, ACTG #350)

Version 6.1
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Document history

Version 1.0 (15 November 1996): Protocol submitted to JHU CHR

Version 1.1 (18 December 1996): Consent statement revised, protocol submitted to JHU CHR

Version 1.2 (08 January 1997): Protocol revised, sent to surgeons for training meeting
- Clarified schedule for replacing implant: Abstract, Consent Statement, Assent Statement
- Removed masking of assignment to cidofovir only or cidofovir plus oral ganciclovir: Section 3.3, Appendix C, Consent Statement, Assent Statement
- Created separate treatment administration sections for cidofovir only group and cidofovir plus oral ganciclovir group: Sections 4.2 and 4.3
- Clarified time of implantation for patient with bilateral disease: Section 4.1.1, Consent Statement
- Referred to SOCA Handbook for criteria for confirming extraocular CMV: Sections 4.1.4 and 4.2.3
- Moved data collection specifications for visual acuity and visual field: From Sections 6.1.1 and 6.1.2 to Section 5.2
- Moved information regarding other morbidities: From Section 6.1.8 to Section 5.3
- Added HIV load determination and analysis: Sections 5.4 and 6.1.7, Appendix C, Exhibit 1
- Moved data collection specifications for quality of life: From Section 6.1.9 to Section 5.5
- Added collection of quality of life data at F01 visit: Section 5.5, Appendix C, Exhibit 1
- Clarified reporting of adverse events: Section 5.6
- Added refraction schedule: Exhibit 1

Version 2.0 (15 January 1997): Protocol sent to clinics and PDMB for review
- Clarified that ophthalmologist decides which eye to operate on first if patient has bilateral disease: Section 4.1.1
- Clarified that, for patients in the implant group, the implant should be inserted in previously uninvolved eyes that develop CMV retinitis lesions: Section 4.1.3
- Added statements that best medical judgment may include switching patients to another study treatment: Sections 4.1.4, 4.2.3, 4.3.4
- Clarified reporting of adverse events: Section 5.6

Version 3.0 (11 March 1997): Protocol revised, sent to clinics for submission to local IRBs
- Dropped cidofovir plus oral ganciclovir group (Abstract, Sections 2.1, 2.2, and 3.3, Appendix C, Consent Statement, Assent Statement)
- Added oral ganciclovir to treatment regimen for patients on cidofovir who relapse: Abstract, Sections 2.1 and 4.2.4, Appendix C, Consent Statement, Assent Statement

Added treatment overview sections: Sections 4.1.1 and 4.2.1
Added flow charts of treatment algorithms: Exhibits 3 and 4
Deleted specifics of sample size calculations from Abstract and Section 2, updated in Appendix C
Added rationale for visual function outcomes: Section 2.3
Changed eligibility criteria: Section 3.1, Appendix C
- Inclusion criteria:
  - Changed proteinuria criterion from less than 1+ to less than 2+
  - Added criterion of predicted creatine clearance greater than 55 mL/min
- Exclusion criteria:
  - Changed criterion regarding preexisting renal insufficiency to history of significant renal disease or dialysis
  - Added criterion regarding use of nephrotoxic agents within 7 days of start of treatment

Changed sections on reinduction and treatment termination to sections on changes in treatment: Sections 4.1.4 and 4.2.4, Appendix C
Changes to section on cidofovir administration: Section 4.2.2
- Cidofovir maintenance infusions must be at least 10 days apart
- Serum creatinine and urine protein must be checked within 48 (not 24) hours of each infusion
- Infusion pump recommended
- Use of probenecid desensitization regimen clarified

Added cidofovir dose adjustment requirement: Section 4.2.3, Appendix C
Added paragraph regarding the use of maximum tolerable antiretroviral therapy: Section 4.4
Changed months to weeks in data collection schedule: Sections 5.1, 5.4, 5.5, 6.1 and 6.4, Appendix C
Added paragraph on procedure at FPRC to maintain masking: Section 5.2
Added requirement for urinalysis and serum or urine pregnancy test to lab assessments: Section 5.4
Added statement that patients and/or their insurance will be billed for the study treatment: Consent Statement

Version 3.1 (05 May 1997): Protocol revised following RG meeting and distributed study wide
Deleted inclusion criterion of negative pregnancy test: Section 3.1, Appendix C
Changed exclusion criterion of pregnancy or lactation to unwillingness to refrain from breast feeding: Section 3.2, Appendix C
Clarified that definition of progression leading to change in treatment includes development of a new lesion: Sections 4.1.4 and 4.2.4

Clarified that if woman becomes pregnant while in the study, her treatment will be decided according to best medical judgment; she will be advised not to breast feed: Sections 4.1.4 and 4.2.4
Corrected criteria for renal toxicity to include 3+ (rather than 2+) proteinuria or greater; persistent 2+ proteinuria is reason for dose reduction: Section 4.2.4
Deleted pregnancy test from lab studies: Section 5.4
Added T-cell subset analysis at weeks 12, 24, 36, and 48: Section 5.4, Exhibit 1
Clarified requirements for reporting ocular adverse events: Section 5.6

Version 4.0 (29 October 1997): Protocol revised following RG meeting and distributed
Deleted inclusion criterion for hemoglobin 7.5 g/dL or greater: Section 3.1, Appendix C
Deleted probenecid desensitization regimen: Section 4.2.2
Clarified that adverse event reporting pertains to those related to CMV disease or its treatment: Section 5.6
Added sections on sample size calculation and analysis principles: Sections 7.1 and 7.2

Version 5.0 (11 January 1999): Protocol revised and distributed study wide
Added section on discontinuation of anti-CMV maintenance therapy in HAART responders: Section 4.3
Added list of nephrotoxic drugs that are not to be used within specified time prior to randomization: Section 3.2, Appendix C
Changed exclusion criterion of preexisting renal insufficiency to presence of renal insufficiency or clinically significant renal disease: Section 3.2, Appendix C
Deleted sentence on completing baseline laboratory assessments within 72 hours of study entry; time window is the same as for other baseline data: Section 5.1

Version 6.0 (15 June 1999): Protocol revised, sent to JHU CHR, and distributed study wide
Changed cidofovir treatment group to systemic therapy group: Abstract, Sections 1.2, 2.1, 2.3, and 4.2, Appendix C, Consent Statement, Assent Statement
Changed "device" to "implant" throughout
Added continued T-cell subset analysis and specimen collection every 12 weeks after F12: Section 5.4, Exhibit 1, Appendix C
Updated sample size calculations: Abstract, Section 7.1, Appendix C
Changed eligibility requirements: Sections 3.1 and 3.2, Appendix C
Inclusion criteria deleted:
Serum creatinine 1.5 mg/dL or less
Predicted creatinine clearance greater than 55 mL/min
Less than 2+ proteinuria

Exclusion criteria deleted:
- Previous or ongoing treatment for CMV disease with cidofovir
- History of significant probenecid allergy or sulfa sepsis syndrome
- History of clinically significant cardiac disease
- Presence of renal insufficiency or clinically significant renal disease
- Use of nephrotoxic drugs within 7 days of start of treatment
- Initiation of ACE inhibitors within 4 weeks of study entry

Exclusion criterion modified:
- Previous or ongoing treatment with the ganciclovir implant changed to treatment with ganciclovir implant in the past 9 months

Updated list of SOCA clinics participating in the GCCRT: Appendix A

Updated list of PDMB members: Appendix B

Revised consent statement to decrease reading level: Appendix D

Added second assent statement for participants aged 13 to 15, original assent statement designated to participants aged 16 and 17: Appendix E, Appendix F

Version 6.1 (09 August 1999): Added list of drugs not to be taken with probenecid: Section 4.2

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Source documents

The following document is partially excerpted and partially adapted from the following source documents:

- Studies of Ocular Complications of AIDS (SOCA) Protocol: Monoclonal Antibody MSL 109 CMV Retinitis Trial (MACRT) (ACTG 294)
- Studies of Ocular Complications of AIDS (SOCA) Protocol: HPMPC Peripheral CMV Retinitis Trial (HPCRT)
- The product inserts for cidofovir, ganciclovir, and foscarnet

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Abstract

The Ganciclovir and Cidofovir CMV Retinitis Trial (GCCRT) is a randomized clinical trial to compare two treatment approaches for both newly diagnosed and relapsed CMV retinitis in people with AIDS. The two approaches are: 1) the ganciclovir intraocular implant plus oral ganciclovir and 2) systemic treatment with any of several available treatment regimens. The primary objective of this study is to compare the efficacy, with respect to preventing vision loss as measured by visual acuity and visual field, of a treatment regimen that incorporates highly active local therapy (ganciclovir implant) to that of systemic treatment regimens.

The trial is a phase IV, randomized, multicenter trial with a parallel treatment design. The design variables for the trial are time to loss of 3 lines (15 letters) or more in best corrected visual acuity and rate of visual field loss in involved eyes. With a sample size of 140 participants (70 per treatment group), the minimum detectable difference in time to visual acuity loss is an increase from 8.2 to 14.6 months, a relative risk of 0.56. Additional outcome variables include mortality, change in retinal area affected by CMV, time to first retinitis progression, time to discontinuation of assigned treatment, quality of life, CMV treatment-related costs, incidence of extraocular CMV, and adverse events.

Patients randomized to the implant group will have the implant surgically inserted at baseline and every 6 to 8 months thereafter in eyes with CMV retinitis, given that the patients have ongoing immune deficiency. Oral ganciclovir will be taken at a dose of 1 gm three times daily. For patients randomized to systemic therapy only, permissible regimens include intravenous ganciclovir, intravenous foscarnet, intermittent intravenous cidofovir, and intravenous ganciclovir induction followed by oral ganciclovir maintenance. Treatment will be administered according to standardized treatment protocols. In patients with relapsed retinitis, combination regimens will be permitted. A decision to not replace the implant as scheduled or to discontinue maintenance systemic treatment may be considered for patients with sustained (greater than 3 months) immune reconstitution due to highly active antiretroviral therapy.

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1. Introduction

1.1 Cytomegalovirus infection in AIDS patients

Cytomegalovirus (CMV) is among the most frequently encountered opportunistic infections in patients with AIDS. Retinitis is the most common manifestation of CMV disease and accounts for 71% to 85% of CMV disease in patients with AIDS.[3, 5] Prior to the advent of highly active antiretroviral therapy (HAART), CMV retinitis was estimated to affect approximately 30% of patients with AIDS sometime between the diagnosis of AIDS and death.[4, 5, 8] CMV retinitis is a relatively late stage manifestation of HIV infection, associated with CD4 + T-cell counts of less than 50 cells/μL.[3, 10, 22]

In the era of HAART, the number of people with AIDS who are sufficiently immuno-suppressed to be at risk for CMV retinitis has decreased. Therefore, the incidence of CMV retinitis has decreased.[6, 19] However, CMV retinitis still occurs, primarily in two groups of patients: 1) those who have never received HAART and 2) those who have failed to respond to HAART or cannot tolerate HAART.

Currently available treatments for CMV suppress viral replication but do not eliminate the virus. Prior to the era of HAART, discontinuation of anti-CMV therapy was associated with prompt relapse of the retinitis.[9] In the current era, patients receiving HAART who have persistent immune deficiency also relapse when anti-CMV therapy is discontinued. However, patients who have immune reconstitution due to HAART may be able to control retinitis without the administration of specific anti-CMV therapy.[7, 13, 23, 31, 32] For such patients, specific anti-CMV treatments may be needed only until sustained immune reconstitution is verified.

