Studies of Ocular Complications of AIDS

SOCA

A Phase II/III Trial of Human Anti-CMV Monoclonal Antibody MSL 109 (MACRT)

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Document history

Version 1 (26 April 1995)

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§4.2.3 CMV viral load: Addition of two 5 mL blood specimens that will be banked for further assays.

§6.1 Data collection schedule: The schedule has been changed from one based on months to one based on weeks. Followup visits will be scheduled every 4 weeks for 48 weeks, then every 12 weeks thereafter.

§6.1 Data collection schedule: Deletion of the requirement for laboratory studies (hematology and serum chemistry) to be done in the 24 hours preceding each treatment. Laboratory studies are required as a part of each scheduled study visit.

§6.2 Ophthalmologic evaluations: The schedule for visual acuity assessments has been changed from every 12 weeks to assessments at every study visit. The schedule for SOCA-style refraction remains once every 12 weeks.

§6.6 Laboratory studies: Blood collections for measurement of MSL 109 and antibodies to MSL 109 levels have been added. Blood (10 mL) will be collected at baseline, 4 weeks (F01), 12 weeks (F03), 24 weeks (F06), 36 weeks (F09), 48 weeks (F12) and every 12 weeks thereafter (all subsequent followup visits). Specimens for antibody assays will be collected on all patients enrolled in the trial. Specimens will be shipped to University of Texas, Galveston for analysis. Instructions as to amount of blood collected for antibody and CMV viral load assays, conditions of specimen treatment, packaging and shipping have been added.

Source documents

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

- AIDS Clinical Trials Group (ACTG) Protocol: A phase II, double-masked, randomized, placebo controlled evaluation of standard therapy vs standard therapy combined with human monoclonal anti-cytomegalovirus antibody (MSL 109) in the therapy of AIDS patients with cytomegalovirus (CMV) retinitis (ACTG 266)

- Studies of Ocular Complications of AIDS (SOCA) Protocol: HPMPC Peripheral CMV Retinitis Trial (HPCRT) (ACTG 281)

- Studies of Ocular Complications of AIDS (SOCA) Protocol: CMV Retinitis Retreatment Trial (CRRT) (ACTG 228)

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Contents

Abstract

The primary objective of the Monoclonal Antibody CMV Retinitis Trial is to compare the safety and efficacy of Human Anti-CMV Monoclonal Antibody versus matched placebo plus active primary treatment, for both newly diagnosed and relapsed CMV retinitis in patients with AIDS.

The trial is designed with a sample size of 325 patients. Interim results of the trial will be reviewed by the Policy and Data Monitoring Board. One of the interim reviews is planned to take place after enrollment and followup of the 76th patient for 24 weeks, and will use, along with other data, results of CMV DNA PCR determinations. The design variable for the overall trial is time to progression of retinitis. Additional outcome measures include mortality, adverse events, change in visual acuity, and change in visual fields.

The two, 1:1 random assignment, treatment groups and their respective treatment administration are:

- MA+: 60 mg MSL 109, intravenously every 2 weeks, concurrent with active primary treatment for CMV retinitis

- Plbo+: matched placebo for MSL 109 every 2 weeks, concurrent with active primary treatment for CMV retinitis

1. Introduction

1.1 Cytomegalovirus infection in AIDS patients

Cytomegalovirus (CMV) is a common opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS).[9,11,13,14,16,17,18,20,21,31,39,42,43] In the era of prophylaxis for *Pneumocystis carinii pneumonia* (PCP) CMV disease rates are estimated to be as high as 45%.[16] End organ disease includes retinitis, pneumonitis, colitis, and esophagitis. Among these syndromes, retinitis may account for up to 85% of CMV disease in patients with AIDS.[11] Although CMV retinitis tends to present as a relatively late manifestation of AIDS (generally occurring in patients with CD4+ cell counts < 100 cells/μL), it is occasionally the initial clinical manifestation of AIDS.[17,40] Peng et al estimate that of patients with CD4+ counts of less than 100, prophylaxed for PCP and treated with AZT, 22% will develop CMV retinitis within three years of AIDS diagnosis.[41] CMV retinitis is the most easily diagnosed and quantified of the CMV end organ diseases, therefore providing a target amenable to the testing of anti-CMV compounds.[30]

1.2 Current treatment for CMV retinitis

Two drugs have been licensed by the Food and Drug Administration for the treatment of CMV retinitis, ganciclovir [Cytovene®, Syntex Laboratories: nine-(1,3-dihydroxy-2-propoxy) methylguanine][9,14,15,17,18,19,31,32,39,42,46,49,55] and foscarnet [Foscavir®, Astra USA, Inc: trisodium phosphonoformate].[25,38,54] Both have been shown to be effective in delaying progression of retinitis. In the Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial (FGCRT), the two drugs showed similar efficacy in controlling retinitis; median time to progression was 53 days for foscarnet and 47 for ganciclovir.[51] Progression ultimately ensues, despite use of either agent.[51,52]

Intravenous ganciclovir is normally administered in two dosing phases: 10 to 14 days at an induction dose of 5 mg/kg twice daily followed by maintenance at 5 mg/kg/day. Maintenance therapy is administered via a long-term central venous line (CVL) such as a Hickman catheter. The major toxicity of ganciclovir is hematologic; severe neutropenia, defined as an absolute neutrophil count (ANC) ≤ 500 cells/μL, occurred in 34% of patients in the FGCRT.[50] Neutropenia is generally reversible and is treated with hemopoietic growth factors such as granulocyte colony-stimulating factor (filgrastim, G-CSF) or granulocyte macrophage colony-stimulating factor (sagramostin, GM-CSF).[12] Even with G-CSF, interruptions of treatment with ganciclovir may still be required. Other adverse events associated with IV ganciclovir are thrombocytopenia, anemia, fever, rash and abnormal liver enzyme levels.

Because of their similar hematologic toxicities, the concomitant use of ganciclovir and zidovudine (AZT) was not recommended initially. However, the introduction of hemopoietic

growth factors has made concomitant use of ganciclovir and zidovudine possible for more patients. Alternatively, patients may be treated with other anti-retroviral drugs such as didanosine (ddi) or zalcitabine (ddc).

