
Cytomegalovirus in Transplantation: Developing Drugs to Treat or Prevent Disease Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**May 2020
Clinical/Antimicrobial**

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs to treat or prevent cytomegalovirus (CMV) disease in patients who have undergone solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT).² Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for the development of drugs and therapeutic biological products to support an indication for treating or preventing CMV disease in post-transplant populations. This guidance is intended to facilitate continued discussions among the Division of Antiviral Products (DAVP), pharmaceutical sponsors, the academic community, and the public.³ This guidance does not address drug development for treating or preventing congenital CMV infection or CMV infection in patients other than those undergoing SOT or HSCT.

This guidance also discusses the use of CMV viremia, measured as DNAemia (CMV deoxyribonucleic acid (DNA) in blood determined by polymerase chain reaction (PCR)), as a validated surrogate endpoint in clinical trials.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*

¹ This guidance has been prepared by the Division of Antiviral Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

² For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

³ In addition to consulting guidances, sponsors are encouraged to contact the DAVP to discuss specific issues that arise during the development of anti-CMV drugs.

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Principles for Clinical Trials (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.⁴

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

CMV is a member of the beta-herpes virus group that causes infection worldwide with variable geographic distribution linked to socioeconomic status. In the United States, CMV seroprevalence ranges from 40 percent to 80 percent (Cannon and Davis 2005; Bate et al. 2010). Primary infection occurs in CMV seronegative hosts and is usually acquired during the first decades of life. In most cases, primary infection is benign and self-limited. However, in patients with immature or compromised immune systems (e.g., transplant recipients, congenitally infected newborns, or patients with acquired immunodeficiency syndrome (AIDS)), primary CMV infection is often symptomatic and is associated with increased morbidity and mortality. As with all herpes viruses, CMV establishes lifelong latency after primary infection; thereafter, intermittent viral shedding and disease reactivation can occur, particularly in hosts with compromised immune systems (Ramanan and Razonable 2013).

CMV is the single most frequent opportunistic pathogen in transplant recipients. The incidence of CMV infection and disease in this population depends on a number of factors, such as transplant type, donor and recipient CMV serostatus, and the level of immunosuppression (Ramanan and Razonable 2013). A transplant recipient is described by nomenclature that first describes the donor's CMV serostatus followed by the recipient's CMV serostatus. For example, D+/R- refers to a seronegative recipient of a transplant from a seropositive donor.⁵

In SOT recipients, observational studies have demonstrated an association between donor and recipient CMV serostatus and risk for CMV disease; D+/R- status is associated with a higher risk (with rates of 50 percent to 60 percent) for developing CMV disease than CMV seropositive recipients (D+/R+ or D-/R+), who have rates of 10 percent to 20 percent (Hartmann et al. 2006). The lowest rate of CMV infection (less than 5 percent) occurs in CMV seronegative SOT recipients who received a transplanted organ from a seronegative donor (D-/R-). In HSCT recipients, CMV seropositive recipients (R+) are at the highest risk for developing CMV disease regardless of the donor's CMV serostatus. Without prophylaxis (treatment administered to all patients at risk for developing CMV disease), approximately 80 percent of CMV seropositive

⁴ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

⁵ CMV serostatus of donor (D) and recipient (R) is designated as D+ or D- and R+ or R-, respectively. The term *CMV seropositive* refers to a donor or recipient with IgG antibodies to a previously acquired CMV infection and the term *CMV seronegative* denotes that anti-CMV IgG antibodies are absent.

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HSCT patients will experience CMV infection in the blood, and without preemptive therapy (treating patients with CMV replication in blood), approximately 30 percent of patients with CMV viremia will develop CMV disease (Ljungman et al. 2010).

The clinical manifestations of CMV infection range from asymptomatic CMV viremia to tissue-invasive (end-organ) CMV disease, including CMV syndrome, a subcategory of CMV disease described only in SOT recipients. Any organ can be infected by CMV; however, CMV pneumonia is the most serious manifestation of CMV infection in HSCT recipients and has been associated with high mortality. In contrast, CMV in SOT recipients has a predilection to replicate in the allograft. CMV infection may also be associated with an increased risk of other opportunistic infections, graft failure, graft rejection, and mortality (Razonable et al. 2013).