1.2 Rationale

Several regimens are FDA-approved for the treatment of CMV retinitis. These include intravenous ganciclovir,[24] intravenous foscarnet,[20] intravenous ganciclovir induction followed by oral ganciclovir maintenance,[1] intermittent intravenous cidofovir,[12, 30] fomivirsen intraocular injections,[21] and the ganciclovir implant.[15, 17] Intravenous ganciclovir and foscarnet regimens involve daily intravenous infusions during the maintenance phase and therefore require a central venous catheter. These regimens have similar efficacy for controlling CMV retinitis.[25, 26, 27, 28] Oral ganciclovir is sometimes used for maintenance therapy after induction with intravenous ganciclovir, but oral ganciclovir appears to be less effective than intravenous ganciclovir for this

purpose.[1, 11, 18] Cidofovir is an intravenously administered nucleotide analog, which has a prolonged duration of effect. Cidofovir can be administered intermittently (once weekly for induction for 2 weeks and then once every 2 weeks for maintenance). Cidofovir is effective in suppressing CMV[16] and prolonging the time to progression.[12, 30]

The ganciclovir implant delivers drug to the retina at a constant rate for 6 to 8 months.[15] The implant appears to be superior to intravenous ganciclovir in terms of controlling progression of the retinitis.[17] However, because the implant delivers ganciclovir only locally, it does not prevent the occurrence of contralateral ocular or visceral disease. In patients treated with the implant alone, the risk of contralateral ocular disease is estimated to be 50% at 6 months; risk of visceral disease is estimated to be 31%.[15] Use of oral ganciclovir in combination with the ganciclovir implant has been shown to reduce this risk of contralateral ocular and visceral disease.[14]

No long-term studies have evaluated whether the superior control of progression afforded by the implant results in superior long-term visual outcomes. Because of the occurrence of surgical complications, the implant could be associated with similar or even worse visual outcomes. In addition, given the improved treatments for HIV disease, the role of aggressive anti-CMV therapy (e.g., the ganciclovir implant) has becomes less certain. Patients receiving HAART who go on to have immune reconstitution may not need long-term, specific anti-CMV therapy. Furthermore, the improved control of progression previously observed with the implant may not translate into better long-term visual outcomes in the era of HAART. That is, the effect of HAART on the immune system may well mitigate any advantage of the ganciclovir implant. As such, the appropriate role of aggressive local therapy has become less clear in recent years.

Therefore, this randomized controlled clinical trial is being conducted to compare a regimen based on aggressive local therapy (the ganciclovir implant plus oral ganciclovir) to systemic therapy only. The systemic treatment only group will be permitted any of the approved systemic therapies, with the choice being determined according to patient preference and/or best medical judgment.

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2. Summary of objectives and design

2.1 Objectives

The trial is an evaluation of two approaches to the treatment of AIDS-related CMV retinitis: 1) aggressive local therapy with the ganciclovir intraocular implant plus oral ganciclovir as prophylaxis against contralateral and extraocular disease and 2) systemic therapy with any of several available treatment regimens. The primary objective of the trial is to compare these treatment approaches with respect to efficacy in preventing vision loss.

The treatment groups also will be compared with respect to mortality, change in area of retinal involvement, time to retinitis progression, time to discontinuation of assigned treatment, quality of life, CMV treatment-related costs, incidence of adverse events, and incidence of contralateral and extraocular CMV.

2.2 Design

The study is a randomized, multicenter clinical trial. Treatment assignment is stratified by clinic and stage of disease and employs a 1:1 assignment ratio between the two treatment groups. For patients assigned to systemic therapy only, the specific treatment regimen is chosen according to best medical judgment. Treatment assignment is not masked to either patients or clinicians. However, reading of fundus photographs to determine both change in retinal involvement and progression is masked.

2.3 Rationale for visual function outcomes

Change in visual acuity and change in visual field were selected as the primary outcomes because of the interest in long-term visual function rather than short-term progression of retinitis. It is expected that time to retinitis progression, determined by masked fundus photograph readings, will be longer for the ganciclovir implant group, based on published data in which the median time was reported as 226 days for patients with the implant,[15] as compared to 50 to 71 days with intravenous ganciclovir,[17, 24, 26, 29] 40 to 59 days with intravenous foscarnet,[20, 26, 29] and 64 and 120 days for patients on cidofovir.[12, 30] However, the comparative risk/benefit profile and the long-term effectiveness of the implant versus systemic treatments in preserving visual function is not known.

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3. Patient enrollment and randomization

Recruitment, assessment of eligibility, and enrollment are to be performed at clinics certified to participate in the trial. Once it has been determined that a patient is eligible for the trial, the specifics of the trial should be explained and discussed. Patients considering participating in the trial will be given the consent statement and other informational materials and should be allowed time, preferably overnight, to decide whether to enroll in the trial. It is important to give patients adequate time to ensure informed consent. All baseline evaluations are to be conducted within the 5 days up to and including randomization. Patients unable to complete the baseline evaluations will not be eligible to participate in the trial.

3.1 Inclusion criteria

- Age 13 years or older
- Diagnosis of AIDS according to current Centers for Disease Control and Prevention (CDC) definition
- Diagnosis of active CMV retinitis by a SOCA-certified ophthalmologist (involvement of any zone or amount of retina is allowed)
- Best corrected visual acuity of 20/100 or better in at least one eye
- At least one lesion 750μ or greater in size that can be photographed
- Karnofsky score of 60 or greater
- Absolute neutrophil count (ANC) of 750 cells/μL or greater
- Platelet count 50,000 cells/μL or greater
- Willingness and ability, with the assistance of a caregiver if necessary, to comply with treatment and followup procedures
- Willingness of all men and women of childbearing potential to practice adequate birth control to prevent pregnancies during the study and for 3 months afterwards
- Collection of all baseline data within 5 days prior to randomization
- Signed consent statement

3.2 Exclusion criteria

- Media opacities that preclude visualization of the fundus of all otherwise eligible eyes
- Treatment for CMV retinitis with the ganciclovir intraocular implant within 9 months of study entry
- Medical problems or drug or alcohol abuse sufficient to hinder adherence to treatment or followup procedures
- Unwillingness to refrain from breast-feeding during the study and for 3 months afterwards

3.3 Randomization

Randomization will be accomplished using an auditable, documented generation scheme that produces a reproducible order of assignment. Randomization will be stratified by clinic and stage of disease (newly diagnosed or relapsed). The randomization schedules will be written and controlled by the SOCA Coordinating Center (CC) and will be designed to yield an expected assignment ratio of 1:1 between the two treatment groups. Assignments will be generated in permuted blocks of varying lengths.

Clinic personnel will obtain treatment assignments from the CC as needed. Treatment assignment will be communicated in one of three ways: by facsimile transmission (fax), by telephone, or by overnight courier. Standard procedure is to fax the assignment to the clinic. Should the assignment not reach the clinic, clinic personnel are instructed to call within 5 minutes, whereupon the assignment is given by telephone. Before a treatment assignment is faxed or given by telephone, all baseline data must be collected, eligibility must be reviewed by the CC, and signed consent must be obtained.

Under some circumstances, the treatment assignment will be sent to the clinic by overnight courier in a sealed envelope. Such circumstances might occur, for example, when treatment is not to begin for several days or when results of baseline tests determining eligibility are pending. When a sealed envelope is used to transmit treatment assignment because of pending eligibility determination, an accompanying note from the CC will indicate to clinic personnel that the envelope should not be opened until and unless the previously pending test results are known to be within protocol eligibility limits. If that patient withdraws consent or otherwise is determined ineligible before the assignment envelope is opened at the clinic, the unopened envelope will be returned to the CC.

3.3 Randomization

Once a treatment assignment is transmitted to clinic personnel by fax or telephone or an assignment envelope is opened, the patient is counted in the assigned treatment group for the primary analysis, regardless of subsequent treatment or adherence to study protocol.

4. Treatment plan

The two treatment groups are:

- Ganciclovir implant and oral ganciclovir (Imp)
- Systemic therapy (Sys)

4.1 Ganciclovir intraocular implant and oral ganciclovir

4.1.1 Overview

A schematic summary of the treatment plan for patients assigned to the Imp group is provided (Exhibit 3). These patients should begin taking oral ganciclovir and should have ganciclovir implants inserted in eyes involved with CMV retinitis as soon as possible after randomization. Should a patient with unilateral retinitis at baseline develop retinitis in the contralateral eye during followup, an implant should be inserted into that eye. If the clinician determines that the retinitis has progressed and is active before the planned exchange of the implant in that eye, the implant should be replaced. If the retinitis continues to progress after a new implant is inserted, the patient should be treated according to best medical judgment. If a patient has unmanageable toxicity due to the implant or oral ganciclovir, the patient should be treated according to best medical judgment.

4.1.2 Surgical placement of implant

A SOCA-certified surgeon is to insert the ganciclovir intraocular implant into all eyes with CMV lesions using generally accepted surgical procedures. For patients with unilateral disease, the implant should be inserted within 10 days of randomization. For patients with bilateral disease, the first implant should be inserted within 10 days of randomization, and the second should be inserted within 10 days of the first (the ophthalmologist may decide which eye should be operated on first). In the interim time between randomization and insertion of the implant(s), treatment may be given according to best medical judgment. The implant is to be exchanged periodically, unless the patient has sufficient immune reconstitution to discontinue anti-CMV therapy (see section 4.3). The target date for exchange of the implant is 7 months after implantation with a window of 30 days on either side of that date.

It is recognized that there are minor variations in surgical procedures for implantation and the use of perioperative medication, and that these variations do not appear to affect clinical outcome. Therefore, this protocol does not mandate a detailed surgical procedure or a specific perioperative medication regimen, but guidelines for these are outlined in the GCCRT Handbook. Postoperative exams for clinical care are recommended to occur 1 day and 1 week following implantation.

4.1.3 Administration of oral ganciclovir

Oral ganciclovir is to be taken at a dose of 1 gm three times a day. The pills should be taken with food. Treatment should be started as soon as possible after randomization.

4.1.4 Changes in treatment

Development of contralateral disease, progression, unmanageable toxicity, and development of visceral disease are all reasons for adjustments in treatment. If a patient develops contralateral disease, the ganciclovir implant is to be inserted in the newly involved eye within 10 days of diagnosis. If a clinician determines that the patient has active retinitis associated with either a new lesion or movement of a lesion border by more than 750 microns in an eye with an implant in place, a new implant should be inserted. If a second progression occurs while the implant is in place, treatment is instituted according to best medical judgment.

Patients also are to be treated according to best medical judgment if unmanageable toxicity occurs. Neutropenia does not necessitate a treatment change if it can be managed as outlined in section 4.4. When relevant, toxicity should be verified by a repeat of laboratory measures. The implant can be left in place unless the patient is experiencing unmanageable complications related to it.

Patients who develop extraocular CMV disease should to be treated according to best medical judgment. For specific criteria for confirming a diagnosis of extraocular CMV disease, see the SOCA General Handbook. If a patient becomes pregnant, current treatment may be continued or changed according to best medical judgment; the woman should be advised not to breast-feed.

4.2 Systemic therapy

4.2.1 Overview

A schematic summary of the treatment plan for patients assigned to the Sys group is provided (Exhibit 4). These patients may receive any approved systemic anti-CMV treatment. If the patient experiences progression of the retinitis, the clinician may determine according to best medical judgment whether to reinduce with the same treatment or to prescribe an alternative treatment. If a patient experiences toxicity, an alternative treatment may be chosen according to best medical judgment. It is strongly recommended that patients with retinitis progression or toxicity be maintained on some form of systemic therapy when feasible to promote the validity of the comparison of the assigned treatments.

4.2.2 Intravenous cidofovir

4.2.2.1 Administration of cidofovir

Cidofovir is to be administered intravenously at 5 mg/kg once weekly for 2 weeks, followed by 5 mg/kg once every other week. The second induction treatment must be administered 7 days after the first treatment. Maintenance treatments must be administered at least 10 days apart. Before each infusion, serum creatinine (including the change from baseline) and urine protein levels must be checked on specimens obtained within 48 hours of the infusion.

The volume of cidofovir to be administered should be calculated using the patient's initial weight, unless a weight change of more than 5% has occurred. The volume of drug should be measured to the nearest tenth of a milliliter, diluted in 100 mL normal saline (0.9% NaCl), and infused over a 1 hour period. The infusion should be supervised by a physician or nurse and may be done on either an inpatient or outpatient basis.