Foscarnet also is given in two dosing phases: a 10 to 14 day induction period followed by long-term maintenance therapy. Maintenance therapy is also given through a CVL such as a Hickman catheter. The induction dose is 60 mg/kg three times daily. The maintenance dose is 90 to 120 mg/kg daily. Foscarnet is excreted by the kidneys and the dose must be adjusted for renal function.

Nephrotoxicity is the major toxicity of foscarnet, occurring in 9 to 43% of patients.[38,50,54] The drug is given over a two hour period with hydration to minimize nephrotoxicity. When severe nephrotoxicity occurs, the use of the drug must be stopped. In the Foscarnet-Ganciclovir CMV Retinitis Trial, 9% of patients experienced nephrotoxicity severe enough (defined as serum creatinine $\geq$ 2.9 mg/dL) to interrupt drug treatment. Other toxicities include electrolyte abnormalities (particularly of calcium and magnesium), penile ulcers, and seizures.[50]

Treatment with ganciclovir or foscarnet halts retinitis progression in 90% of treated patients. However, despite continued maintenance therapy, relapse occurs in 85% of patients within 4 months.[51] Furthermore, periods of remission shorten as the number of relapses increase. Median times to first, second, and third relapse as measured by time to re-initiation of induction therapy were 121, 64, and 43 days, respectively, for patients treated with either ganciclovir or foscarnet.[51] The accelerating rate of relapse may be due to the development of drug resistant viral strains, deteriorating immune function, or a combination of these and other factors. Strains of virus resistant to ganciclovir[2,4,8] or foscarnet[7] have been isolated from patients treated with each of these drugs.

Other treatments now available as licensed or experimental treatments for CMV retinitis include oral ganciclovir, intravitreous injections of ganciclovir, foscarnet or cidofovir, intravenous infusion of cidofovir and ganciclovir intraocular implants.

1.3 MSL 109

MSL 109 [Protovir™ (sevirumab; formerly SDZ MSL 109, 89-109), Protein Design Labs, Inc.] is a human monoclonal antibody of the IgGI-kappa subclass with a molecular weight of approximately 150,000 daltons. MSL 109 is the product of a hybrid cell line constructed by fusion of a non-antibody producing murine x human hybrid myeloma to a human B lymphocyte stimulated in vitro by human CMV antigens isolated from the Towne strain of CMV.[24] It has

demonstrated neutralizing activity in vitro against all laboratory strains and clinical isolates of CMV tested to date. The antibody recognizes an 82,000 dalton viral surface antigen which is the same antigen as the 86,000 dalton molecule (gH) identified as the target for a neutralizing murine monoclonal antibody against human CMV.[24,48,47] Lakeman et al, have documented that 1.25 μg/mL of MSL 109 is at or above the ED_{50} for all CMV strains tested in vitro including ganciclovir-resistant strains.[22] The ED_{50} is below 0.5 μg/mL for a large number of laboratory and clinical isolates in studies performed at UTMB-Galveston and at Protein Design Labs, Inc. (PDL).[34,35,45] The ED_{50} of MSL 109 for 15 laboratory and clinical isolates studies at PDL ranged from 0.02 to 0.48 μg/mL. MSL 109 and Fab fragments of MSL 109 neutralize CMV in vitro in the absence of complement.[45] These data as well as other published data on other anti-gH antibodies, suggest that these agents may inhibit viral entry into cells. This mechanism of action is distinct from that of any non-antibody antiviral agents currently being evaluated for their utility in the treatment of CMV infections. Nokta et al, have recently demonstrated the additive anti-CMV effects of MSL 109 in combination with either ganciclovir or foscarnet in vitro.[33,34,35]

Human and "humanized" monoclonal antibodies offer several potential advantages. The first is reduction or possible elimination of immunogenicity when compared to murine and chimeric antibodies. A second potential advantage of such "next-generation" monoclonal antibodies is prolongation of serum half-lives as well as biodistribution that mimics that of normal human immunoglobulins even after repeated injections. The third potential advantage is that such human and "humanized" antibodies have normal immunoglobulin constant regions and can thus activate the complement cascade and/or mediate antibody-dependent cellular cytotoxicity (ADCC).

In the early 1980s, Östberg and his collaborators developed a technology that facilitates the isolation and production of pure human monoclonal antibodies.[37] They developed a proprietary (mouse X human) cell line, SPAZ-4, and subsequently fused this cell line with B lymphocytes from a variety of sources. By choosing donors with pre-existing immunity (e.g., to CMV, HSV, or VZV) or who were immunized (e.g., with HBV vaccine, tetanus toxoid) they were able to isolate and propagate stable "triomas" producing pure human monoclonal immunoglobulins. Although other techniques have been utilized to generate monoclonal antibodies, this approach has yielded three human antibodies (two anti-CMV antibodies and one specific for the HBV HBsAg) which have already been in clinical trials as well as several promising clinical candidates (anti-VZV and anti-HSV). Two human antibodies to CMV have been characterized and studied in patients. Several "humanized" antibodies also have been produced but have not been developed further because of the advanced stage of the clinical development of the human anti-CMV monoclonal antibodies.

Toxicology studies have been performed in adult and neonatal primates. No clinical, laboratory, or pathological abnormalities attributable to administration of MSL 109 were noted in

these studies at doses of up to 16 mg/kg in adult and 100 mg/kg in neonatal animals. In addition, MSL 109 was administered, at intervals, to non-human primates at a dose level of 0.5 mg/kg for periods of from one month to one year without evidence of immunogenicity. These data confirm that this normal human monoclonal immunoglobulin is safe, well tolerated, and non-immunogenic even when administered for periods of up to one year. This lack of immunogenicity of MSL 109 in non-human primates stands in marked contrast to results seen with both murine and chimeric antibodies.

Intravenous administration of MSL 109 has been shown to diminish virus isolation from the blood and ocular tissues as well as to diminish observable ocular inflammation and retinitis in a rabbit model of human CMV retinitis.[5] These findings were confirmed by both ophthalmoscopic and histopathologic evaluation of ocular tissues. Combination of MSL 109 with ganciclovir was shown in preliminary experiments to be more effective than either agent administered alone in this model system.[6] It was also demonstrated in these experiments that MSL 109 distributed to the aqueous and vitreous humors. Aqueous levels were greater than those measured in the vitreous (2.8-8.9% of MSL 109 serum levels). It was concluded that MSL 109 penetrated ocular tissues and was effective in this model system.