In general, because of the increased morbidity and mortality associated with CMV disease in transplant recipients, preventing CMV disease is generally recognized as a better strategy than treating established CMV disease. Prophylactic therapy and preemptive therapy are the two major strategies used for prevention (Boeckh and Ljungman 2009; Tomblyn et al. 2009; Razonable et al. 2013; Kotton et al. 2018). Both strategies have been shown to be effective for preventing CMV disease in SOT and HSCT recipients.

Currently, limited therapeutic options for treating or preventing CMV disease in transplant recipients are available. As of May 2020, only five drugs have received FDA approval for systemic use for treating or preventing CMV disease: letermovir, ganciclovir and its prodrug valganciclovir, foscarnet, and cidofovir. Letermovir is approved for CMV prophylaxis in CMV seropositive recipients of an allogeneic HSCT; ganciclovir and valganciclovir are approved for preventing CMV disease in transplant recipients and for treating CMV retinitis in immunocompromised patients, including patients with AIDS. Foscarnet and cidofovir have received FDA approval only for treating CMV retinitis in AIDS patients. Moreover, ganciclovir, valganciclovir, foscarnet, and cidofovir are associated with significant toxicities. These findings, coupled with the emergence of resistance to available drugs (Lurain and Chou 2010; Komatsu et al. 2014), strongly support the urgent need for new therapeutic agents that are effective and less toxic.

During the past 15 years, all phase 3 trials designed to support marketing applications for CMV drugs were prophylaxis trials in SOT and/or HSCT recipients. The primary endpoint used in these prophylaxis trials in SOT recipients was the incidence of CMV disease, including both symptomatic CMV infection (also called CMV syndrome) and/or tissue-invasive CMV disease (e.g., CMV colitis, hepatitis, or pneumonia). CMV syndrome is defined better in SOT recipients than it is in HSCT recipients, mainly because the symptoms associated with CMV syndrome can have several other causes in the setting of HSCT, including other viral infections. Until recently, the primary endpoint used in prophylaxis trials in HSCT patients was the incidence of tissue-invasive CMV disease.

However, the results of recent trials revealed that in the current era of preemptive therapy for CMV viremia based on optimized PCR assays, the incidence of tissue-invasive CMV disease in HSCT recipients at 6 months post-transplantation was less than 5 percent (Marty et al. 2011). These results call into question whether trials with tissue-invasive CMV disease as an endpoint

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in HSCT patients are feasible, considering the sample sizes needed for such trials given the low frequency of CMV disease in these patients. The accumulated clinical literature supports the premise that CMV viremia predicts development of CMV disease in transplant recipients (Gor et al. 1998; Emery et al. 1999; Emery et al. 2000; Jang et al. 2012; Natori et al. 2018) and that CMV viremia predicts mortality (Green et al. 2016). Prophylaxis or preemptive therapy for CMV viremia prevents CMV disease (Green et al. 2016), the suppression of viremia is associated with clinical resolution of CMV disease (Åsberg et al. 2007), and CMV prophylaxis in HSCT recipients is associated with decreased mortality (Marty et al. 2017).

These observations have prompted the FDA to consider CMV viremia (DNAemia) as a validated surrogate endpoint to be used as a part of a composite endpoint to support traditional approval. Therefore, traditional approval for new drug applications (NDAs) for CMV prophylaxis trials in HSCT recipients can be based on a composite endpoint defined as either the occurrence of tissue-invasive CMV disease or the initiation of anti-CMV preemptive therapy based on clinically significant CMV DNAemia. The use of CMV DNAemia as a part of a composite endpoint for other indications (e.g., treatment) is also discussed in this guidance.

III. DEVELOPMENT PROGRAM

A. General Drug Development Considerations

1. Early-Phase Development Considerations

General considerations pertinent to nonclinical development and early clinical development are outlined in this section. Sponsors considering developing drugs for treating or preventing CMV disease are encouraged to communicate with the FDA through the pre-investigational new drug application (pre-IND) consultation program.^{6,7} Pre-IND consultation with the FDA is optional. It may be particularly helpful for sponsors with limited experience in the IND process or for sponsors who want to obtain FDA recommendations for developing drugs with unique considerations based on mechanistic action, novel treatment approaches, or the use of novel biomarkers.

a. Pharmacology/toxicology development considerations

Pharmacology/toxicology development for CMV antiviral drugs should follow existing guidance for drug development. For detailed recommendations regarding pharmacology/toxicology development for single antiviral drugs and for two or more new investigational drugs to be used in combination, sponsors should consult the following ICH guidances on nonclinical safety studies: For small molecules, see the ICH guidance for industry *M3(R2) Nonclinical Safety*

⁶ <https://www.fda.gov/drugs/pre-ind-consultation-program/division-anti-viral-products-davp-pre-ind-letter-instruction>.