Each administration of cidofovir is to be accompanied by intravenous hydration with 2 liters of normal saline (or a lesser volume equal to 3% of body weight for patients weighing less than

50 kg). The intravenous hydration should be infused at a constant rate (use of a standard infusion pump is recommended). The first liter of saline should be infused over a 1 to 2 hour period immediately before infusion with cidofovir. The second liter of saline is to be infused over a 1 to 3 hour period and may be started either during infusion with cidofovir or immediately afterward. The cidofovir infusion may be piggybacked with the second liter.

Patients receiving cidofovir also are to receive 4 grams of probenecid (eight tablets of 500 mg each) with each infusion. Four tablets are to be taken 3 hours before infusion, two tablets 2 hours after completion of infusion, and two tablets 8 hours after completion of infusion. For patients weighing less than 50 kg, probenecid doses should be halved. Patients should be encouraged to eat before taking each dose of probenecid to help reduce the occurrence of nausea. Additionally, anti-emetics such as prochlorperazine (Compazine®) may be given to reduce nausea associated with probenecid ingestion.

4.2.2.2 Contraindications to cidofovir

Treatment with cidofovir should not be initiated if a patient has:

- a serum creatinine greater than 1.5 mg/dL;
- a predicted creatinine clearance of 55 mL/min or less; or
- proteinuria of 2+ or greater.

Treatment with cidofovir is to be terminated when renal toxicity occurs. Renal toxicity is defined as any of the following:

- an increase in serum creatinine of 0.5 mg/dL or more from baseline;
- proteinuria 3+ or greater persistent after intravenous hydration; or
- serum creatinine greater than 2.0 mg/dL.

Treatment with cidofovir also may be terminated for any other grade 3 or 4 adverse event that, in the physician's opinion, is judged to be due to cidofovir (with the exception of grade 3 or 4 neutropenia, which may be managed as outlined in section 4.4). All measurements related to the adverse event should be confirmed by repeat measurements before stopping treatment. If the urinalysis performed prior to treatment indicates proteinuria of 3+ or greater, the second measurement should be performed after the patient has received the first liter of hydration. If the repeat measurement indicates proteinuria of 2+, the dose of cidofovir should be reduced (see section

4.2.2.3). If treatment with cidofovir is terminated due to toxicity, it is strongly recommended that patients be maintained on some form of systemic therapy when feasible.

Patients who are found to have severe reactions to probenecid must discontinue treatment with cidofovir. For those experiencing mild allergic reactions to probenecid, the use of prophylactic or therapeutic oral corticosteroids or antihistamines such as diphenhydramine (Benadryl®) will be allowed.

Because of the nephrotoxic potential of cidofovir, other potentially nephrotoxic drugs should not be taken within 7 days of a cidofovir infusion. Such agents include:

- Amphotericin B (including liposomal formulations)
- Foscarnet
- Intravenous pentamidine
- Intravenous aminoglycosides (e.g., tobramycin, gentamicin, and amikacin)
- Vancomycin
- NSAIDs, if use is, in the opinion of the study physician, of sufficient amount to produce concern regarding nephrotoxicity
- Contrast dye
- Adefovir

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 therefore should not take their AZT on days when cidofovir and probenecid are administered.

The following are other drugs that interact with probenecid and should not be taken within 24 hours of any dosage intake of probenecid:

- Acetaminophen (Tylenol)
- Acyclovir
- Angiotensin-converting enzyme (ACE) inhibitors
- Benzodiazepines (eg. Valium)
- Clofibrate
- Methotrexate
- Furosemide (Lasix)
- Aminosalicylic acid
- Barbiturates
- Bumetanide

- Famotidine
- Nonsteroidal anti-inflammatory drugs
- Theophyllines

4.2.2.3 Dose adjustment

If a patient experiences an increase in serum creatinine from baseline of 0.3 to 0.4 mg/dL or 2+ proteinuria persistent after the first liter of hydration, the dose of cidofovir will be decreased to 3 mg/kg.

4.2.2.4 Other changes in treatment

If a clinician determines that a patient has active retinitis associated with either a new lesion or movement of a lesion border by more than 750 microns, a patient receiving maintenance doses of cidofovir may be re-induced with 5 mg/kg once a week for 2 weeks and then returned to the regimen of 5 mg/kg every other week. Alternatively, the patient may be switched to another treatment, chosen according to best medical judgment. It is strongly recommended that patients with progression be maintained on some form of systemic therapy when feasible.

Patients who develop extraocular CMV disease should to be treated according to best medical judgment. For specific criteria for confirming a diagnosis of extraocular CMV disease, see the SOCA General Handbook. If a patient becomes pregnant, current treatment may be continued or changed according to best medical judgment; the woman should be advised not to breast-feed.

4.2.3 Intravenous and oral ganciclovir

4.2.3.1 Administration of ganciclovir

For induction therapy, 5 mg/kg of ganciclovir is to be administered every 12 hours for 14 days. Hematology and serum chemistry should be monitored 2 to 3 times per week.

After induction therapy is completed, maintenance therapy should commence with either intravenous or oral ganciclovir. Intravenous ganciclovir should be administered at 5 mg/kg every 24 hours. Oral ganciclovir should be taken (with food) at a dosage of 1,000 mg three times per day. Hematology and serum chemistry should be monitored once every week or two during maintenance therapy.

4.2.3.2 Contraindications to ganciclovir

Ganciclovir (intravenous or oral) should not be administered if the patient's absolute neutrophil count (ANC) is less than 500 cells/μL or the platelet count is less than 25,000 cells/μL. Management of neutropenia is discussed in section 4.4. Treatment with ganciclovir may be reinstated after recovery of the ANC and platelet count. If treatment with ganciclovir is terminated due to toxicity, it is strongly recommended that patients be maintained on some form of systemic therapy when feasible.

4.2.3.3 Dose adjustment

If a patient receiving intravenous ganciclovir develops renal impairment, the dose of ganciclovir should be reduced. For patients receiving oral ganciclovir, dose reduction should be considered if renal impairment develops.

Intravenous ganciclovir dose reduction should be carried out as follows:

Predicted creatinine clearance (mL/min)	Induction dose (mg/kg)	Dosing interval (hours)	Maintenance dose (mg/kg)	Dosing interval (hours)
≥70	5.0	12	5.0	24
50 - 69	2.5	12	2.5	24
25 - 49	2.5	24	1.25	24
10 - 24	1.25	24	0.625	24
<10	1.25	3 times/week, following hemodialysis	0.625	3 times/week, following hemodialysis

For patients on hemodialysis, dosing should not exceed 1.25 mg/kg 3 times per week, following each hemodialysis session. Intravenous ganciclovir should be given shortly after completion of the hemodialysis session, since hemodialysis has been shown to reduce plasma levels by approximately 50%.

Oral ganciclovir dose reduction may be carried out as follows:

Predicted creatinine clearance (mL/min)	Dose
≥70	1000 mg tid
50 - 69	500 mg tid
25 - 49	500 mg bid
10 - 24	500 mg qd
<10	500 mg 3 times/week, following hemodialysis

Dose reduction also may be considered for patients with neutropenia, anemia, or thrombocytopenia that is not severe (i.e., does not meet the criteria in section 4.2.3.2 for interrupting treatment).

4.2.3.4 Other changes in treatment

If a clinician determines that a patient has active retinitis associated with either a new lesion or movement of a lesion border by more than 750 microns, a patient receiving maintenance therapy with intravenous or oral ganciclovir may be re-induced with intravenous ganciclovir at 5 mg/kg every 12 hours for 2 weeks and then returned to the maintenance regimen. Alternatively, the patient may be switched to another treatment regimen, chosen according to best medical judgment. It is strongly recommended that patients with progression be maintained on some form of systemic therapy when feasible.

Patients who develop extraocular CMV disease should be treated according to best medical judgment. For specific criteria for confirming a diagnosis of extraocular CMV disease, see the SOCA General Handbook. If a patient becomes pregnant, current treatment may be continued or changed according to best medical judgment; the woman should be advised not to breast-feed.

4.2.4 Intravenous foscarnet

4.2.4.1 Administration of foscarnet

Foscarnet should be administered by controlled intravenous infusion. The induction dose for foscarnet is either 90 mg/kg every 12 hours or 60 mg/kg every 8 hours for 14 to 21 days. Hematology and serum chemistry should be monitored 2 to 3 times per week.

After induction therapy is completed, maintenance therapy should commence at 90-120 mg/kg every 24 hours. It is recommended that patients be started on maintenance treatment with a dose of 90 mg/kg/day; escalation to 120 mg/kg/day may be considered for patients who have early retinitis progression or who tolerate foscarnet well. Hematology and serum chemistry should be monitored once every week or two during maintenance therapy.

Hydration may reduce the risk of nephrotoxicity from foscarnet. It is recommended that 750-1000 mL of normal saline be given prior to the first infusion of foscarnet. With subsequent infusions, hydration fluid may be given concurrently in the amount of 750-1000 mL with 90-120 mg/kg of foscarnet and 500 mL with 40-60 mg/kg of foscarnet.

4.2.4.2 Contraindications to foscarnet

Foscarnet should not be administered if creatinine clearance falls below 0.4 mL/min/kg. Dose reduction for patients whose creatine clearance is in the range of 0.4 mL/min/kg to 1.4 mL/min/kg is described in section 4.2.4.3. If treatment with foscarnet is terminated due to toxicity, it is strongly recommended that patients be maintained on some form of systemic therapy when possible.

Use of foscarnet in combination with potentially nephrotoxic drugs should be avoided, unless the potential benefits outweigh the risks to the patient. Such drugs include aminoglycosides, amphotericin B, and intravenous pentamidine. Also, because foscarnet decreases serum concentrations of ionized calcium, concurrent treatment with other drugs known to influence serum calcium concentrations should be used with caution. Abnormal renal function has been reported in connection with the use of foscarnet in combination with ritonavir and/or saquinavir.

4.2.4.3 Dose adjustment

If a patient receiving intravenous foscarnet develops renal impairment, defined as a predicted creatinine clearance between 0.4 mL/min/kg and 1.4 mL/min/kg, the dose of foscarnet should be reduced as shown in the table below:

Predicted creatinine clearance (mL/min/kg)	Induction dose (mg/kg)	Maintenance dose (mg/kg) Based on 90 Q24h	Based on 120 Q24h
>1.4	60 Q8h or 90 Q12h	90 Q24h	120 Q24h
>1.0 - 1.4	45 Q8h or 70 Q12h	70 Q24h	90 Q24h
>0.8 - 1.0	50 Q12h	50 Q24h	65 Q24h
>0.6 - 0.8	40 Q12h or 80 Q24h	80 Q48h	105 Q48h
>0.5 - 0.6	60 Q24h	60 Q48h	80 Q48h
≥0.4 - 0.5	50 Q24h	50 Q48h	65 Q48h
<0.4	Not recommended	Not recommended	Not recommended

4.2.4.4 Changes in treatment

If a clinician determines that a patient has active retinitis associated with either a new lesion or movement of a lesion border by more than 750 microns, a patient receiving maintenance therapy with foscarnet may be re-induced at 90 mg/kg every 12 hours for 2 weeks and then returned to the regimen of 90 mg/kg every 24 hours. Alternatively, the patient may be switched to another treatment regimen, chosen according to best medical judgment. It is strongly recommended that patients with progression be maintained on some form of systemic therapy when feasible.

Patients who develop extraocular CMV disease should be treated according to best medical judgment. For specific criteria for confirming a diagnosis of extraocular CMV disease, see the SOCA General Handbook. If a patient becomes pregnant, current treatment may be continued or changed according to best medical judgment; the woman should be advised not to breast-feed.

4.2.5 Other systemic therapies

Use of other, investigational systemic therapies may be permitted. Such therapies will be reviewed as the situations arise.