The preliminary results of two Phase I/II clinical trials of MSL 109 in patients with AIDS have been reported. In one trial patients with AIDS who were CMV seropositive and shedding CMV in their urine were studied.[44] Cohorts of 4 patients were entered, with 3 patients receiving MSL 109 and 1 patient receiving 300 mg/kg IVIG (Sandoglobulin®) every two weeks for 24 weeks. Seven patients received Sandoglobulin® and 23 patients received MSL 109. MSL 109 recipients received 0.125 mg/kg (6 patients), 0.5 mg/kg (3 patients), 1.0 mg/kg (7 patients), 2.0 mg/kg (3 patients) and a 10 mg/kg "loading dose" followed by 1 mg/kg (3 patients). Only one drug-related adverse effect, a mild headache, was reported during this trial. During the course of the trial one patient developed peripheral CMV retinitis and four patients developed sight-threatening retinitis requiring therapy with ganciclovir.

In the second Phase I/II trial, AIDS patients with CMV retinitis were treated with an induction regimen of either ganciclovir or foscarnet.[53] MSL 109 therapy was begun at the time of initiation of maintenance therapy with either of these two standard antiviral drugs. Patients received up to 8 doses of MSL 109 of 1.0 mg/kg (4 patients), 2.0 mg/kg (5 patients), 5.0 mg/kg (3 patients), or fixed doses of 20 mg (3 patients) or 80 mg (2 patients) every two weeks. MSL 109 was well tolerated; in addition, there was no evidence of drug-related exacerbation of CMV retinitis during the period of its administration. The median time from initiation of either ganciclovir or foscarnet until retinitis progression was approximately 200 days in patients receiving MSL 109 adjunctive therapy. Although preliminary, these data compare favorably with other trials, in which the median time to progression of CMV retinitis in patients receiving either

ganciclovir or foscarnet alone is approximately 100 days. There is no evidence that human anti-human antibodies developed in any of the patients treated with MSL 109. Trough serum levels of MSL 109 in patients receiving doses of 1 mg/kg intravenously every two weeks were greatly in excess of the in vitro ED_{50}.

1.4 Rationale

MSL 109 is a human monoclonal anti-CMV antibody which has been shown to be safe and well tolerated in a variety of Phase I trials, including a study where it was combined with either ganciclovir or foscarnet in AIDS patients with CMV retinitis.[53] MSL 109 has been shown to neutralize both laboratory and clinical isolates of CMV, at concentrations ($ED_{50} \approx 0.5$ μg/mL) that are easily achieved and maintained in patients with AIDS. Nokta and colleagues have shown that MSL 109 has additive antiviral activity in vitro with either ganciclovir or foscarnet.[33,34,35] Dunkel et al.[5,6] have documented that MSL 109 is active as a single agent in the rabbit model of CMV retinitis and, in preliminary studies, that this activity is enhanced by co-administration of ganciclovir. MSL 109 has thus far been shown to be free of any evidence of serious clinical or laboratory adverse effects. MSL 109 serum levels in both patients and non-human primates document a long terminal elimination half-life of between 2 and 3 weeks. No antibody to MSL 109 has been detected in either bone marrow transplant recipients or in AIDS patients in two studies in each of these populations.

In the study, by Tolpin et al, of 17 patients with CMV retinitis, doses of MSL 109 (ranging from a fixed dose of 20 mg to 5 mg/kg) were administered intravenously every two weeks starting at approximately the time of the initiation of maintenance therapy with standard clinical therapy (ganciclovir or foscarnet).[53] MSL 109 was well tolerated in all patients and there was no evidence of exacerbation of CMV retinitis either during or after its administration, although some patients progressed while on therapy.

The median time from initiation of ganciclovir or foscarnet induction therapy until progression of CMV retinitis, as assessed clinically, in patients treated on this protocol was approximately 100 days longer than observed historically with either standard antiviral agent alone, i.e., 200 days for combination therapy with MSL 109.[53] In the FGCRT the median time to first reinduction was 121 days.[51] Thus the MACRT has been designed to detect a 50% increase in median days to progression, or a time to progression of 180 days, taking into account the 200 day median time to progression seen by Tolpin.

Not all patients with CMV retinitis who are treated with available therapy respond to these medications. Both ganciclovir and foscarnet must be administered several times a day during

induction therapy, and daily during the period of maintenance treatment. Administration of ganciclovir is complicated in AIDS patients who are on AZT or who have limited marrow reserve, because of its inherent myelotoxicity. Foscarnet has been shown to be nephrotoxic and to have multiple effects on mineral metabolism. As suggested above, the addition of MSL 109 to either of these two antiviral drugs could increase the number of patients with CMV retinitis who initially respond, could prolong the time to progression during maintenance therapy, and could diminish the emergence of resistant strains of the virus. In the future it also may be possible to lower the doses or prolong the duration between doses of standard antiviral agents during maintenance therapy.

Because of these data it is felt that a study of this human monoclonal antibody to CMV, MSL 109, is warranted. The current study is designed to explore 60 mg IV of MSL 109 plus primary treatment compared to matched placebo plus primary treatment.

2. Objectives and design summary

The primary objective of the Monoclonal Antibody CMV Retinitis Trial is to compare the safety and efficacy of Human Anti-CMV Monoclonal Antibody (MSL 109) plus active primary treatment versus matched placebo plus active primary treatment, for both newly diagnosed and relapsed CMV retinitis in patients with AIDS.

The 325-patient trial will use a two-stage design in which the results from 76 patients enrolled and evaluated in the first stage will be used to decide whether to proceed to the full recruitment goal, to modify the protocol, or to terminate the trial. The design variables for the first stage are change in CMV virologic load and time to progression of retinitis. The design variable for the overall trial is time to progression of retinitis. Additional outcome measures include mortality, adverse events, change in visual acuity, and change in visual fields.

The two treatment groups and their respective treatment administration are:

- MA+: 60 mg MSL 109, intravenously every 2 weeks, along with active primary treatment for CMV retinitis

- Plbo+: matched placebo for MSL 109 (identical vehicle without antibody), intravenously every 2 weeks, along with active primary treatment for CMV retinitis

Treatment administration of supplemental therapy, MSL 109 or placebo, will be interrupted if a grade 3 or grade 4 adverse event, in the physician's opinion, is judged to be due to supplemental treatment.