⁷ <https://www.fda.gov/drugs/pre-ind-consultation-program/getting-started-division-antiviral-products-pre-ind-process>.

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Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (January 2010); for biological products and other biotechnology-derived pharmaceuticals, see the ICH guidance for industry *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (July 1997).

We recommend carcinogenicity studies if the expected treatment duration, including intermittent use, is 6 months or longer (e.g., prophylaxis indications).⁸ Carcinogenicity studies can be submitted with an initial marketing application (i.e., NDA or biologics license application) or as required postmarketing studies.

For drugs to be used in combination, ICH M3(R2) includes a discussion of nonclinical safety studies appropriate in a combination drug development setting involving two early-stage entities.⁹ ICH M3(R2) defines early-stage entities as compounds with limited clinical experience (i.e., phase 2 studies or earlier). In general, nonclinical combination studies of an early-stage entity plus an approved therapy are not recommended.¹⁰ Therefore, unless data from nonclinical studies of an early-stage entity suggest a potential for serious synergistic toxicity with an approved therapeutic drug, combination toxicology studies are not recommended.

b. Nonclinical virology development considerations

Nonclinical virology studies can facilitate initial dose selection, enable the design of a clinical proof-of-concept study, and support an antiviral drug claim. The sponsor should conduct studies to support initial human trials before submitting an IND. Nonclinical virology studies for treating or preventing CMV should follow existing guidance for drug development.¹¹ Additional recommendations for nonclinical and clinical virology assessments specific to developing drugs for treating or preventing CMV disease are summarized throughout this guidance.

• **Mechanism of action**

The sponsor should investigate the mechanism by which a drug exhibits anti-CMV activity by using cell culture and biochemical, structural, and/or genetic studies to evaluate the effect of the drug on relevant stages of the virus life cycle and to identify the CMV target protein or proteins for direct-acting antiviral drugs. Mechanism-of-action investigations should include appropriate controls for assessing the specificity of anti-CMV activity, which may include assessments of activity against other CMV proteins, relevant host proteins, other viruses, and/or cells infected with investigational drug-resistant CMV variants. Biochemical or subcellular quantitative assays

⁸ See the ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* (March 1996).

⁹ See ICH M3(R2), section XVII., Combination Drug Toxicity Testing.

¹⁰ See the guidances for industry *Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment* (November 2017) and *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015).

¹¹ See the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency* (June 2006).

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supporting the mechanism of action should report the inhibitory concentration values (IC₅₀ and IC₉₀).

- **Antiviral activity data from cell culture studies**

The sponsor should characterize antiviral activity of an investigational drug in cell culture to identify a target plasma concentration for evaluation in CMV-infected patients. The sponsor should assess the antiviral activity of investigational drugs by using CMV laboratory isolates as well as several (more than 20) geographically and temporally distinct isolates, the majority of which should be U.S. isolates. The 50 percent and 90 percent effective concentration values (EC₅₀ and EC₉₀) should be determined. These studies should include different CMV types (i.e., the four gB (UL55) genotypes (gB1 through gB4) and the two gH (UL75) genotypes (gH1 and gH2)). Additional analyses with worldwide isolates are encouraged. If differences in susceptibility are observed for different clinical isolates, the sponsor should conduct additional genotypic and phenotypic characterizations to identify genetic polymorphisms that may affect CMV susceptibility to the investigational drug. The sponsor should also assess sequestration of the drug by serum proteins and determine a serum-adjusted EC₅₀ value. We recommend evaluating the drug's antiviral activity at different concentrations of human serum and extrapolating the EC₅₀ value in the presence of 100 percent human serum.

- **Combination antiviral activity relationships**

If future combination therapy is anticipated, early in development the sponsor should characterize combination antiviral activity relationships between the investigational drug and approved drugs for CMV. The sponsor should identify any combinations for which the investigational drug is antagonistic by using cell culture assays. The sponsor should also assess each component of a drug that contains multiple novel agents (e.g., combinations of monoclonal antibodies) individually for antagonism with approved drugs. For all combination antiviral activity assessments, the sponsor should provide combination index values when the two agents are combined at their individual EC₅₀ values, and studies should include controls for cytotoxicity. The sponsor should also assess combination antiviral activity relationships for nucleos(t)ide and deoxynucleos(t)ide CMV investigational drugs with approved nucleos(t)ide and deoxynucleos(t)ide antiviral drugs targeting other viruses (e.g., hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV-1)), as appropriate, before testing combinations of the agents in co-infected patients.