4.3 Discontinuation of anti-CMV maintenance therapy in HAART responders

It has been reported in several small case series that patients who have substantial improvements in immune function while taking highly active antiretroviral therapy (HAART) may safely discontinue anti-CMV maintenance therapy. Because of the potential for adverse effects with any specific anti-CMV therapy, it is recommended that anti-CMV maintenance therapy be discontinued for patients who are HAART responders (as defined below) during the time when there is evidence of sustained immune reconstitution. However, in selected patients (e.g., those with bilateral foveal-threatening lesions, unilateral blindness, or unilateral foveal-threatening lesions) it may be appropriate, based upon the judgment of the physician and the wishes of the patient, to continue anti-CMV maintenance therapy.

The following guidelines should be used in making decisions about anti-CMV maintenance therapy:

- A patient is considered to have immune reconstitution and to be a candidate for discontinuation of anti-CMV maintenance therapy when the CD4+ T-cell count has risen by a minimum of 50 cells/μL to a level of over 100 cells/μL. Furthermore, because of the lag in the improvement in specific immunity relative to rising CD4+ T-cell counts, the rise in CD4+ T-cell count should be sustained for a minimum of 3 months before discontinuation of anti-CMV maintenance therapy is considered.

- Patient may remain off anti-CMV maintenance therapy until the CD4+ T-cell count falls below 50 cells/μL. Anecdotal evidence has suggested that patients with CD4+ T-cell counts below this level relapse without anti-CMV maintenance therapy.

4.4 Management of neutropenia

If a patient develops grade 3 or 4 neutropenia (i.e., ANC count less than 500 cells/μL), filgrastim therapy should be instituted. The recommended initial dose of filgrastim is 300 μg (1 vial) three times per week. After one week, the ANC level should be checked; the recommended dose modifications are as follows:

- If the ANC level remains at 500 cells/μL or less, the dose of filgrastim should be increased to 300 μg (1 vial) daily. If after 7 days of therapy, the ANC remains at 500 cells/μL or less, the filgrastim dose should be increased to 600 μg (2 vials) daily (maximum dose). If the ANC level is still 500 cells/μL or less 1 week later, treatment with the medication causing the neutropenia should be terminated.

- When the ANC level is > 500 cells/μL, the frequency of filgrastim administration should be reduced on a weekly basis as follows:

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

- If ANC falls to 500 cells/μL or below after dosage reduction, resume the dosage that previously maintained ANC at a level greater than 500 cells/μL and recheck ANC after 1 week. Escalate or reduce doses as described above.

4.5 Concomitant medications

Patients assigned to receive the implant should not receive systemic anti-CMV drugs other than oral ganciclovir unless they develop visceral disease or toxicity or have more than one episode of retinitis progression. Patients assigned to systemic therapy should not receive an implant or intravitreal injections unless they experience treatment toxicity or retinitis progression, and further systemic therapy is considered to be against best medical judgment. Otherwise, there are no formal restrictions on concomitant medications. Other drugs should be used in accordance with accepted prescribing practices. Medical requirements for nephrotoxic medications may necessitate temporary interruption of cidofovir or foscarnet treatment.

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 study. All patients should be on maximum tolerable antiretroviral therapy. As currently practiced, such therapy usually is a combination regimen involving three or more drugs, including at least one protease inhibitor or non-nucleoside reverse transcriptase inhibitor.

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5. Data collection plan

5.1 Data collection schedule

Data will be collected from all patients in the trial according to the schedule presented in Exhibit 1. This represents a data collection schedule, not a patient care schedule. Additional visits for treatment administration (e.g., cidofovir is administered every 2 weeks for maintenance), postoperative checkups following insertion of the ganciclovir implant, adverse events, or other patient care needs should occur as necessary. However, patient data will not be collected at these additional visits, except for information about adverse events. Forms for scheduled study visits will include questions about treatment occurring between these visits.

All baseline examinations for eligibility must be completed within the 5 days up to and including the day of randomization. A patient will not be randomized until these evaluations are completed.

Followup evaluations will be conducted every 4 weeks for 48 weeks following randomization and every 12 weeks thereafter. All patients, regardless of treatment assignment, will have the same data collection schedule. All patients will be followed until death or until a common study closeout, which is planned to occur 24 weeks after randomization of the last patient.

5.2 Ophthalmologic evaluations

Ophthalmologic examinations will be conducted at all scheduled visits, including measurement of intraocular pressure and slit lamp examination for cells and flare in the anterior chamber. Also at all visits, best corrected visual acuity with refraction will be assessed, and fundus photographs will be taken. Visual acuity will be measured using logarithmic visual acuity charts,[25] and fundus photos will be taken using a wide-angle camera such as a Canon 60° camera. (A Topcon camera may be used if prior approval is received from the FPRC. Approval will be based on the ability of clinic photographers to produce adequate photographs with the Topcon.) Visual field examinations will be performed at baseline and every 12 weeks thereafter using the Diabetic Retinopathy Study visual field protocol.[25] Procedures for visual acuity, refraction, fundus photography, and visual fields are described in the SOCA Manual.

Prior to evaluation of the photographs by graders, a technician will screen them for visibility of the ganciclovir implant. When it is detected, the technician will use opaque tape to obscure the affected parts of the photographs. In order to maintain masking, a sample of photographs not

showing the implant (some likely to be in other treatment groups) will be masked in similar fashion, and the graders will be informed of this practice.

5.3 Medical history and physical exam

Each patient will be evaluated for study eligibility prior to being randomized into the trial. Data to be collected include the patient's current level of functioning (Karnofsky score), prior treatment for CMV retinitis, use of anti-CMV prophylactic agents, health history prior to the onset of AIDS, date of AIDS diagnosis, index disease for AIDS diagnosis, history of other opportunistic infections and manifestations of AIDS, and history of treatment for HIV. General health information and data on CMV treatment will continue to be collected throughout the trial at every followup data collection visit. Such data will include the incidence of extraocular CMV disease and other opportunistic infections, changes in study treatment, and health care utilization related to CMV treatment.

5.4 Laboratory studies

The following laboratory assessments will be done at every data collection visit:

- Serum chemistry profile: creatinine, blood urea nitrogen, total bilirubin, sodium, potassium, chloride, bicarbonate, glucose, albumin, globulin, uric acid, phosphate, calcium, alkaline phosphatase, SGOT (AST), and SGPT (ALT).
- Hematology profile: CBC with differential and platelet count.
- Urinalysis: specific gravity, pH, glucose, blood/hemoglobin, and protein.

Urine protein and serum creatinine tests will be done within 48 hours of all cidofovir infusions.

Blood and urine will be collected for CMV culture at baseline. T-cell subset analysis will be conducted at baseline and every 12 weeks thereafter. Blood specimens will be collected for plasma banking at baseline, 4 weeks and 12 weeks, and every 12 weeks thereafter. CMV load will be assessed by quantitative PCR from all banked plasma specimens. All specimens except those collected at 4 weeks also will be analyzed for HIV load. In addition, banked plasma specimens may be used for other studies.

The amount of blood collected at any one study visit for laboratory studies should not exceed 50 mL. The amount of blood for serum chemistry, hematology, and T-cell subset analysis is restricted to a total for all three tests of no more than 24 mL. Tubes of blood collected for CMV and HIV load should be filled to capacity.

5.5 Quality of life

A questionnaire will be used to measure health status and qualitative vision assessment at baseline, 4 weeks after randomization, and at 12-week intervals after randomization. The questionnaire was developed from the Medical Outcome Study Short-form General Health Survey and includes items relevant to vision and HIV infection.

5.6 Adverse experiences

Data on ocular and other adverse experiences will be logged and submitted with followup data collection forms as these events occur. Certain adverse experiences, as outlined below, are to be recorded on the Adverse Event form and submitted to the CC within 24 hours of the time at which clinic personnel learn about the event. The CC will be responsible for distributing safety reports to SOCA participating sites and for initiating communications with SOCA-related IRBs as appropriate.

All occurrences of endophthalmitis and retinal detachment are to be reported on an Adverse Event form regardless of treatment assignment. Grade 3 and 4 occurrences of vitreous hemorrhage, hypotony, uveitis, and cataract also are to be reported regardless of treatment assignment. For patients who receive ganciclovir implants, grade 3 and 4 occurrences of implant extrusion are to be reported. Definitions and gradings of these ocular complications may be found in the GCCRT Handbook.

Other adverse experiences are to be reported if they are serious or severe (grade 3 or 4) and are thought to be related to CMV disease or treatment for CMV disease. (CMV disease refers to ocular or extraocular disease, and treatment refers to study or non-study treatments for ocular or extraocular CMV disease.) Such adverse reactions include any side effects, injuries, toxicities, or sensitivity reactions. Association with a drug is defined as "a reasonable possibility that the experience may have been caused by the drug" (21 CFR §312.32). An adverse event is considered serious if it: (1) is fatal or life threatening, (2) is permanently disabling, or (3) requires or prolongs a hospitalization. Congenital anomaly, cancer, or overdose are always considered "serious". Severity gradings of many common adverse reactions are defined in the SOCA General Handbook. For events not specifically charted for severity in the SOCA General Handbook, a general guide for estimating the grade level is given therein. Grade 4 events are characterized as involving extreme limitation in activity with significant assistance required or as requiring significant medical intervention/therapy with hospitalization or hospice care probable. Grade 3 events are characterized as involving marked limitation in activity with some assistance usually required or as requiring medical intervention/therapy with hospitalizations possible.

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6. Outcome measures

6.1 Change in visual acuity

Time from baseline until loss of 3 lines (15 letters) or more in best corrected visual acuity is the design outcome measure. Because patients with the intraocular implant may experience some temporary visual acuity loss following surgery, the outcome measure is limited to visual acuity loss occurring at least 4 weeks after randomization.

6.2 Change in visual field

The rate of change in visual field will be expressed as the decrease in the number of total degrees of field per month.[27]

6.3 Mortality

Time to death will be measured from the date of randomization. This measure will be censored at study closeout for patients still living.

6.4 Change in area of retinitis

The percentage of retinal area covered by CMV lesions will be determined by the FPRC every 12 weeks. Graders will use a standardized grid placed over fundus photographs to determine the retinal area covered by CMV lesions. (Retinal involvement in zone 3 will not be evaluated because zone 3 is not depicted completely in fundus photographs.) The rate of change in area of retinitis will be expressed as the percent of total retinal area lost per month.

The edge of a CMV lesion is often difficult to determine. The difficulty arises in part because of the presence of small (110 to 400 μ) white foci of active retinitis ("satellites") surrounded by retina that appears normal in a zone of variable width adjacent to the solid white marginal zone of the lesion. In the assessment of lesion area, the junction of the satellite zone and the normal retina, designated as the "satellite margin," will be used as the lesion border. The satellite zone is often observed to fill in and become solidly involved during the first 2 to 4 weeks

of treatment, thus leading to a false impression of increasing lesion area unless care is taken to include the satellite zone in the lesion area.

6.5 Time to retinitis progression

Time to first progression of retinitis after randomization will be measured by masked readings of fundus photographs by the FPRC. As in the assessment of lesion area, the junction of the satellite zone and the normal retina will be used as the lesion border. The criteria defining retinitis progression are:

- Advancement of the edge of an existing lesion by one-half the diameter of the optic disc (750 μ*) perpendicularly from the edge and along at least a 750 μ border length; or
- Occurrence of a new lesion at least one-quarter disc area in size (if a circle, this is a lesion at least 750 μ in diameter), separate from the previous lesion in the same eye or in a previously uninvolved eye.

6.6 Time to discontinuation of assigned treatment

Time to the discontinuation of assigned treatment will be measured from the date of randomization. This measure will be censored for patients still on assigned treatment at the close of the study.

6.7 CMV and HIV load

Measures of plasma CMV load, adjusted for baseline levels, will be compared between the treatment groups. HIV load will be compared between the treatment groups and, if appropriate, will be used as a covariate in other analyses.

* 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 realistic estimate.