Treatment assignment will be random, using an assignment ratio of 1:1 for MA+ to Plbo+, stratified by both clinic and stage of CMV retinitis (newly diagnosed vs relapsed), and masked to both patient and treating physician.

The overall recruitment goal is to enroll 325 patients in 17 months. Data will be collected at baseline, every 4 weeks for the first 48 weeks, and every 12 weeks thereafter until the end of the trial. There will be a common closeout for the trial 48 weeks following enrollment of the last patient.

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

3. Patient enrollment

Recruitment, assessment of eligibility, and enrollment will be performed at participating SOCA clinics (Appendix A). Once it has been determined that a patient is eligible for the trial, the specifics of the trial will be explained and discussed. Patients considering participating in the trial will be given the consent statement and other informational materials and will be allowed at least 24 hours to decide whether to enroll in the trial. All baseline evaluations will be conducted prior to randomization and within the 5 days up to and including randomization. Patients unable to complete the baseline evaluations will not be eligible for participation in the trial.

3.1 Inclusion criteria

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

- 13 years or older at entry
- Diagnosis of AIDS according to the current Centers for Disease Control and Prevention (CDC) definition
- Diagnosis of active CMV retinitis as determined by a SOCA-certified ophthalmologist at time of enrollment
- At least one photographable lesion whose size is one-quarter or more optic disc area
- Currently receiving (for relapsed patients) or scheduled to receive (for newly diagnosed patients) drugs for primary treatment of CMV retinitis that are not contraindicated for use with MSL 109
- Visual acuity, in at least one eye that meets other eligibility criteria, of 3 or more letters on ETDRS chart at 1 meter distance (Snellen equivalent 5/200). Patients with poorer visual acuity may be enrolled if the visual acuity impairment is possibly reversible (eg, due to optic disc edema) and vision is at least light perception in that eye
- Karnofsky score of 60 or more

- Willingness and ability, with the assistance of a caregiver if necessary, to comply with treatment and followup procedures
- Signed consent statement

3.2 Exclusion criteria

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

- Current treatment with intravenous immune globulin (IVIG), CMV immune globulin (CMVIG), alpha-interferon (alpha-IFN), gamma-interferon (gamma-IFN), or interleukin-2 (IL-2)
- Media opacity that precludes visualization of the fundus in all eyes meeting eligibility criteria
- Active medical problems, including drug or alcohol abuse, that are considered sufficient to hinder compliance with treatment or followup procedures
- Retinal detachment, not scheduled for surgical repair, in all eyes meeting other eligibility criteria

3.3 Randomization

Randomization will be accomplished using an auditable, documented generation scheme that produces a reproducible order of assignment. Stratification will be by both clinic and stage of CMV retinitis (newly diagnosed vs 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 for MA+ to Plbo+. Assignments will be generated in permuted blocks of varying lengths.

Treatment assignment will be to one of 8 medication bin IDs (corresponding to 8 bins in the clinic pharmacy labeled A1 through H8). Half of the medication bin IDs will correspond to MSL 109 and the other half to the placebo. Clinic personnel will be masked as to which medication corresponds to each ID. Eight bins will be employed so that if the identity of the contents of one bin should become known, that of the remaining bins will not.

Clinic personnel will obtain medication bin ID assignments as needed from the CC 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 five minutes, whereupon the assignment is given by telephone. Before a medication bin ID 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 medication bin ID 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 pending eligibility determination triggers the sealed envelope method of medication bin ID assignment transmission, an accompanying note from the CC will indicate to clinic personnel that the envelope should not be opened unless and until the previously pending test results are known to be within protocol eligibility limits. If that patient withdraws consent or is otherwise determined ineligible before the envelope is opened at the clinic, the unopened medication bin ID assignment will be returned to the CC.

Once a medication bin ID assignment code 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 compliance.

4. Outcome measures

4.1 Design outcome measure

The outcome measure used for sample size analysis is time to first progression of retinitis after randomization. Retinitis progression will be measured by masked readings of fundus photographs by the Fundus Photograph Reading Center (FPRC). The criteria defining retinitis progression are:

(1) Advancement of the edge of an existing lesion by one-half the diameter of the optic disc (1/2 disc diameter = 750 μ[1]) perpendicularly from the edge and along $\geq$ 750 μ of it; or

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

In this trial, photographic outcome measures will include the above and more advanced degrees of progression, such as movement of retinitis borders by $\geq$ 1,500 μ or $\geq$ 3,000 μ, and change in extent of retinitis.

The edge of a CMV lesion is often difficult to determine. The difficulty arises in part because of the presence of small (100 to 400 μ diameter) 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 progression, the junction of the satellite zone and the normal retina, designated the "satellite margin," will be used. The satellite zone is often observed to fill in and become solidly involved during the first 2 to 4 weeks of treatment, and this may lead to a false impression of progression unless care is taken to measure progression from the satellite margin.

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

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

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

4.2 Additional outcome measures

4.2.1 Mortality

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

4.2.2 Visual function

Visual function will be measured by SOCA certified personnel according to standard procedures as outlined in the SOCA Handbook. Visual acuity will be measured at each followup visit. Visual fields will be measured, and refraction performed, at baseline and every 12 weeks thereafter until the common closeout date.

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

Changes in visual fields will be measured using a Goldmann perimeter. Evaluations will be conducted according to procedures developed by the Diabetic Retinopathy Study (DRS). Results of visual field assessments will be recorded on standardized data collection forms.

4.2.3 CMV viral load

Viral load will be measured for the first 76 patients (stage 1 only) at baseline and followup visits 1, 3, and 6. This will consist of quantitative plasma polymerase chain reaction (PCR). Specimens will also be banked in order to allow for further studies to be conducted. Such tests

might include quantitative leukocyte PCR, CMV antigenemia, CMV branched DNA, or other testing.

5. Treatment plan

5.1 Treatment groups

Upon entering the trial, patients receiving, or scheduled to receive, a primary treatment for CMV retinitis will be randomized to one of two supplemental therapy groups:

MA+ - MSL 109, 60 mg IV, given every 2 weeks
Plbo+ - MSL 109 matched placebo IV, given every 2 weeks

5.2 Administration

The patient's primary CMV treatment should follow that currently used by the patient or as prescribed by the patient's physician. If the patient's primary CMV treatment includes induction and maintenance doses, reinduction should proceed by usual clinical guidelines. Drugs or devices for primary CMV retinitis therapy will **not** be supplied.