- **Cytotoxicity and mitochondrial toxicity**

The sponsor should quantify directly the cytotoxic effects of the drug, including those that target the host, for the cells used to assess CMV antiviral activity. A 50 percent cytotoxic concentration (CC₅₀) should be determined, and the therapeutic index (CC₅₀ value/EC₅₀ value) should be calculated. The sponsor should assess cytotoxicity by using various human cell lines and primary cells cultured under proliferating conditions for several cell divisions and nonproliferating conditions.

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The sponsor should assess mitochondrial toxicity in both glucose- and galactose-containing media (Marroquin et al. 2007). In addition, for nucleoside analogs, the sponsor should evaluate the inhibition of mitochondrial ribonucleic acid polymerase as well as the potential inhibition of host DNA and/or RNA synthesis (Arnold et al. 2012). Positive controls for mitochondrial toxicity studies should be relevant to the class of the investigational drug whenever possible.

The sponsor should conduct these biochemical and cell-based assessments for potential cellular and mitochondrial toxicity as a complement to in vivo toxicology assessments and not in lieu of in vivo studies. Results from these studies should be interpreted in the context of the in vivo toxicology, nonclinical, and clinical pharmacokinetic data to help assess clinical risk. Antibodies specifically targeting viral proteins are unlikely to be cytotoxic and FDA typically would not recommend these assessments.

- **Considerations for antisense RNA and siRNA candidates**

Knockdown of viral protein expression via antisense RNA and siRNA has shown promise for the development of antiviral drugs. Drugs of this nature, which bind to a nucleic acid target, present potential mismatch issues that could lead to species-specific toxicities not detected in classical toxicity studies. Therefore, in addition to the cytotoxicity and toxicology assessments, we recommend that the following bioinformatic studies be conducted for drugs that target a nucleic acid:

- Potential off-target matches should be identified in the human transcriptome, regardless of tissue expression. For each of these, available information on mouse knockouts and human genetic diseases should be described. A plan for monitoring for significant off-target effects should be included in clinical trial protocols.
- The conservation among the candidate off-target human genes should be determined with their respective mouse genes that are three or fewer mismatched bases different from the drug to determine if these sites are sufficiently conserved in the mouse such that toxicities related to off-target matches would be present in mice.
- Potential off-target matches should be identified in the human mitochondrial transcriptome (see <https://omictools.com/the-mitochondrial-genome-browser-tool> or <http://www.mtodb.igp.uu.se/>, as well as other public sources for mitochondrial genome information).
- The variation within the off-target matches should be determined in the transcriptomes of different populations in the United States to assess whether different populations would be more susceptible than others to off-target effects.
- The effect of different mismatches with respect to off-target effects should be determined (i.e., comparing purine to purine versus other mismatches).

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- **Antiviral activity in animal models¹²**

Demonstrating CMV antiviral activity in an animal model is not required. However, if such studies are conducted and provided as part of nonclinical development, reported data should include the CMV strain designation, gB (UL55) and gH (UL75), genotypes (as well as any other CMV genes used for characterization, if known (Puchhammer-Stöckl and Görzer 2006)), the EC₅₀ value of the challenge virus, time course plots of viral load data for each animal, and an assessment of resistance development.

- **Resistance and cross-resistance**

The ability of CMV to develop resistance when subjected to drug pressure should be examined in appropriate cell culture models selecting and characterizing genotypically and phenotypically several independent resistant isolates. The sponsor should determine and validate amino acid substitutions associated with the development of resistance to the investigational drug by introducing the changes into the CMV genome (e.g., using bacterial artificial chromosome technology) and determining the fold-shift in susceptibility relative to the parental strain using appropriate cell culture and/or biochemical assays. Results from these studies should be used to: (1) characterize the genetic barrier to resistance (e.g., number of mutations required to confer reduced susceptibility, number of passages); (2) predict whether the genetic barrier for resistance may vary as a function of concentration of the investigational drug; (3) reveal potential resistance pathways and the potential for cross-resistance with other anti-CMV drugs; (4) assess the potential effect of polymorphisms at amino acid positions associated with resistance using available sequence databases; (5) provide preliminary information on assays that may be used in clinical studies; and (6) support the drug's hypothesized mechanism of action. Resistant viruses selected in cell culture can provide important controls for assessing clinical isolates phenotypically.