6.8 Other morbidity

The incidence of extraocular CMV disease, other opportunistic infections, and adverse events will be compared between the treatment groups.

6.9 Quality of life

Changes in quality of life measures from baseline will be compared between treatment groups.

6.10 Treatment costs

Treatment costs will include those incurred during the trial in the treatment of both retinitis and extraocular CMV disease as well as costs of the management of complications of therapy. Data collected at scheduled visits on treatment and medical history forms about CMV-related treatment received (including time and personnel required) and tests performed will be used to estimate utilization of resources. Data on adverse events collected at unscheduled visits will contribute additional information to these estimates of resources used. Visits, treatments, tests, and other procedures will be assigned standard costs obtained from sources such as the Resource Based Relative Value Scale and the cost index for Diagnosis Related Groups.

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7. Biostatistics

7.1 Sample size calculations

The sample size of 140 participants (70 per treatment group) is based largely on pragmatic considerations of the availability of patients and resources. The SOCA clinics have seen a marked decrease in the number of CMV retinitis cases since the introduction of HAART. It is projected that 140 patients can be enrolled by July of 2001 given the participation of 20 clinics in this trial.

The minimum detectable differences between the two treatment groups[2] for the outcome of loss of 3 or more lines of visual acuity in eyes with CMV retinitis is an increase from 8.2 months to 14.6 months (relative risk of 0.56). The minimum detectable difference was estimated using event data from the HPMPC Peripheral CMV Retinitis Trial (HPCRT) and the MACRT; the logrank test; two-sided $\alpha = 0.05$; power = 0.80; 20% inflation of the sample size to account for loss to followup and possible heterogeneity of effect among multiple systemic treatments; and 56% prevalence rate of bilateral disease at baseline.

7.2 Data analysis

General analysis principles include the following:

- The primary analysis will be performed according to patients' original treatment assignment (intention-to-treat), regardless of administered treatment.
- All patients, including those who are found to be ineligible after randomization or those who withdrawal from the study, will be counted in their assigned treatment group once that treatment assignment has been revealed.
- All events following randomization will be counted.

Analyses will be done to look for differences in outcome between the two treatment groups. Results of analyses will be presented both unadjusted and adjusted. Covariates to be used for adjusting treatment group effects will include the stratification variables (clinic and stage of disease) and other baseline risk factors chosen using clinical judgment and/or variable selection procedures such as forward selection. Post-randomization confounders, including compliance, will be examined, acknowledging the potential bias of this practice. Analyses by administered treatment will also be performed. Treatment effects will be examined across various subgroups.

Regression models for comparing the two treatment groups with respect to each outcome will be developed as appropriate for each type of outcome. Statistical techniques to be used are Cox regression for time-to-event data such as mortality or loss of 3 or more lines in visual acuity; log-linear models for count data such as adverse events, extraocular CMV, opportunistic infections, hospitalizations, and sepsis; and Generalized Estimating Equations (GEE) for repeated measures of continuous data such as change in CMV load and change in visual fields. Assessment of the fit of the models will be made using residual plots and other measures of goodness of fit.

Standard errors of estimates from the log-linear models will take account of possible over-dispersion with respect to the assumed models. Robust variance estimation techniques for Cox regression and GEE will be employed.

8. Treatment effects and performance monitoring

8.1 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 manufacturers. The members of the PDMB are listed in Appendix B.

Treatment monitoring reports similar to those described by Meinert and Tonascia and developed for trials currently coordinated in the Johns Hopkins Center for Clinical Trials will be used for the GCCRT. Recommendations by the PDMB for continuing, modifying, or stopping the trial will be based upon safety and efficacy issues (e.g., change in visual acuity, area of retinitis, visual field, and CMV load). The PDMB recommendations will be submitted to the SOCA investigators, the NEI, and other collaborators for approval and implementation. The PDMB will meet and review interim data every 6 months, or more often if necessary, throughout the course of the trial.

As has been the practice in other SOCA trials, no formal stopping rule based on p-values is planned. However, such rules may serve as useful guidelines in the decision-making process. Stochastic curtailment approaches (based on conditional power and type I errors) also can be helpful. The PDMB will have the ultimate choice regarding the approaches used for decision-making.

Monitoring of the accumulating data presented semi-annually at PDMB meetings will include treatment group comparisons of baseline characteristics as well as the primary and secondary outcomes using estimates of the difference between the treatment groups and variability of these estimates.

8.2 Performance monitoring

Performance monitoring will include comparisons of enrollment, baseline variables, protocol deviations, and missing data by clinic. Clinic performance data will be presented at both the PDMB and Research Group meetings.

9. Patient rights and responsibilities

9.1 IRB approvals

This protocol will be submitted to the Institutional Review Board (IRB) of participating centers for review and approval. Clinics may not recruit 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.

9.2 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 SOCA CC. 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. As indicated on the consent statement, data also may be released to the pharmaceutical sponsor, the FDA, or other regulatory concerns for monitoring purposes without further 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 additional written consent of the patient.

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10. Biohazards

It is probable that blood 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.

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Exhibit 1. Procedures required at scheduled visits

	Visit code/Target week from randomization															
weeks	BL 0	F1 4	F2 8	F3 12	F4 16	F5 20	F6 24	F7 28	F8 32	F9 36	F10 40	F11 44	F12 48	F13 60	F14 72	F15... 84...
Ophthalmologic exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Visual acuity and refraction	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fundus photography	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Visual field	x			x			x			x			x	x	x	x
Medical history	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x															
CMV cultures of blood and urine	x															
Blood for CMV load*	x	x		x			x			x			x	x	x	x
Blood for HIV load*	x			x			x			x			x	x	x	x
T-cell subsets	x			x			x			x			x	x	x	x
CBC, serum chemistry, urinalysis	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Quality of life	x	x		x			x			x			x	x	x	x

*Specimen collected for plasma banking

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Exhibit 2. Design schematic

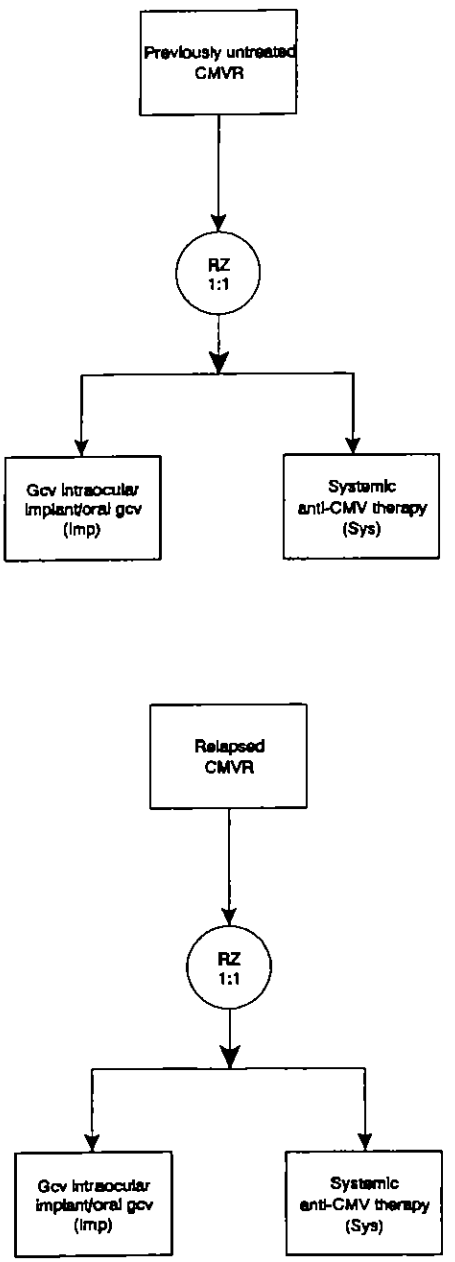

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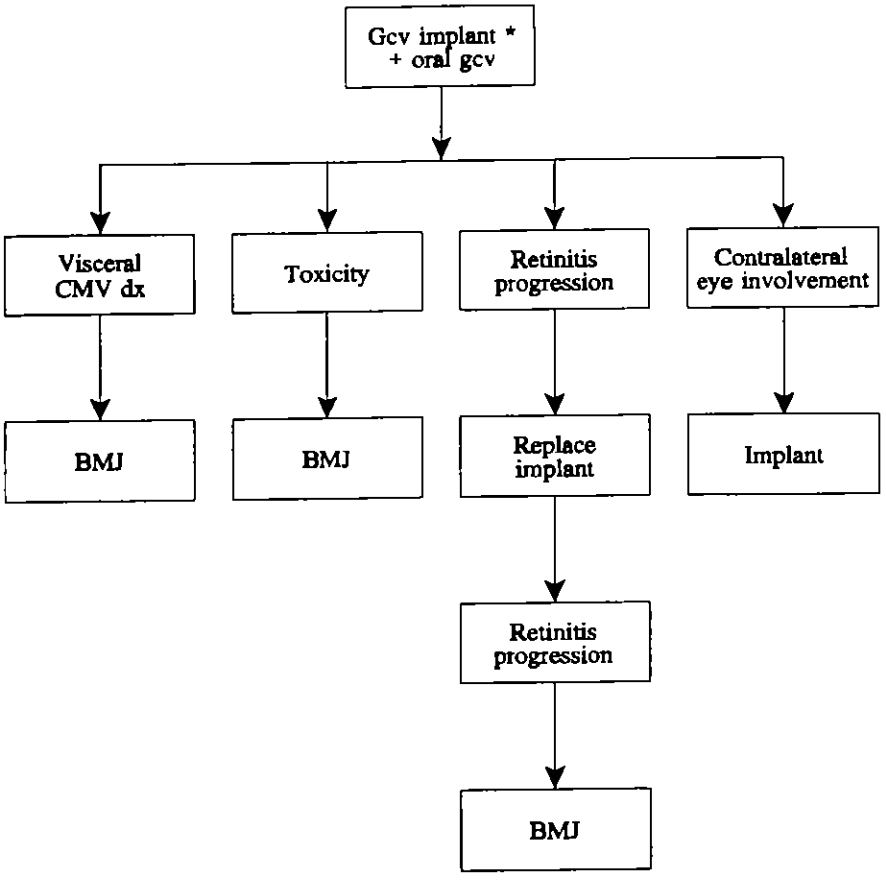
Exhibit 3. Ganciclovir implant treatment algorithm



* Implant to be replaced every 6-8 months unless patient has sufficient immune reconstitution to allow discontinuation of anti-CMV therapy.

