**COG-ACCL1932: Letermovir Prophylaxis for Cytomegalovirus in Pediatric Hematopoietic Cell Transplantation**

***FAST FACTS***
**Eligibility Reviewed and Verified By**
**_____ MD/DO/RN/LPN/CRA Date _____**
**_____ MD/DO/RN/LPN/CRA Date _____**
**Consent Version Dated_____**

**PATIENT ELIGIBILITY:**
**Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.**

___1. Timing
All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below. Enrollment and confirmation of negative plasma CMV PCR must be completed prior to the Study Treatment Period start, Day +1 post-transplant. **Plasma CMV PCR testing must be sent as well as resulted within the 7-day window prior to the start of the Study Treatment Period.** Patients who test positive for plasma CMV PCR after enrollment but prior to the start of the Study Treatment Period will be removed from study. See Section 8.2 Off Study criteria. To limit the likelihood of positive plasma CMV PCR prior to start of study treatment period, it is recommended that study enrollment proceed *after* patients start their preparative regimen.

Participants randomized to Arm A must receive their first dose of the prophylaxis (study drug) post transplant Day +1 (±1 day). See Section 4 for Treatment Plan.

___2. Randomization
Randomization will take place only after a patient is enrolled via OPEN. The treatment will be randomly assigned based on the statistical design of the trial.

___3. Age
≥2 years and <18 years at the time of enrollment

___4. Weight
Weight must be ≥18 kg. For patients <12 years of age and expected to receive cyclosporine, weight must be ≥ 30kg.

___5. Treatment Plan
Planned allogeneic HCT (bone marrow, peripheral blood stem cell, or cord blood transplant).

___6. Diagnosis
Patient must be CMV sero-positive (i.e., recipient CMV immunoglobulin G positive)

___7. Timing
Patient is eligible for entry only if it is feasible for plasma CMV PCR testing to be sent and resulted within the protocol mandated time period (see Section 3.1.4).

**Reminder**: *As noted in Section 3.1.4, to limit the likelihood of positive plasma CMV PCR post-enrollment and prior to start of Study Treatment Period, it is recommended that patient enrollment proceed after patients start their transplant preparative regimen*.

___8. Performance Level
Patient must have a performance status corresponding to Lansky/Karnofsky scores > 50

**Note**: Use Lansky for patients ≤ 16 years of age and Karnofsky for patients > 16 years of age. For further reference, see Performance Status Scales Scoring under the Standard Sections for Protocols among Protocol Reference Materials provided on the COG Member Website: https://members.childrensoncologygroup.org/prot/reference_materials.asp

___9. Organ Function
- Adequate renal function defined as an estimated glomerular filtration rate > 15 mL/min/1.73 $m^2$ and not receiving dialysis
- Adequate liver function defined as:
  - Total bilirubin ≤ 2.5 mg/dL and SPGT (ALT) ≤ 10 x upper limit of normal (ULN) for age

**Note: For the purpose of this study, the ULN for SGPT (ALT) has been set to the value of 45 U/L*

The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.

Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix III.

**EXCLUSION CRITERIA**

___1. Expected inability to tolerate oral formulation (e.g., unable swallow whole tablets) of letermovir

**Note:** *Determination of ability to tolerate the oral formulation will be based on a self-assessment or caregiver assessment; eligible subjects and their caregiver will be shown a life size picture of a tablet (or actual tablet) and confirm ability to swallow whole tablet in order to meet study eligibility. See Appendix VIII.*

___2. Hypersensitivity to letermovir or any component of the formulation.

___3. History of CMV end organ disease within 6 months (180 days) prior to enrollment

**Note:** *CMV end organ disease based on proposed definitions by Ljungman et al.48 and inclusive of proven or probable disease. See* Section 10.2 *for working definitions.*

___4. Prior Therapy

Receipt of prior allogeneic HCT within one year of study enrollment.

___5. Planned Therapy Exclusions
- Planned prophylactic administration of other anti-CMV medications or cellular products during the study, including:
  - high dose acyclovir (defined as doses ≥1500 mg/$m^2$ IV or ≥3200 mg oral (patients ≥ 40 kg) or ≥ 2400 mg/$m^2$ (patients < 40 kg) per day)
  - high dose valacyclovir (defined as doses ≥3000 mg/day in patients > 20 kg)
  - foscarnet
  - ganciclovir
  - valganciclovir
  - CMV-directed cytotoxic T lymphocytes
- Planned receipt of the following contraindicated medications during the study treatment period; contraindicated medications must be discontinued at least 14 days prior to Day +1.
  - Contraindicated medications for all patients:
    - pimozide
    - ergot alkaloids
  - Contraindicated medications for patients planned to receive cyclosporine:
    - Bosentan
    - Lovastatin
    - Pitavastatin
    - Rosuvastatin
    - Simvastatin
    - See Section 4.1 for the concomitant therapy restrictions for patients during treatment.

___6. Pregnancy and Breastfeeding
- Female patients who are pregnant since fetal toxicities and teratogenic effects have been noted in certain animal reproduction studies with letermovir. A pregnancy test is required for female patients of childbearing potential.
- Lactating females who plan to breastfeed their infants.
- Sexually active female patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their letermovir treatment and through at least 4 weeks after the last dose of letermovir.