Supplemental therapy (MSL 109 or matching placebo) will be provided by PDL as single-dose ampules or vials containing 10 ml of solution; the MSL 109 will have a concentration of 6 mg/ml. The solution should be stored under refrigeration at 2 to 8°C (36 - 46°F). The solution should **not** be frozen or shaken.

A SOCA certified pharmacist will withdraw the entire ampule contents, under aseptic conditions, into a syringe through an 18 gauge or larger needle, expel air and attach a MILLEX-GV 25mm 0.2 micrometer (μM) filter (provided by PDL - no filter substitutions may be made) and either a sheathed needle or a "butterfly" infusion set suitable for injection.

The solution contains no preservatives and should be used within 4 hours of opening the ampule in order to prevent the growth of bacteria. The syringe-filter-needle assembly should be kept refrigerated until transportation. The assembly should be transported with a cold pack. While it is not imperative that the solution be refrigerated during the 4 hour period of time between opening of the ampule and administration, if the solution is refrigerated and then transported with a cold pack until administration, it may be used for up to a 12 hour period beginning with the opening of the ampule.

Supplemental therapy will be given intravenously as an undiluted solution. The first dose of the supplemental therapy is to be administered intravenously over 20 minutes. Use of a syringe pump is recommended. If the treatment is well tolerated it may be administered as an IV bolus thereafter.

Supplemental therapy may be administered IV through either a peripheral or central venous line. It should be administered at a downstream port close to the point of entry to prevent uptake of the agent by the plastic tubing. If administered via catheter or heparin-lock, flush with saline before and after (do **not** use heparin). If administered via butterfly infusion set, the syringe should

be removed from the tubing following administration and the line flushed with sterile normal saline for injection to ensure that all of the solution is injected. Do **not** dilute the solution. Do **not** administer the solution in conjunction with other drug solutions, as compatibility studies have not been performed.

Therapy should be started as soon as possible after randomization, ideally within 24 hours. Each administration of supplemental treatment must be observed and documented by a health care professional. Observation must continue for at least 30 minutes following each administration of supplemental therapy. The first dose must be observed in the clinic. If administered in conjunction with other IV therapy, supplemental therapy should be administered first. This will decrease the amount of time required for MSL 109 post-administration observation. After the initial treatment at randomization, MA+ or Plbo+ is to be administered once every 2 weeks, with contiguous administration windows and a minimum time between administrations of 7 days.

5.3 Criteria for treatment interruption

Treatment with MA+ or Plbo+ is to be interrupted if the patient experiences a grade 3 or 4 adverse event that, in the physician's opinion, is judged to be due to the supplemental treatment. If primary therapy is interrupted or terminated, the supplemental therapy should be continued.

Patients will be followed for 48 weeks after the last patient is enrolled. Treatment will continue after that time period, but no followup data will be collected except for vital status.

6. Data collection plan

6.1 Data collection schedule

Data will be collected from all patients in the trial according to the schedule presented in Table 1. This represents a data collection schedule, not a patient care schedule. More frequent visits for patient care may be scheduled based on the judgment of the treating physicians.

All baseline examinations for eligibility must be completed within the 5 days up to and including the day of randomization. All baseline laboratory assessments should be performed within 72 hours prior to study entry. A patient will not be randomized until these evaluations are completed.

Followup evaluations will be conducted every 4 weeks for 48 weeks following randomization, then every 12 weeks thereafter. Patients receiving matched placebo will have the same data collection schedule as those receiving treatment. All patients will be followed until death or a common study closeout. Study closeout will occur 48 weeks after randomization of the last patient.

6.2 Ophthalmologic evaluations

Best corrected visual acuity will be assessed at all scheduled data collection visits. Assessment of best corrected visual acuity with refraction and visual field examinations will be performed every 12 weeks. An eye examination and fundus photographs will be taken at every data collection visit. Fundus photos are taken using a Canon 60° wide-angle camera. A Topcon camera may be used if prior approval is received from the FPRC. Approval will be based on the ability of center photographers to produce adequate photographs with the Topcon. Procedures for refraction, visual acuity, visual fields, and fundus photography are described in the SOCA Handbook.

6.3 History

Each patient will be reviewed for the specific study eligibility criteria prior to being randomized into the trial. A history of prior treatment for CMV or use of anti-CMV prophylactic agents will be collected at baseline. A medical history and concomitant treatment history will be taken at every data collection visit. The history includes health history prior to the onset of AIDS, date of AIDS diagnosis, index disease for AIDS diagnosis, occurrence of other opportunistic infections and manifestations of AIDS, and treatment history for HIV and CMV. The patient's current level of functioning will be assessed using the Karnofsky performance scale, which is described in the SOCA Handbook.

Additionally, adverse events and changes in study treatment will be logged and submitted with data collection forms after every followup visit.

6.4 Quality of Life interviews

A Quality of Life interview will be conducted at baseline and every 12 weeks thereafter.

6.5 Physical examinations

A physical examination will be performed at the baseline visit.

6.6 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.

Lymphocyte subset analysis will be conducted at baseline only.

Antibody studies will be conducted at baseline, followup visits 1, 3, 6, 9, 12, and every followup visit (every 12 weeks) thereafter. These studies include assessments of MSL 109 and antibody to MSL 109 levels.

Additionally, viral load will be assessed, via quantitative plasma PCR, in specimens from stage 1 patients (first 76 patients) only. Collection of blood specimens, both for plasma PCR and for potential additional studies will occur at baseline and followup visits 1, 3, and 6.

For purposes of human subjects' protection the amount of blood to be collected at any one study visit for laboratory studies should not exceed 50 mL. The amount of blood for serum chemistry, hematology, and lymphocyte subset analysis is restricted to no more than 24 mL, total for all three tests. Tubes of blood collected for viral load and antibody testing should be filled to capacity.