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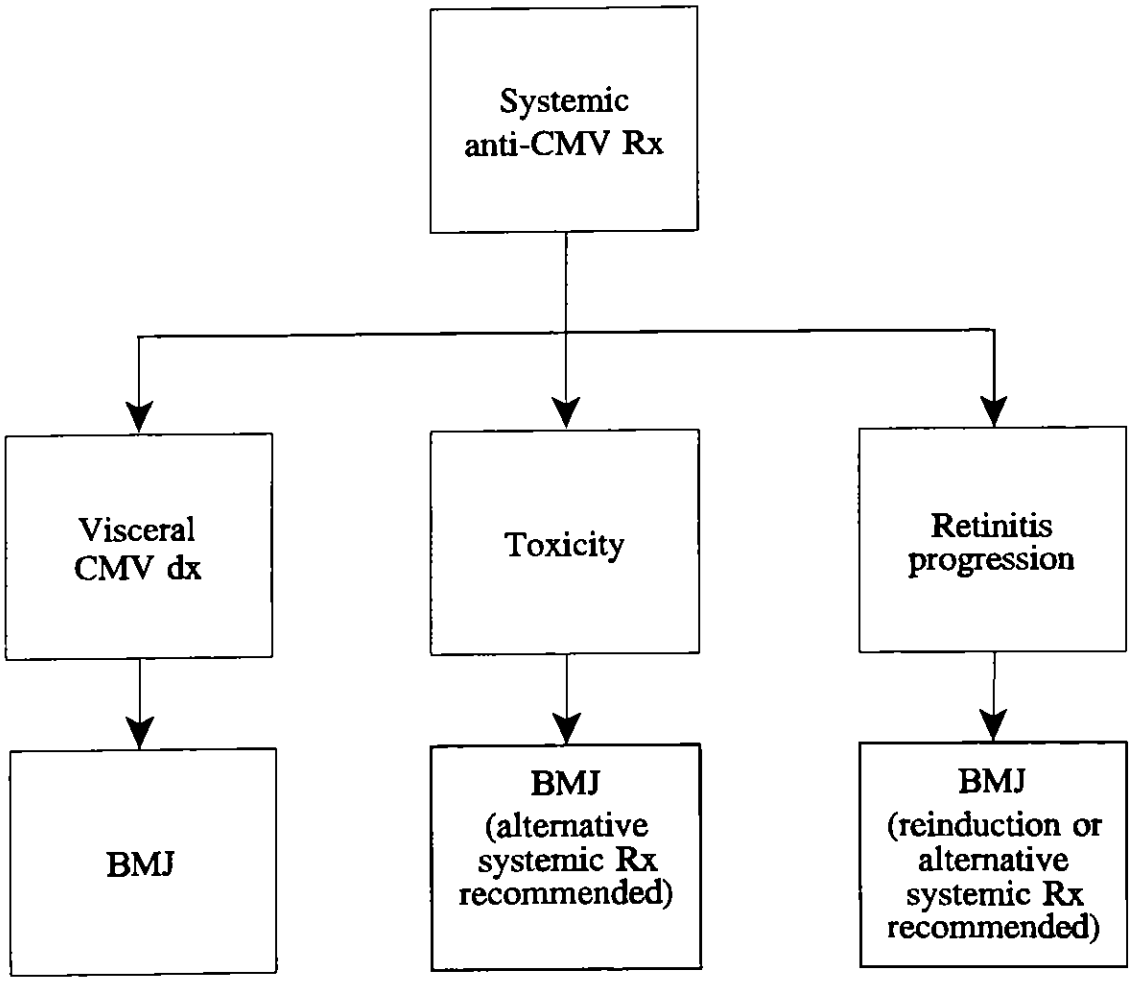
Exhibit 4. Systemic treatment algorithm



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Appendix A: SOCA centers

SOCA ID	Institution	Director
SOCA clinical centers		
BCM	Cullen Eye Institute Baylor College of Medicine Houston, TX	Richard A. Lewis, MD
EU	The Emory Clinic, Inc. Emory University Atlanta, GA	Daniel F. Martin, MD
IU	Indiana University Indianapolis, IN	L. Joseph Wheat, 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
NJMS	Univ of Medicine & Dentistry at New Jersey Newark, NJ	Ronald Rescigno, MD
NU	Northwestern University Chicago, IL	David Weinberg, MD
NYU	Department of Ophthalmology New York University Medical Center New York, NY	Dorothy Friedberg, MD, PhD

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Appendix A: SOCA centers

SOCA ID	Institution	Director
PENN	University of Pennsylvania Medical Center Philadelphia, PA	Charles Nichols, MD
UCI	Department of Ophthalmology University of California Los Angeles, CA	Baruch Kuppermann, MD, PhD
UCLA	Jules Stein Eye Institute University of California Los Angeles, CA	Gary N. Holland, MD
UCSD	Shiley Eye Center University of California San Diego, CA	William R. Freeman, MD
UCSF	Beckman Vision Center University of California San Francisco San Francisco General Hospital San Francisco, CA	Todd Margolis, MD, PhD
UM	Bascom Palmer Eye Institute University of Miami Miami, FL	Janet Davis, MD
UNC	University of North Carolina at Chapel Hill Chapel Hill, NC	David Wohl, MD
USC	Doheny Eye Institute University of Southern California, School of Medicine Los Angeles, CA	Jennifer Lim, MD
USF	University of South Florida Tampa, FL	Peter Reed Pavan, MD
UTMB	University of Texas Medical Branch Galveston, TX	Helen Li, MD
WU	Washington University School of Medicine Saint Louis, MO	*pending*

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Appendix A: SOCA centers

SOCA ID	Institution	Director
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 Photograph Reading Center Department of Ophthalmology University of Wisconsin Madison, WI	Matthew Davis, MD
NEI	Project Office National Eye Institute Bethesda, MD	Natalie Kurinij, PhD
NIAID	ACTG Operations Office National Institute of Allergy and Infectious Disease Rockville, MD	Beverly Alston, MD
Support centers		
Central Specimen Repository	McKesson Bioservices Corporation Rockville, MD	Donald Nolde

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Appendix B: Policy and Data Monitoring Board

Name	Institution/study position
Voting	
John Phair, MD (Chairman)	Infectious Disease Specialist Northwestern University Department of Medicine
Brian Conway, MD	Ophthalmologist University of Virginia Department of Ophthalmology
Barry Davis, MD, PhD	Biostatistician University of Texas School of Public Health
Argye Hillis, PhD	Biostatistician Baylor University Department of Biology
Robert Nussenblatt, MD	Ophthalmologist National Eye Institute
Harmon Smith, PhD	Theologian Duke University Department of Theology
Richard Whitley, MD	Infectious Disease Specialist University of Alabama Departments of Pediatrics, Microbiology and Medicine

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Appendix B: Policy and Data Monitoring Board

Name	Institution/study position
Non-voting	
Beverly Alston, MD	Infectious Disease Specialist NIAID
Matthew Davis, MD	Ophthalmologist FPRC Director
Douglas Jabs, MD, MS	Ophthalmologist Study Chairman
Natalie Kurinij, PhD	Project Officer NEI
Curtis Meinert, PhD	Biostatistician CC Director
James Tonascia, PhD	Biostatistician CC Deputy Director

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Appendix C: Design summary

Title

- Ganciclovir-Cidofovir CMV Retinitis Trial (GCCRT)

Objective

- In patients with AIDS and CMV retinitis, compare the efficacy and safety of aggressive local therapy with the ganciclovir implant plus oral ganciclovir to systemic therapy with any of several available treatment regimens

Type of study

- Randomized, parallel treatment design
- Multicenter
- Fixed sample size, 70 per group
- Phase 4

Stratification

- Clinic
- Stage of disease: newly diagnosed or relapsed

Treatment groups

- Ganciclovir intraocular implant and oral ganciclovir (Imp)
- Systemic therapy (Sys)

Outcomes

- Design variables:
  - Decrease of ≥ 3 lines (15 letters) from baseline in best corrected visual acuity as measured by the ETDRS method
  - Rate of loss of visual field
- Other variables:
  - Mortality
  - Change in area of retinitis
  - Time to progression
  - Time to discontinuation of assigned treatment
  - Blood CMV and HIV load
  - Other morbidity: extraocular CMV and adverse events
  - Quality of life
  - CMV treatment-related costs

Masking

- Masked reading of fundus photographs

Sample size calculation for loss of visual acuity

- Assumptions:
  - α=0.05 (two-sided)
  - power (1-β)=0.80
  - 4-yr accrual period (2.4 patients per month in the first two years and 3.6 patients per month in the last 2 years)
  - 6 months of followup after the last patient is accrued
  - loss to followup and heterogeneity of effect among systemic treatments requiring 20% inflation of sample size
  - median time to loss of $\geq$ 3 lines of visual acuity equal to 8.2 months for patients receiving systemically administered therapy (MACRT)
- Sample size: 70 per treatment group, total of 140 patients
- Detectable differences: increase in median time to visual acuity loss from 8.2 to 14.6 months (RR=0.56)
- Method: log rank

Inclusion criteria

- Age 13 years or older
- Diagnosis of AIDS according to current Centers for Disease Control and Prevention (CDC) definitions
- Diagnosis of active CMV retinitis by SOCA-certified ophthalmologist
- Best corrected visual acuity of ≥20/100 (≥50 standard letters on an ETDRS chart) in at least one eye affected by CMV retinitis
- At least one lesion 750μ or greater in an eligible eye that can be photographed
- Karnofsky score of 60 or greater
- Absolute neutrophil count (ANC) of 750 cells/μL or greater
- Platelet count of 50,000 cells/μL or greater
- Willingness of all men and women of childbearing potential to practice adequate birth control to prevent pregnancies during the study and for 3 months afterwards
- Willingness and ability, with the assistance of a caregiver if necessary, to comply with treatment and followup procedures
- Collection of all baseline data within 5 days prior to randomization
- Signed consent statement

Exclusion criteria

- Media opacity that precludes visualization of the fundus of all otherwise eligible eyes
- Treatment with the ganciclovir implant within 9 months prior to study entry
- Unwillingness to refrain from breast-feeding during the study and for 3 months afterwards
- Medical problems or drug or alcohol abuse sufficient to hinder adherence to treatment or followup procedures

Treatment administration

- Imp: Ganciclovir intraocular implant every 6-8 months and oral ganciclovir at 1 gm 3 times a day
- Sys: Systemic anti-CMV therapy given at approved doses; combination therapies may be given to patients who have relapsed disease

Changes in treatment

- For ganciclovir implant group:
  - Patients who develop contralateral disease will have the implant inserted in the newly involved eye
  - Patients who have two progressions while implant(s) in place will be treated according to best medical judgment
  - Patients who have unmanageable toxicity will be treated according to best medical judgment
- For systemic therapy group:
  - Patients who progress while receiving treatment may be reinduced with the same treatment or switched to another treatment, according to best medical judgment; it is strongly recommended that patients remain on a systemic form of treatment
  - Patients who experience treatment-related toxicity may be switched to another treatment according to best medical judgment; it is strongly recommended that patients remain on a systemic form of treatment
- Patients in either group will be treated according to best medical judgment if the patient:
  - Develops extraocular CMV (must be confirmed)
  - Becomes pregnant

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Cessation of CMV treatment in HAART responders

Guidelines for the cessation of specific anti-CMV treatment are:

- Stopping treatment may be considered for patients who have been on HAART for a minimum of 3 months and who have a CD4+ cell count of 100 or greater
- Reinstitution of treatment is recommended for patients whose CD4+ cell count falls below 50

Data collection

- Ophthalmologic exam, best corrected visual acuity, refraction, fundus photographs, CBC, serum chemistry, urine chemistry, and medical history (including incidence of extraocular CMV disease and other opportunistic infections, changes in study treatment, and health care utilization related to CMV treatment) at every study visit
- Visual fields at baseline and every 12 weeks thereafter
- Blood CMV load at baseline, at 4 weeks and 12 weeks, and every 12 weeks thereafter
- Blood HIV load at baseline and every 12 weeks thereafter
- Lymphocyte analysis at baseline and every 12 weeks thereafter
- Blood and urine CMV cultures and physical exam at baseline
- Quality of life assessment at baseline, 4 weeks, 12 weeks, and every 12 weeks thereafter

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Appendix D: GCCRT consent statement

People with AIDS often get an infection in their eyes due to cytomegalovirus (CMV). The infection is called CMV retinitis. It can cause loss of sight. However, treatment can help prevent loss of sight.

Doctors can use several drugs to treat CMV retinitis. At this time, the drugs include foscarnet, ganciclovir, cidofovir, and formivirsen. Foscarnet is given by daily injections into a vein. Ganciclovir can be given by daily injection, by putting an implant that contains the drug into the eye, or by mouth (pills). The ganciclovir pills are usually given after a patient has had 2 weeks of daily ganciclovir injections or has received the implant. Cidofovir is given by injection into a vein once a week for 2 weeks and then every other week after that. Formivirsen is given by injection into the eye every week or every other week. Other possible treatments for CMV retinitis are experimental. They are being tested in research studies.

1. Reason for study

We are doing a study to compare two ways to treat CMV retinitis. The two ways are 1) treatment with the ganciclovir implant plus ganciclovir pills or 2) treatment with systemic drugs only. (Systemic drugs are those that are injected into a vein or taken by pill.) These ways to treat CMV retinitis are different because one involves surgery to put medicine directly in the eye and the other does not. The implant is a small object that a surgeon inserts in the eye. The implant releases drug slowly for 6 to 8 months. Systemic drugs reach the eye from your blood. They need to be given much more often.