Resistance studies should include evaluation of the potential for cross-resistance, both to approved drugs and to drugs in development (when possible), particularly focusing on those in the same drug class and other classes with the same viral target. The sponsor should determine the antiviral activity of approved drugs against viruses resistant to the investigational drug and the antiviral activity of the investigational drug against viruses resistant to approved drugs. The resistance and cross-resistance studies may be important to support studies in patients who have developed resistance to approved treatments.

Some deoxynucleoside analogs for treating CMV infection have also been found to have antiviral activity against HIV-1 and can select for resistant variants (Tachedjian et al. 1995; Lisco et al. 2008; McMahon et al. 2008). Sponsors of such drugs should determine the cell culture antiviral activity of the active moiety against HIV-1 because these may be used in HIV-1-infected patients. If the drug demonstrates antiviral activity, the sponsor should determine the development of resistance to the investigational drug genotypically and phenotypically by

¹² We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

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selecting resistant HIV-1 variants. Resistance studies should include evaluation of cross-resistance to approved nucleos(t)ide reverse transcriptase inhibitors for HIV-1.

- **Targeting host factors**

For drugs targeting host factors, the sponsor should assess polymorphisms in the human population to determine whether the drug will be more or less effective in different populations. If a nonclinical assay to assess the drug effect is available (e.g., assays that are used to evaluate the binding activity of drugs targeting a specific receptor), the sponsor should evaluate the target host protein/factor from each of the key racial groups in the United States to determine whether race may be a factor in efficacy. Additionally, the sponsor should collect samples during clinical trials to determine the genotype of subjects who respond less favorably to treatment. We recommend that drugs targeting host functions be evaluated in animal models to demonstrate activity and assess for the potential for toxicities in infected animals.

- **Developing monoclonal antibodies**

The development of monoclonal antibodies (mAbs) for treating or preventing CMV disease should follow the same recommendations described above. In addition, the sponsor should assess the conservation (identity) at each amino acid position for the mAb binding site in available CMV sequence data for each CMV type/subtype as well as the dependence of binding upon the target protein's conformation. The sponsor should also identify the amino acid residues that may affect susceptibility for any isolates showing reduced susceptibility in cell culture studies. Sponsors developing monoclonal antibodies should evaluate any potential detrimental effects of the antibody, such as antibody-dependent enhancement of infection (Manley et al. 2011), and Fc-mediated, complement-dependent cytotoxicity.

c. **General considerations for phase 1 and phase 2 clinical development**

In general, the sponsor should conduct phase 1 trials to assess pharmacokinetics and safety of the investigational drug and, when possible, antiviral activity. Phase 2 trials should characterize doses of the investigational drug with regard to both antiviral activity and safety for further study in phase 3 trials. Specific trial design issues for CMV drug development depend on the intended indication and the intended patient population (SOT or HSCT recipients).

The following recommendations and examples provide information for potential phase 1 and phase 2 trial designs for CMV antiviral drugs.

- **Phase 1a/first-in-human studies**

For the first-in-human studies, we recommend studies in healthy adult subjects to assess safety, pharmacokinetics, and the ability to achieve target concentrations based on cell culture antiviral activity studies. The sponsor can also conduct single-dose and short-duration multiple-dose pharmacokinetic studies in subjects at risk for CMV disease (e.g., immunocompromised hosts), particularly if nonclinical data indicate that a drug may be genotoxic or otherwise unacceptable for studies in healthy volunteers.

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- **Phase 2 proof-of-concept trials**

For other antiviral drugs (e.g., drugs for treating HIV-1, HBV, or HCV infection), proof of concept for antiviral activity generally is demonstrated via short-term administration of the investigational drug to chronically infected patients with measurable levels of circulating virus. A reduction from baseline in plasma viral load over days or weeks is assessed to establish initial antiviral activity and to evaluate exposure-response relationships. For anti-CMV drugs, proof-of-concept trials may be somewhat more challenging because transplant recipients with CMV DNAemia are typically started immediately on antiviral treatment and generally would not be considered candidates for delaying approved treatments to participate in short-term monotherapy trials of investigational drugs without proven activity in humans.