Whole blood for virologic assays will be collected into three 5 mL EDTA (purple-top) tubes. Whole blood for antibody assays will be collected into one 10 mL serum separator tube. Serum separator tubes will be provided by Protein Design Labs. After collection, the serum separator tube will be centrifuged for 5 to 7 minutes at 1500 to 1700 rpm. Refrigerate samples if packaging for shipment does not occur immediately.

Samples are to be packaged at a temperature between 2 and 8° Centigrade, according to the procedure described in the SOCA MACRT Manual, and shipped by overnight/next morning delivery to the University of Texas Medical Branch (UTMB) at Galveston. Packaging and shipping materials will be supplied by Protein Design Labs. Friday blood collections are discouraged; however, if necessary, UTMB will arrange to receive specimens on Saturday. If specimens are shipped for Saturday receipt at UTMB, notify UTMB personnel before 4:30 pm Central time (Daylight Saving Time is in effect during appropriate seasons) on Friday afternoon. Notify Ms. Pat Turk at (409) 772-4979.

6.7 Adverse reactions

Adverse experiences include any side effects, injuries, toxicities, or sensitivity reactions. All adverse events (including grade 1 and grade 2 events) must be recorded on the appropriate data forms. An adverse event is considered serious (grade 4) 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". For events not specifically charted for severity in the SOCA 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 those 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 are characterized as those requiring medical intervention/therapy with hospitalizations possible.

As there are requirements for reporting serious adverse events associated with the use of the study drug to the FDA, clinic personnel are responsible for notifying the SOCA CC (410/955-8175) within 24 hours of learning about a serious (grade 4) or severe (grade 3) event that is associated with the study treatment, including the death of a study patient. The term "associated with the use of the drug" means "that there is a reasonable possibility that the experience may have been caused by the drug." (21 CFR §312.32) The CC will then notify the Sponsor. The SOCA CC will be responsible for distributing safety reports to SOCA participating sites and for initiating communications with SOCA-related IRBs.

6.7 Adverse reactions

If a patient experiences a serious or severe adverse event considered likely to be related to study drug, MA+ or Plbo+, treatment of that patient will be interrupted. Supplemental treatment should be continued if primary CMV retinitis therapy is interrupted for independent reasons.

7. Biostatistics

7.1 Staged approach

Because of the limited amount of data available on the efficacy of MSL 109 for treatment of patients with CMV retinitis, a two-stage group sequential design will be implemented. An interim analysis will be initiated after 76 of the 325 patients have been enrolled. Data from the patients enrolled in the first stage will be used to compare both the change in CMV viral load (measured by quantitative plasma CMV DNA polymerase chain reaction (PCR)) and time to progression by treatment group. If the second stage is implemented as currently planned, the final analyses will combine data from both stages, emphasizing time to progression and the long-term relative safety and efficacy of MA+ vs Plbo+.

7.2 Sample size

The sample size of 325 patients for this trial (approximately 162 per treatment group) is based on the comparison of data from the Tolpin study and the FGCRT, which taken together, allow the calculation that MSL 109 may prolong time to progression by at least 50%. It is also based on the resources available for conduct of the trial. Duration of recruitment (325 patients in 17 months) was estimated using enrollment from the FGCRT (14 patients / month) and the CMV Retinitis Retreatment Trial (11.1 patients / month), then reduced to 75% due to system resource limitations.

The power to detect a clinically meaningful difference in median time to progression is 0.91, using an estimated minimum clinically significant increase in median time to progression of 50% (from 48 to 72 days for newly diagnosed patients and from 35 to 52.5 days for relapsed patients for Plbo+ vs MA+, respectively). Power was calculated based on the logrank test using a two-sided Type I error of 0.05, a one year followup after recruitment goal is achieved, and a 30% increase in sample size due to loss to followup, treatment lag effects, non-compliance, and heterogeneity of effects due to stage of CMV retinitis. If the assumptions on which the sample size calculation were based do not accurately reflect the truth, the requisite sample size will be altered, according to newly obtained information, by decision of the SOCA Policy Data and Monitoring Board (PDMB).

In the first stage, the minimum detectable difference in CMV DNA, given a power of 0.80, a two-sided Type I error of 0.05, and 38 patients per treatment group is 0.65 standard deviation units of CMV DNA. The conditional power to detect a 50% increase in median time to

progression if the trial continues to the end of stage 2, given the observed data show no difference at the end of stage 1, is 0.71.

7.3 Treatment effects monitoring

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

The PDMB will meet to review the short-term safety and efficacy data collected in the first stage on the first 76 (38 MA+, 38 Plbo+) patients randomized into the trial. Treatment monitoring reports similar to those described by Meinert and Tonascia[29], and developed for trials currently coordinated in the CCT will be used for MACRT. Recommendations by the PDMB for continuing, modifying or stopping the trial will be based upon safety and efficacy issues (change in CMV virologic load and time to retinitis progression). The PDMB recommendations will be submitted for approval to both the SOCA Steering Committee and the drug sponsor. In addition to the scheduled meeting at the end of the first stage, 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, p-value based, stopping rule is planned. Such stopping rules have utility in settings where there is a single design outcome, and no interest in any other outcome, and where there is little or no concern with respect to issues of safety. Use of formal stopping rules[36] are not recommended.[29] The difficulty with all such rules is that, even at best, they cannot be delineated, in advance, to deal with the variety of conditions that can arise during a trial that may lead to its termination or modification. Most PDMBs, of which the Director or Deputy Director of the SOCA CC have been members, have operated without use of formal stopping rules. Typically, data monitoring committees take account of the overall trend of the data, its internal consistency, as well as the clinical importance of the difference observed, in making a recommendation for change. However, such rules have served as a useful guidelines in the decision-making process in some settings.[3] Some form of stochastic curtailment (based on conditional power and Type I errors) also may be helpful.[23] The PDMB will have the ultimate choice regarding the approaches used for decision-making.

In addition, no formal adjustment procedures are recommended for p-values resulting from multiple looks associated with interim monitoring. Again, this philosophy comes from observing the behavior of data monitoring committees. In actuality, it is expected that large numbers of

comparisons will be performed, hence, p-values will be used more as descriptive statistics than as indicators of truth.