The treatments we are studying are not new. Doctors can prescribe them for anyone who has CMV retinitis. We are studying these treatments because their long-term effects have not been compared. In earlier studies, the implant appeared to control CMV disease within an eye better than other treatments. However, we do not know whether controlling the disease better means that patients actually see better. There are other things we do not know about the treatments. We want to learn about the chance that the retinitis will spread to the other eye. This chance might be greater with the implant plus ganciclovir pills than with treatments given by injection into a vein. An eye problem called retinal detachment might occur more often with the implant. Also, patients with CMV retinitis who respond well to treatments for HIV may not require long-term treatment for their eye disease. They may be able to have systemic CMV treatment for a few months and then stop the treatment. Some doctors and patients may prefer this over eye surgery. Our study will allow us to compare these two ways of treating CMV retinitis.

2. Study plan

We will divide patients who enroll in this study into two groups. Each group will be treated in one of the two ways described above. That is, Group 1 will have surgery to insert the implant. They also will take ganciclovir pills. Group 2 will receive systemic treatment only. The group that a patient is assigned to will be decided by chance, much like flipping a coin. Patients will have an equal chance (1 in 2) of being assigned to either of the treatment groups.

Patients assigned to have eye surgery will have one operation if only one of their eyes has CMV retinitis. They will have two separate operations if both eyes are affected. The patient will receive local anesthesia before surgery to make the area around the eye numb. (The patient may be sedated but is conscious.) The surgery for one eye must take place within 10 days after a patient enrolls. If a patient is to have an implant in the second eye, this surgery must take place within the next 10 days. Patients in Group 1 also are to take ganciclovir pills three times a day.

The implants are to be replaced after 7 months. However, if your retinitis gets worse before this time, the implant will be replaced earlier. If your retinitis keeps getting worse after the implant is replaced, your treatment will be changed. Also, if you have a bad reaction to the implant, your treatment will be changed. In either of these cases, you and your doctor will decide what treatment you should try next.

Patients assigned to receive systemic treatment (Group 2) will decide with their doctor which drug is best for them. Treatment should begin within a few days. In the first few weeks of treatment, all systemic treatments involve injections of the drug (ganciclovir, foscarnet, or cidofovir) into a vein.

Treatment with ganciclovir or foscarnet starts with two injections into a vein every day for 2 or 3 weeks. After that, you usually get just one injection per day. However, if you are taking ganciclovir, you have another option. After the first few weeks of injections, you may take ganciclovir pills three times each day. Foscarnet injections are given with up to 1 liter of fluid (salt water). The fluid helps to prevent damage to your kidneys. Treatment with ganciclovir or foscarnet takes about 2 hours for each injection.

Cidofovir injections are given once per week for the first 2 weeks and then every other week after that. Before each cidofovir treatment you will need to have about 1 liter of fluid injected into a vein. Also, before and after the injection, you will need to take probenecid pills. The pills and fluid help to prevent damage to your kidneys. It takes about 3 hours to inject the medicine and fluid into your vein.

If you are assigned to Group 2 and your retinitis gets worse during treatment, you and your doctor have several choices. You may continue treatment with the drug you are taking, add another drug to your treatment, or change to another systemic treatment. If you continue with your treatment, you will get injections more often for a few weeks, like you did when you first started the treatment. If you have a bad reaction to a treatment, you may need to stop treatment for a short time. Or your doctor may change the dose of your treatment. If you need to switch to a new treatment, you and your doctor will decide what new treatment is best for you.

If you respond well to treatments for HIV, your CMV retinitis may become inactive. If so, you and your doctor may decide to stop your retinitis treatment. Your response to HIV therapy will be measured by your CD4+ T-cell counts. To check on your CMV retinitis, your doctor will look into your eyes and take pictures of the inside of your eyes. If you have an implant, stopping treatment means that the implant will not be replaced after it has run out of drug. You also will stop taking your ganciclovir pills. If you stop systemic treatment, you will stop getting injections or stop taking pills. Even if you stop treatment, we still want you to return for study visits. If your retinitis becomes active again, you will need to restart treatment.

3. Study visits and procedures

We will schedule you to come to the clinic for regular visits if you enroll in this study. Visits will be once every month for the first year and every 3 months after that. You or the clinic staff can schedule other visits if you need them. We expect the study to last about 2 years.

Each scheduled visit will involve an eye exam. For each eye, we also will take fundus photographs (pictures of your retina) and measure your visual acuity (how well you can see an eye chart). For the eye exam and fundus photographs, we need to give you eye drops to dilate your eyes. Afterwards, you will not be able to drive, read, or watch television for about 2 hours, sometimes longer. You will need to plan for getting home after the visit. Some visits will involve measuring your visual field (your ability to see things that are not directly in front of you). These procedures are part of regular medical care for someone who has retinitis. They are not extra procedures done just for this study.

At each visit we also will ask you questions about your health and the medicines you are taking. We will collect 1 to 3 tablespoons of blood. A blood specimen will be sent to a central facility for storage. In the future that specimen may be tested for viruses. It also may be tested for other things related to CMV or HIV infections. The first visit also will include a general physical exam.

4. Risks and benefits

All drugs have side effects. Patients and their doctors must weigh the risks of taking a drug against the possible benefits of treatment.

Most patients who have the ganciclovir implant put in their eye(s) have a short-term decrease in their vision after surgery. Vision usually improves in 2 to 4 weeks. In addition, surgery to place the implant into the eye can sometimes lead to other problems. These problems include infection or inflammation in the eye, detachment of the retina, or cataract.

The most common side effect of ganciclovir injections or pills is a decrease in blood cells, especially white blood cells. A decrease in white cells occurs in about 33% of people taking ganciclovir. This side effect is even more common when patients take ganciclovir and AZT at the same time. Having low white blood cell counts may increase a patient's risk of infection. A decrease in platelets occurs in about 20% of people taking ganciclovir. Low counts of platelets or other types of blood cells may cause weakness, fatigue, and sometimes severe bleeding. If these side effects occur, the doctor starts other treatment to help increase the patient's blood cell counts. If the blood cell counts do not go back up, the CMV treatment will be changed or stopped. It is not known whether ganciclovir causes cancer in humans, but this is a possible side effect. The drug has caused cancer in mice and rats. Researchers have found tumors in these animals when using doses both higher and lower than the doses used in humans.

About 30% of people taking foscarnet have decreased kidney function. Kidney function is measured by checking the levels of certain substances in the blood. If this side effect occurs, the doctor will reduce the dose of foscarnet. About half (50%) of people who take foscarnet have changes in the levels of certain minerals in their blood. (The minerals are calcium, magnesium, and phosphate.) However, only a small percentage (5%) have large changes in the mineral levels. Symptoms of large changes in mineral levels include tremors, tingling and numbness in the hands and feet, cramps, and sometimes seizures. Your doctor will prescribe mineral supplements or other kinds of treatments if necessary. A decrease in red blood cells (anemia) occurs in about one-third (33%) of people taking foscarnet. Anemia causes people to feel tired. It can be treated with drugs to increase red blood cell levels. In severe cases, it can be treated with blood transfusions. Other side effects are uncommon, occurring in less than 10% of patients treated with foscarnet. These side effects include inflammation of veins, nausea and vomiting, headache, and fatigue.

The most serious side effect of cidofovir is kidney damage. About 25% of people treated with this drug have had signs of kidney damage. When kidney damage occurs, it can be severe and may not go away. Patients getting cidofovir will also receive a drug called probenecid to reduce the chance of kidney damage. Probenecid may have side effects, which include skin rashes, fever, nausea, vomiting, and low blood pressure. Some people develop allergies to

probenecid. Other possible side effects of cidofovir include damage to the heart, inflammation and low pressure inside the eye, and low blood cell counts. Inflammation and low pressure inside the eye can result in a loss of vision. Low blood cell counts may increase the risk of infection. In addition, some patients have reported hair loss, headache, nausea, vomiting, and diarrhea. It is not known whether cidofovir causes cancer in humans, but this is a possible side effect. Cidofovir injected under the skin or into a vein has caused cancer in mice and rats. Researchers have found tumors in these animals when using doses both higher and lower than the doses used in humans.

The effects of ganciclovir, foscarnet, and cidofovir on the human egg, sperm, or unborn child are not known. Both women and men should practice active birth control methods while enrolled in this study. If you become pregnant, you and your doctor will decide whether to change your treatment. Women who are breast feeding cannot take part in this study.

The risks of using a vein to take blood samples or to give treatment are small. They include pain, infection, and redness, swelling, and bruises where the needle is put through the skin.

You may benefit from the care you will receive if you join the study. You and your doctor(s) will get the results of all of your tests. The eye exams and fundus photographs will allow us to watch your disease closely. This care may give you a better chance to preserve your sight. The treatments may stop the infection from spreading within your eye or to other parts of your body. Beyond that, you may help to improve treatments for other people with AIDS and CMV retinitis.

You may choose not to be in this study. You also may get out of the study at any time. If you choose not to be in the study, this choice will not affect your medical care. You may receive one of the treatments we are studying without being in the trial, or you may take part in another study.

5. Rights and responsibilities

All people who take part in this study have certain rights and responsibilities. Your rights include the following:

- The choice to enter the study is up to you.
- You can leave the study at any time and still get the same quality of medical care at this institution. However, we will still want to find out how you are doing even if you withdraw. Knowing the status of all patients at the end of the trial is important.
- Clinic staff will answer any questions or discuss concerns you may have now or in the future.

People who enroll in this study also have certain responsibilities. The success of the trial depends on patients coming to the clinic for regular visits. Regular visits are important so that we can collect the data needed to compare the treatments. You will be asked to:

- Come to the clinic for regular visits as scheduled.
- Work with clinic staff to complete the trial procedures and to provide information about your health.
- Tell clinic staff about changes in your address and phone number.
- Tell clinic staff if you become pregnant.

If you know now that you will not be able to do these things, you should not join the study.

6. Privacy and confidentiality

Every effort will be made to protect your privacy and to keep your data confidential.

- We will use a number and a 5-letter code, only, to identify your study records. We will collect personal information (home and work addresses and phone numbers and the names of two friends or relatives). However, these will not be entered into the data files used for this study.
- Only study personnel will have access to your data.
- We will not identify you or give data about you to anyone outside the study without your written consent. However, the companies that make the drugs or the FDA may review your medical record. This part of their duty to evaluate the treatments used.
- We will not identify you when we publish the results of the study.

7. Other things to consider

The study treatments and other costs for your care will be billed to you and/or your insurance company (or Medical Assistance). At the close of the trial, we will tell you how well the study treatments worked. Then you and your doctor can make choices about your future treatment.

8. Consent

Before you agree to enroll, make sure that you have answers to all your questions about the trial. The principal investigator, Dr. _____, and the clinic staff at _____ (phone number) will answer any questions you have about this study, now or later. If you believe that you have been injured by taking part in the study or that you are not being treated fairly, you may contact the person named above. You also may contact the _____ (name of IRB and Institution) at _____ (phone number) or The Johns Hopkins University's Office for Research Subjects at (410) 955-3193. Either the principal investigator or the people in the offices named above will answer your questions. If necessary, they will help you get medical care if you feel you have been injured in the study.

GCCRT Ganciclovir-Cidofovir

Appendix D: GCCRT consent statement

The purpose of this study has been explained to me. I have had my questions answered. I understand that if I have questions later on, I can contact a clinic staff member at _____ (phone number). I agree to participate in the study.

_____ / / Clinic ID code: __ __ __ __
Participant's signature Date

Patient ID#: __ __ __ __

_____
Print participant's name

Patient name code: __ __ __ __ __

_____ / /
Witness to consent procedure Date

_____
Print witness' name

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Appendix E: GCCRT assent statement for ages 16 and 17

This assent statement is for patients who ages 16 or 17. A parent or guardian of the patient should read and sign the consent statement before the patient is enrolled.