**Note**: *No contraception measures are needed specifically during letermovir treatment for male trial participants who have pregnant or non-pregnant female partner(s) of reproductive potential. Contraception measures may be required for other aspects of the HCT procedure.*

**REQUIRED OBSERVATIONS:**

**Required Clinical and Laboratory Evaluations and Study-Specific Observations**
All participants will undergo local weekly screening for plasma CMV DNAemia through Week 14, with additional testing as clinically indicated. Subjects in both study arms will be followed for presence of CMV infection through Week 48, with increasingly longer intervals between CMV screens.

**Observation**
***Local Clinical and Laboratory Evaluations***
- **Physical Exam**
- **Weight (kg)**
- **CBC with diff/platelets**
- **Creatinine***

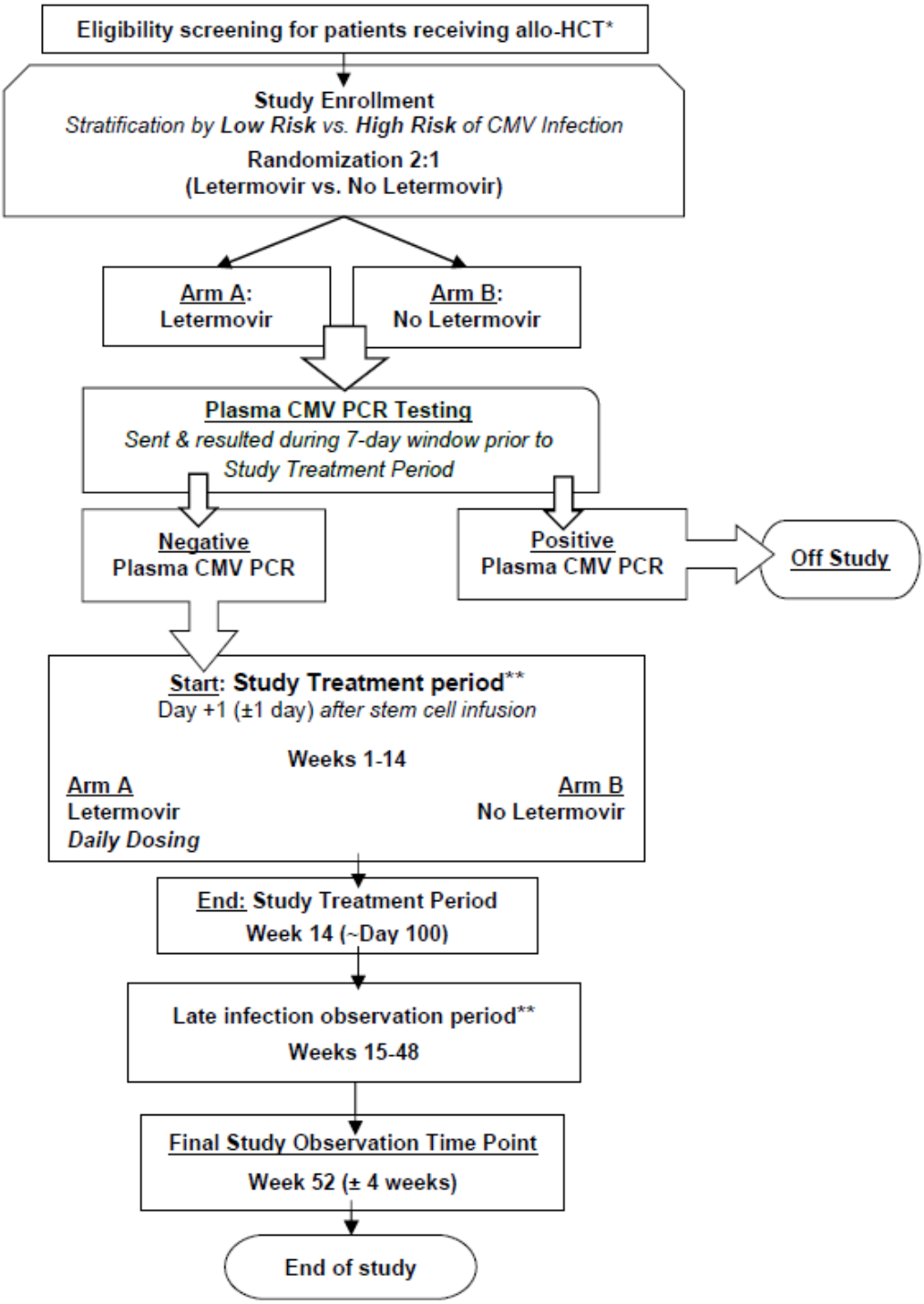
***Required Protocol Evaluations and Specimen Collection***
- **Plasma CMV PCR [1] -** Once [2]

[1] CMV PCR testing must be sent from plasma (whole blood or serum values are not acceptable)
[2] Baseline plasma CMV PCR testing must be sent within 7 days prior to the start of the study treatment period and also resulted prior to the start of the treatment period. Patients with positive plasma CMV PCR in this pre-HCT period will be removed from study. See Section 8.2.
* As clinically indicated; flexibility is permitted to accommodate clinical scheduling if necessary.

**TOXICITIES AND DOSAGE MODIFICATIONS:**
See Section 5

**BIOLOGY REQUIREMENTS:**
See Section 7.2.2 for optional blood specimen.

**TREATMENT PLAN:**




* See Section 3.2 for eligibility criteria
** See details in Section 4 for Treatment Plan, Section 7 for Observations