7.4 Data analysis

General analysis principles include:

- Primary analysis by original treatment assignment (intention-to-treat) regardless of administered treatment
- Counting all patients, including ineligibles or withdrawals, into their assigned treatment group after treatment assignment has been revealed
- Counting all events following randomization

Comparisons between the two treatment groups will be presented both unadjusted and adjusted. Covariates to be used for adjusting treatment group effects will include the two stratification variables, clinic and stage of CMV retinitis, and other baseline risk factors chosen using clinical judgement and/or variable selection procedures such as forward selection. Post-randomization confounders, including compliance, will be examined acknowledging the potential bias of this practice.[10] The treatment group effect will also be examined across various subgroups, including stage of CMV retinitis.

Regression models for comparing the two treatment groups with respect to each outcome will be developed as appropriate to each type of outcome. Statistical techniques to be used are Cox regression for time-to-event data such as first progression or mortality[1]; log-linear models for count data such as adverse events, extra-ocular CMV, opportunistic infections, hospitalizations and sepsis; and Generalized Estimating Equations (GEE) for repeated measures of continuous data such as change in CMV virologic status, change in visual acuity, change in visual fields, and change in quality of life measures. 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.[28] Robust variance estimation techniques for Cox regression[27] and GEE[26] will be employed.

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. P-values will be presented as descriptive statistics without adjusting for multiple looks, multiple outcomes, or multiple comparisons.

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

8. Patient rights and responsibilities

8.1 IRB approvals

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

8.2 Confidentiality of patient data

All patient data will be kept in a secure place. Name, social security number, address, and other such personal data will not be used by the 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.

9. 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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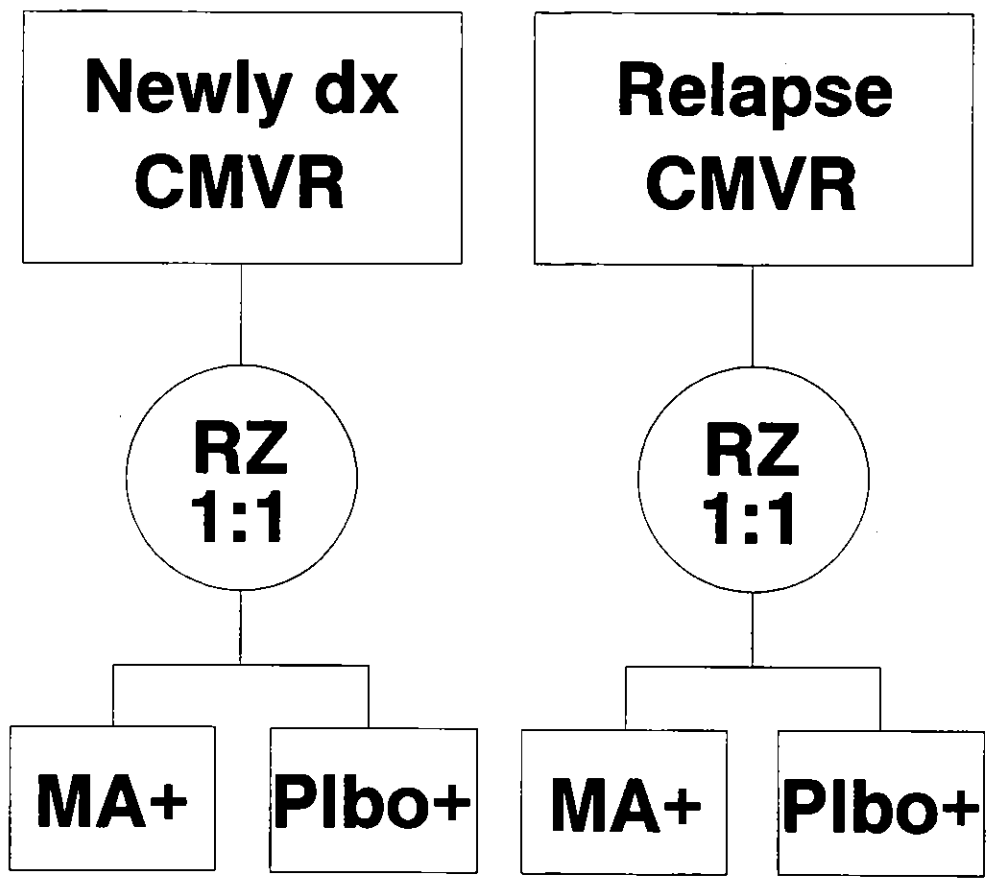
Exhibit 1. MACRT procedures required at scheduled visits

	Visit code/Target week from randomization																
	BL	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	...
weeks	0	4	8	12	16	20	24	28	32	36	40	44	48	60	72	84	...
History																	
Medical History	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Treatment History	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse event assessment		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Eligibility Review	x																
Eye																	
Visual Acuity	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Refraction	x			x			x			x			x	x	x	x	x
Eye Exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fundus Photograph	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Visual Fields	x			x			x			x			x	x	x	x	x
Lab																	
Viral load (stage 1)																	
CMV DNA PCR	x	x		x			x										
Other	x	x		x			x										
Antibody testing																	
MSL 109	x	x		x			x			x			x	x	x	x	x
Antibody to MSL 109	x	x		x			x			x			x	x	x	x	x
Other																	
Hematology, Serum Chemistry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lymphocyte Subset Analysis	x																
Other																	
Quality of Life Interview	x			x			x			x			x	x	x	x	x
Physical Exam	x																

Exhibit 2. Design schematic



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
JHU	Wilmer Ophthalmological Institute Johns Hopkins University Baltimore, MD	James P. Dunn, MD
LSU	LSU Eye Center Louisiana State University New Orleans, LA	Bruce Barron, MD
MSK	Memorial Sloan Kettering Cancer Center Cornell Medical Center New York, NY	Murk-Hein Heinemann, MD
MSMC	Mount Sinai Medical Center New York, NY	Alan H. Friedman, MD
NYU	Department of Ophthalmology New York University Medical Center New York, NY	Dorothy Friedberg, MD, PhD
NU	Northwestern University Chicago, IL	David Weinberg, MD
UCLA	Jules Stein Eye Institute University of California Los Angeles, CA	Gary N. Holland, MD

Monoclonal antibody CRT

Appendix A: SOCA centers

SOCA ID	Institution	Director
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	James O'Donnell, MD
UM	Bascom Palmer Eye Institute University of Miami Miami, FL	Janet Davis, MD
UNC	University of North Carolina at Chapel Hill Chapel Hill, NC	Charles van der Horst, MD
NJMS	Univ. of Medicine & Dentistry at New Jersey Newark, NJ	Ronald Rescigno, MD
USF	University of South Florida Tampa, FL	Peter Pavan, MD W. Sanderson Grizzard, MD