You have an eye infection called CMV retinitis. Your doctor can prescribe several treatments for it. Some involve getting shots into a vein or taking pills. Others involve putting medicine directly in the eye. We are not sure which way of treating CMV retinitis is the best. We are doing a study to compare these two types of treatment to learn whether one works better than the other. If you agree to be in this study, you will be assigned to one of these two types of treatment. Which one you get will be picked by chance, like flipping a coin.

One of the treatment methods involves having an eye operation and taking pills. In the operation, a surgeon puts an implant that contains medicine into your eye. (If you have retinitis in both eyes, an implant will be placed in each eye.) Your eye(s) will be made numb for the surgery. The surgeon will put a new implant into your eye after 7 months or if your eye disease gets worse. You also will take pills three times a day. The medicine in the implant and in the pills is called ganciclovir. If you have a bad reaction to the implant or the implant does not work in your eye, your treatment will be changed. You and your doctor will decide what new treatment is best for you.

The second treatment method involves getting shots of medicine into a vein. The medicine could be any of three drugs: ganciclovir, foscarnet, or cidofovir. Ganciclovir and foscarnet shots are given twice a day for the first 2 weeks. Cidofovir shots are given once a week for the first 2 weeks. After these first 2 weeks, you will either have more shots into a vein of the same medicine, or you will take ganciclovir pills. If you continue to get ganciclovir or foscarnet shots, they will be given once a day. If you continue to get cidofovir shots, they will be given once every 2 weeks. It takes a few hours to give each shot of ganciclovir, foscarnet, or cidofovir. The medicine must be given along with fluid (salt water) injected into a vein.

If you are getting shots or taking pills and your retinitis gets worse, you and your doctor will decide whether you should keep taking the same drug, add another drug, or switch to another treatment. If you keep taking the same drug, you will need to get shots more often for a few weeks, like you did when you first started the treatment. If you have a bad reaction to the drug, your doctor will treat the problem, and may switch you to another treatment. Your doctor will consider other treatments that are given as shots or pills. You and your doctor will decide what new treatment is best for you.

Some patients need to stay on CMV treatment for the rest of their lives. Others may be able to stop CMV treatment after a few months. Those who can stop CMV treatment are patients who respond well to treatments for their HIV. If you respond well to HIV treatment, your doctor will talk with you about stopping CMV treatment. However, if your CMV retinitis becomes active again, you will need to restart treatment.

GCCRT Ganciclovir-Cidofovir

You will need to come to the clinic for checkups once a month for the first year and every 3 months after that. On the first visit, a doctor will examine your whole body. At every checkup, we will take pictures of the inside of your eyes, test your vision, and do blood tests. The blood tests will require about 2 to 3 tablespoons of blood. We also will ask you questions about your health and the medicines you are taking.

All treatments have side effects. You and your doctor must weigh the risks of side effects against the possible benefits of treatment.

If you have an implant put in your eye(s), you most likely will not see as well right after the surgery. Your vision should improve in 2 to 4 weeks. Also, the eye surgery sometimes causes problems that affect your vision and require more treatment. Such problems include infection, retinal detachments, and cataracts.

The most common side effects of ganciclovir when given by injection into a vein or taken by pill are low blood cell counts. Low blood cell counts can lead to infection, severe bleeding, weakness, or fatigue. If your blood cell counts are low, the doctor will give you medicine to help increase your blood cell counts. If your blood cell count does not go back up, you will stop taking ganciclovir.

The most common side effect of foscarnet, a drug given into a vein, is decreased kidney function. You will receive fluid injected into your vein along with the drug to help prevent kidney damage. If this side effect occurs, your doctor will reduce your dose of foscarnet or switch you to another treatment. Some people have changes in the levels of certain minerals in their blood. Also, some have a decrease in red blood cells (anemia). Anemia causes people to feel tired all the time. Your doctor will watch your mineral levels and blood cell counts. He or she will prescribe medicines to help with side effects if necessary.

The most serious side effect of cidofovir, another drug given into a vein, is kidney damage. About 25% of people treated with this drug have had signs of kidney damage. Sometimes the kidney damage is severe and does not go away. If you get this drug, we will try to prevent kidney damage. We will inject fluid into your vein before and after you receive the drug. Giving fluid helps to "flush" your kidneys. We also will give you pills before and after your injection that help the kidneys. These pills are called probenecid. Probenecid sometimes causes skin rashes, fever, nausea, and vomiting. Some people are allergic to it.

Some of the drugs used to treat CMV retinitis have caused cancer in mice and rats. We do not know whether they can cause cancer in people, but this is a possible side effect of the treatments. The drugs also may affect eggs, sperm, or a developing fetus. If you have sex, you should practice safe sex. If a woman becomes pregnant, she and her doctor will decide whether to change her treatment.

Using a vein to take blood samples or to give treatment has some risks. The risks include pain, infection, and redness, swelling, and bruises where the needle is put through the skin.

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Appendix E: GCCRT assent statement for patients ages 16 and 17

You may benefit from the care you will receive. We will examine your eyes and take pictures of them to watch your disease. This may give you a better chance to preserve your sight. The treatments we use may stop the infection from spreading within your eye or to other parts of your body. Also, you may help to improve treatments for other people with AIDS and CMV retinitis.

You may choose not to be in this study. You also may get out of the study at any time. At any time you may ask the doctors or clinic staff at this center doing the study questions. They include Dr._____ or _____ . If you choose not to be in the study, it will not affect your usual medical care. No one involved in running the study will be angry with you.

We would like you to discuss this study with others before you decide whether to take part in it. If you want, you can get more details about the study from the Consent Statement.

_____ ___/___/___ Clinic ID code: ___ ___ ___ ___

Signature of patient Date

Patient ID#: ___ ___ ___ ___

Patient name code: ___ ___ ___ ___ ___

FOR GCCRT STAFF ONLY:
I have reviewed the contents of the Informed Consent Statement with _____ at his or her level of understanding. I feel he or she understands the study requirements.

_____ ___/___/___

Signature of GCCRT staff member Date

GCCRT Ganciclovir-Cidofovir

Appendix F: GCCRT assent statement for ages 13 to 15

This assent statement is for patients who are ages 13 to 15. A parent or guardian of the patient should read and sign the consent stateent before the patient is enrolled.

You have an eye infection called CMV retinitis. Your doctor can give you different drugs for it. Some drugs are given as shots into a vein or as pills. Others involve putting drug directly in the eye. We are not sure which is the best way. We are doing a study to compare these two ways. If you agree to be in this study, you will be assigned to one of the two ways, getting shots or putting drug in the eye. The one you get will be picked by chance, like flipping a coin.

Putting drug in the eye requires having an eye operation. A surgeon puts an implant that contains a drug into your eye. (If you have infection in both eyes, an implant will be placed in each eye.) Your eye(s) will be made numb for the surgery. You also will take pills three times a day. The drug in the implant and in the pills is called ganciclovir. The surgeon may replace the implant after 7 months. If you have a bad reaction to the implant or the implant does not work in your eye, your treatment will be changed. You and your doctor will decide what new treatment is best for you.

Three different drugs can be given by shots into a vein. You and your doctor will decide which drug to use. The three drugs are: ganciclovir, foscarnet, and cidofovir. Ganciclovir and foscarnet shots are given twice a day for the first 2 weeks. Cidofovir shots are given once a week for the first 2 weeks. After these first 2 weeks, you may have more shots into a vein of the same drug, or start to take ganciclovir pills. Ganciclovir or foscarnet shots will be given once a day after the first 2 weeks. Cidofovir shots will be given once every 2 weeks after the first 2 weeks. Ganciclovir pills are given 3 times a day. It takes a few hours to give each shot of ganciclovir, foscarnet, or cidofovir. The shot must be given along with fluid (salt water) injected into a vein.

If your retinitis gets worse while you are getting the shots or taking the pills, you and your doctor will decide what to do. You may keep taking the same drug or change to another drug. If you have a bad reaction to the drug, your doctor will treat the problem. Your doctor also may change you to another drug. Your doctor will give you another drug that is given as shots or pills.

Some patients need to stay on a CMV drug for the rest of their lives. Others may be able to stop drug after a few months. Patients who respond well to treatments for their HIV may be able to stop taking CMV drug. If you respond well to HIV treatment, your doctor will talk with you about stopping your CMV drug. However, if your CMV retinitis becomes active again, you will need to start taking CMV drug again.

You will need to come to the clinic for checkups once a month for the first year. The checkups are every 3 months after the first year. At every visit, we will take pictures of the inside of your eyes, test your vision, and do blood tests. The blood tests will require about 2 to 3 tablespoons of blood. We also will ask you questions about your health and the medicines you are taking.

GCCRT Ganciclovir-Cidofovir

Appendix F: GCCRT assent statement for ages 13 to 15

All drugs have side effects. You and your doctor must weigh the risks of side effects against the possible benefits of taking the drug.

If you have an implant put in your eye(s), you will not see as well right after the surgery. Your sight should improve in 2 to 4 weeks. Eye surgery sometimes causes problems that affect your sight. These problems may require more treatment. Such problems include infection, retinal detachments, and cataracts.

The most common side effects of ganciclovir shots or pills are low blood cell counts. Low blood cell counts can lead to infection, severe bleeding, weakness, or fatigue. If your blood cell counts are low, the doctor will give you medicine. If your blood cell count does not go back up, you will stop taking ganciclovir.

The most common side effect of foscarnet is decreased kidney function. Fluid will be injected into your vein with the drug to help prevent that. If this side effect occurs, your doctor will lower the dose of foscarnet or give you another drug. Some people have changes in the levels of certain minerals in their blood. Also, some have a decrease in red blood cells (anemia). Anemia causes people to feel tired. Your doctor will check your mineral levels and blood cell counts. He or she will prescribe drugs to help with side effects if needed.

The most serious side effect of cidofovir is kidney damage. About 25% of people treated with this drug have had signs of kidney damage. Sometimes the damage is severe and does not go away. We will try to prevent kidney damage. We will inject fluid into your vein before and after you receive the drug. We also will give you pills that help the kidneys. These pills are called probenecid. The pills sometimes causes skin rashes, fever, upset stomach, and vomiting. Some people are allergic to it.

Some of the drugs used to treat CMV retinitis have caused cancer in mice and rats. We do not know if they cause cancer in people. The drugs also may affect eggs, sperm, or an unborn baby. If you have sex, you should practice safe sex. If a woman gets pregnant, she and her doctor will decide if her treatment should be changed.

Using a vein to take blood samples or to give treatment has some risks. The risks include pain, and infection. There may be redness, swelling, and bruises where the needle is put through the skin.

You may benefit from the care you will receive. We will examine your eyes and take pictures of them to watch your disease. This may give you a better chance to save your sight. The drugs we use may stop the infection from spreading in your eye or to other parts of your body. Also, you may help to improve treatments for other people with AIDS and CMV retinitis.

You may decide not to be in this study. You also may get out of the study at any time. At any time you may ask the doctors or clinic staff at this center questions. They include Dr._____ or _____. If you decide not to be in the study, it will not affect your medical care. No one involved in the study will be angry with you.

GCCRT Ganciclovir-Cidofovir

Appendix F: GCCRT assent statement for ages 13 to 15

We would like you to discuss this study with others before you decide to take part in it. If you want, you can get more details about the study from the Consent Statement.

_____ ___/___/___ Clinic ID code: ___ ___ ___ ___

Signature of patient Date

Patient ID#: ___ ___ ___ ___

Patient name code: ___ ___ ___ ___ ___

FOR GCCRT STAFF ONLY:
I have reviewed the contents of the Informed Consent Statement with _____ at his or her level of understanding. I feel he or she understands the study requirements.

_____ ___/___/___

Signature of GCCRT staff member Date