Phase 2 trial design options to demonstrate proof of concept could include evaluation of reductions in CMV DNAemia or CMV replication in other compartments in patients with measurable virus with or without overt disease. Selection of patients and concomitant treatment are key considerations to avoid situations in which patients would not receive adequate standard of care (SOC). Examples of such designs include:

- Randomized, placebo-controlled, dose-ranging trial in which the investigational drug or placebo is added to SOC treatment (e.g., ganciclovir) or, in some cases, could be directly compared with SOC treatment in patients being treated for CMV viremia. The treatment period would be short (2 to 3 weeks), with a switch to SOC for the remaining duration of therapy. Antiviral activity is assessed as the degree of reduction in plasma CMV DNAemia from baseline after 2 to 3 weeks of treatment or proportion of patients with CMV DNAemia below the lower limit of quantitation (LLOQ) (target not detected or target detected) at a specified time point or rate of reduction of CMV DNA. A similar proof-of-concept trial could also be conducted in patients with CMV DNAemia that is resistant to SOC therapy.
- Assessment of antiviral activity in renal transplant recipients at low risk for progression to tissue-invasive CMV disease (e.g., D-/R+) with CMV viruria or low-level CMV viremia in a placebo-controlled trial with a switch to rescue therapy for progressive viremia above a prespecified threshold may be feasible in some settings.
- Randomized, placebo-controlled, dose-ranging trial to measure reductions in CMV shedding in semen or in urine in asymptomatic patients with underlying immune suppression, such as HIV-1 infection, who generally would not be treated for asymptomatic CMV infection.

Before adding the investigational drug to other approved therapies, the sponsor should assess the potential for drug-drug interactions, as drug interaction studies may be recommended if there is a likelihood of a pharmacokinetic interaction.

Ideally, doses selected for early phase 2 trials should provide plasma and/or tissue drug exposures that exceed by severalfold the protein binding-adjusted, cell culture EC₅₀ value of the

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drug. When evaluating doses, the sponsor should also take into account any safety margins previously identified in both animal toxicology studies and studies conducted in healthy volunteers.

The sponsor can use results from proof-of-concept antiviral activity trials to guide dose selection for subsequent phase 2b or phase 3 trials in which anti-CMV therapy is studied for longer durations.

- **Phase 2b trials**

The same trial designs discussed for phase 3 (section III. B., Phase 3 Efficacy Trial Considerations) could be used for phase 2b trials; however, phase 2b trials generally should include more doses and fewer subjects per arm compared with phase 3 trials. The primary goal in phase 2b trials should be to determine doses and durations based on safety and efficacy considerations for further evaluation in phase 3 trials. Further dose discrimination for efficacy and safety can be evaluated in phase 3 trials with greater statistical power to detect smaller differences.

Trial randomization should be stratified according to baseline characteristics predicted to have a significant effect on treatment outcome (e.g., donor and recipient CMV serostatus). Initial trials should include frequent CMV virologic monitoring and individual and trial stopping rules for poor virologic outcomes (e.g., virologic breakthrough or relapse or progression to CMV disease). Protocols should include opportunities for patients with virologic failure or clinical progression to receive appropriate therapeutic rescue regimens. The sponsor should collect and include in final study reports and/or other appropriate regulatory submissions efficacy outcome data from all subjects, including those who received a therapeutic rescue regimen or regimens, as these data could be informative for future clinical trials. As safer and more tolerable and efficacious drugs become available, we anticipate that the risk-benefit considerations for patient populations will evolve.

Specific information recommended to support phase 3 trials includes:

- Single- and multiple-dose pharmacokinetics and safety in healthy subjects or other populations, as appropriate
- Antiviral (anti-CMV) activity data from phase 2 clinical trials
- Human safety data in approximately 100 patients for the highest dose that will be evaluated further in phase 3 trials
- Data from clinical trials or other sources supporting the proposed doses and duration of study drug chosen for further study
- Drug-drug interaction data if in vitro and/or in vivo study results suggest a potential for a drug interaction with other drugs likely to be used concomitantly in phase 3 trials

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For an end-of-phase 2 meeting, efficacy and safety data from each of the regimens under study in phase 2 trials should be available to select drug regimens and patient populations for study in phase 3.