Monoclonal antibody CRT

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 Laboratory/ Repository	University of Texas Medical Branch (UTMB) Galveston, TX	Richard Pollard, MD
Drug Distribution Center	Ogden BioServices Corporation Rockville, MD	Mark Walls, RPh

Appendix B: Policy and Data Monitoring Board

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

Monoclonal antibody CRT

Appendix B: Policy and Data Monitoring Board

Name	Institution/study position
Non-voting (cont'd)	
Douglas Jabs, MD	Ophthalmologist Study Chairman
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Appendix C: MACRT design summary

Title of trial

- Monoclonal Antibody CMV Retinitis Trial (MACRT)

Objective

- Evaluate the relative safety and efficacy of Human Anti-CMV Monoclonal Antibody (MSL 109) treatment versus matched placebo (Plbo+) treatment as supplemental treatment to active primary treatment for CMV retinitis in patients with AIDS

Type of trial

- Phase II/III
- Multicenter, masked, placebo-controlled, randomized
- Two-stage group sequential design in which 76 patients are enrolled and evaluated in the first stage and the results of which are used to decide whether to continue to the full 325 patient trial, amend the trial, or terminate the trial

Stratification

- Clinic
- Stage of CMV retinitis: newly diagnosed vs. relapsed

Treatment groups (abbreviations)

- MSL 109 (MA+)
- Placebo (Plbo+)

Treatment administration

- MA+: 60 mg MSL 109, intravenously every two weeks as supplemental treatment along with active primary treatment for CMV retinitis
- Plbo+: matched placebo for MSL 109 (identical vehicle without antibody), intravenously every two weeks as supplemental treatment along with active primary treatment for CMV retinitis
- Administration of supplemental treatment must be observed and documented by a health care professional: first dose for each patient must be observed in the clinic

Treatment interruption

- Grade 3 or grade 4 adverse event judged, by the physician, to be due to supplemental treatment

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Masking

- Double-masked (ie, masked to treating physician, clinic personnel, and patient) supplemental treatment for CMV retinitis
- Unmasked active primary treatment for CMV retinitis
- Masked reading of fundus photographs
- Unmasked Policy and Data Monitoring Board

Outcomes

Design variables

- Stage 1
  - Change in CMV viral load
  - CMV retinitis progression as determined by reading of fundus photographs
- Stage 2
  - CMV retinitis progression as determined by reading of fundus photographs

Other variables

- Mortality
- Adverse events
- Clinician assessment of CMV retinitis progression
- Visual fields
- Visual acuity
- Morbidity
  - Extra-ocular CMV
  - Opportunistic infections
  - Hospitalizations
  - Sepsis
- Quality of Life

Inclusion criteria

- Age 13 or older
- Diagnosed with AIDS according to current Centers for Disease Control and Prevention (CDC) definitions
- Diagnosed with active CMV retinitis by SOCA-certified ophthalmologist
- At least one photographable lesion, 1/4 or more optic disc area in size
- Currently receiving (for relapsed patients), or scheduled to receive (for newly diagnosed patients), active primary treatment for CMV retinitis that is not contraindicated for use with MSL 109
- Karnofsky score of 60 or more

- Visual acuity in at least one eye which meets other eligibility criteria of 3 or more letters on the ETDRS chart at 1 meter (Snellen equivalent of 5/200)
- Willingness and ability (with assistance of a caregiver if necessary) to comply with treatment and followup procedures
- Signed consent

Exclusion criteria

- Treatment with intravenous immune globulin (IVIG), CMV immune globulin (CMVIG), alpha-interferon (alpha-IFN), gamma-interferon (gamma-IFN), or interleukin-2 (IL-2)
- Media opacity that precludes visualization of the fundus in all eyes which meet other eligibility criteria
- Active medical problems, including drug and alcohol abuse, sufficient to hinder compliance with treatment or followup procedures
- Retinal detachment in all eyes which meet other eligibility criteria

Data collection schedule

- Baseline
- Followup: every 4 weeks for first 48 weeks; every 12 weeks thereafter to common closeout date
- In stage 1 only, quantitative plasma CMV DNA polymerase chain reaction (PCR) will be performed at baseline, 4 weeks, 12 weeks, and 24 weeks

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Sample size calculations

Combined across stages:

- Total sample size = 325, approximately 162 per treatment group
- Assignment ratio = 1:1 for MA+ vs Plbo+
- Type I error = 0.05 (two-sided)
- 30% increase in sample size
  - 20% increase due to loss to followup, treatment lag effects, and noncompliance
  - 10% increase due to heterogeneity of effects in patients with newly diagnosed CMV retinitis vs relapsed CMV retinitis
- Recruitment rate = 19 patients/month
  = [(14 newly diagnosed patients/month + 11.1 relapsed patients/month) × 0.75]
- Recruitment period = 17 months
- Minimum followup = 48 weeks
- Estimated event rates (based on FGCRT)
  - Median time to progression in Plbo+ group in newly diagnosed patients = 48 days
  - Median time to progression in Plbo+ group in relapsed patients = 35 days
- Estimated proportion of newly diagnosed patients = 50%
- Estimated (minimum clinically significant) increase in median time-to-progression = 50%
- Estimated power = 0.91
- Method of calculation
  - Logrank test

Stage 1:

- Sample size = 76, 38 per treatment group
- Minimum detectable effect of CMV DNA, given 80% power, type I error level of 0.05, and 38 patients per treatment group = 65% standard deviation units of CMV DNA
- Conditional power = 0.71 to detect a 50% increase in median time to progression if the trial continues to the end of stage 2 given the observed data show no difference at the end of stage 1

Data analysis

- Plbo+ vs MA+
- Primary analysis by assigned treatment group
- All events after randomization will be counted

Monoclonal antibody CRT

Appendix C: MACRT Design Summary

Safety monitoring plan

- Review of data by Policy and Data Monitoring Board (PDMB) at semiannual meetings or more often if necessary
- Recommendations for protocol modifications or early termination of the trial will be made by the PDMB (no formal stopping rules)