2. Drug Development Population

The drug development population for efficacy trials should be transplant recipients at risk for CMV disease, including:

- HSCT recipients
- SOT recipients, including kidney, liver, heart, lung, pancreas, and other SOT recipients

FDA may recommend supportive data to define safety and pharmacokinetics before trials are conducted in specific subgroups. This may include data from hepatic or renal impairment trials and drug-drug interaction trials (e.g., drug-drug interaction trials with immunosuppressants used post-transplantation).

Trials should include adequate U.S. subject representation to ensure the applicability of trial results to the U.S. population. An adequate representation of sexes, races, ages, and virus types is also recommended during drug development. Sponsors should share their pretrial initiation work with the FDA to ensure the sites selected have a sufficient number of subjects from these populations (e.g., women, Black/African Americans, Hispanic/Latinos, Asian Americans) to enroll in phase 2 and phase 3 clinical trials. Extending trial site enrollment caps to allow for enrollment of underrepresented populations can also help to increase trial diversity.

3. Efficacy Considerations

Sponsors can submit a marketing application to gain approval of a drug for a single indication (prophylaxis or treatment) in one or more populations or can submit a marketing application for multiple indications. Generally, applications include at least two adequate and well-controlled trials.¹³ However, two trials may not be needed for every indication and population. Generally, FDA would consider trials for different indications (prophylaxis or treatment) and in different populations (HSCT or SOT recipients) supportive of each other. Sponsors should consult the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) regarding circumstances in which one phase 3 clinical trial may be supportive of approval.

¹³ See section 505(d) of the Federal Food, Drug & Cosmetic Act (FD&C Act)(21 U.S.C. 355(d)).

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Because CMV disease in transplant recipients is considered serious and life-threatening, and because only limited therapeutic options are available to treat or prevent CMV disease, investigational drugs for CMV may be eligible for fast track, priority review, or breakthrough therapy designation.¹⁴

4. Safety Considerations

The FDA recommends that sponsors engage in early discussions with the DAVP on trial designs as well as on the proposed size of the safety database that depends on the patient population and proposed indication. Because CMV disease is serious and life-threatening in immunocompromised patients, a safety database of 300 to 500 patients who received the proposed dose and duration of the drug generally should be sufficient to assess risk-benefit for an initial marketing application. FDA may recommend a safety database with fewer patients for investigational drugs that demonstrate substantial improvement in efficacy and safety compared with currently available therapeutic options. On occasion, specific findings from nonclinical or clinical development may lead FDA to recommend a larger safety database to adequately evaluate potential drug toxicity. If significant safety signals emerge during drug development, we may recommend that the safety database be increased or that specific safety studies be conducted. For marketing applications containing trials evaluating treatment of CMV disease in patients who have failed or developed resistance to approved treatments, a safety database of approximately 300 patients may be recommended.

Ideally, safety data from controlled and comparative trials are recommended to assess the safety of an investigational drug. We recommend that sponsors provide controlled and comparative safety data to an approved and clinically accepted SOC treatment (or placebo, if appropriate). In some situations, we may recommend uncontrolled or historically controlled data as supportive data for marketing applications.

B. Phase 3 Efficacy Trial Considerations

1. Trial Design

Phase 3 trial design depends on the proposed indication or indications and the intended population or populations for use. Following are examples of trial designs that could be considered for evaluating CMV antiviral therapy in transplant recipients.

a. Preventing CMV disease

Preventing CMV disease in transplant recipients includes both prophylaxis (administering an anti-CMV drug to at-risk subjects with no evidence of CMV DNAemia or CMV disease) and preemptive therapy (preventing CMV disease by treating subjects with CMV DNAemia). The

¹⁴ See sections 506(a) and (b) of the FD&C Act (21 U.S.C. 356(a) and (b)) and the current Prescription Drug User Fee Act goals letter, which is available at <https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf>. For more information, see the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).

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following sections discuss examples of trial designs for CMV prophylaxis or preemptive therapy in SOT or HSCT populations.

- **CMV prophylaxis trials in SOT recipients**

Examples of clinical trial designs that can be considered for evaluating CMV prophylaxis in SOT recipients include the following:

- *Noninferiority Trials.* In a randomized, double-blinded, active-controlled trial, high-risk (D+/R-) SOT recipients would be randomized to receive the SOC regimen or the investigational drug for at least 100 days (200 days for kidney transplant recipients) post-transplantation. The primary endpoint would be the proportion of subjects who develop CMV disease (CMV syndrome or tissue-invasive CMV disease). The duration of follow-up depends on the duration of prophylaxis, type of organ transplant, and other factors, such as expected timing of immune recovery post-transplantation. In general, subjects should be followed for an adequate time to ensure that they are not at increased risk for late-onset CMV disease.

The size of the noninferiority margin would depend on the specific patient population being studied as well as other factors. Sponsors should discuss with the DAVP their justification for the proposed noninferiority margin, the proposed trial design, the data analysis plan, and plans for long-term follow-up postmarketing. See the Appendix for additional considerations regarding clinical trials to evaluate CMV prophylaxis in liver transplant recipients.

- *Superiority Trials.* In a randomized, double-blinded superiority trial, the SOC would be used as comparator. Alternatively, in an add-on superiority trial, transplant recipients would be randomized to receive the investigational drug plus SOC or SOC alone. The primary endpoint would be the incidence of CMV disease.

- **CMV prophylaxis trials in HSCT recipients**

Examples of clinical trial designs that can be considered for evaluating CMV prophylaxis in HSCT recipients include the following:

- *Noninferiority Trials.* In a randomized, double-blinded, active-controlled trial, high-risk (CMV seropositive) HSCT recipients would be randomized to receive the SOC regimen or the investigational drug for at least 100 days post-transplantation. The primary endpoint would be a composite endpoint defined as the occurrence of either tissue-invasive CMV disease or the initiation of anti-CMV preemptive therapy based on clinically significant CMV DNAemia. The endpoint would likely be driven by the incidence of CMV DNAemia. The FDA considers CMV viremia (DNAemia) a validated surrogate endpoint whose use in efficacy studies would enable the Agency to grant traditional approval for NDAs for prophylaxis trials in HSCT recipients.

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- *Superiority Trials.* A superiority trial of the investigational drug using a blinded comparison against the SOC may be appropriate in CMV seropositive HSCT recipients. Enrolled transplant recipients would be randomized to receive SOC or the investigational drug for at least 100 days post-transplantation or until a time when most patients are expected to achieve immune recovery.¹⁵ Alternatively, in an add-on superiority trial, transplant recipients would be randomized to receive the investigational drug plus SOC or SOC alone. The primary endpoint would be a composite endpoint, as defined above.

- **Preemptive therapy in SOT or HSCT recipients**

Preemptive therapy (antiviral therapy initiated when CMV DNAemia is detected at a level above a predetermined threshold without evidence of tissue-invasive CMV disease or CMV syndrome) depends on frequent and regular monitoring for CMV DNAemia. The goal of preemptive therapy is to prevent tissue-invasive CMV disease. In the past, establishing universal quantitative viral thresholds for initiation of preemptive therapy has been difficult because of differences in assay performance and sample type (whole blood versus plasma) but may now be more feasible with the publication of the World Health Organization standard for CMV DNA quantification (Fryer et al. 2010) and with the availability of approved assays.¹⁶

Some examples of preemptive therapy trial designs that could be used in these populations include:

- *Superiority Trials.* Superiority trials of the investigational drug versus intravenous ganciclovir or oral valganciclovir, or add-on superiority trials in which subjects are randomized to the investigational drug or placebo added to an SOC background therapy (e.g., intravenous ganciclovir or oral valganciclovir), may be feasible. In superiority trials for this indication, efficacy could be assessed using the clinical endpoint of the absence of CMV disease (tissue-invasive CMV disease or CMV syndrome in SOT recipients or tissue-invasive CMV disease in HSCT recipients) or by using a composite endpoint (undetectability of CMV DNAemia and absence of CMV disease at a specific time point).

Other trial designs could include duration of treatment or dose-ranging superiority trials in which shorter and longer durations of treatment or higher versus lower doses are compared. Superiority of the longer duration or of the higher dose would demonstrate efficacy of the investigational drug.

b. Treating CMV disease

The following section discusses considerations for clinical trial design for treating CMV disease in SOT or HSCT recipients, including treating CMV infections resistant or refractory to current SOC therapy.

¹⁵ Other treatment durations may be proposed based on scientific rationale.

¹⁶ <https://www.fda.gov/medical-devices/vitro-diagnostics/nucleic-acid-based-tests>.

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- **Treating CMV disease in SOT and HSCT recipients**

In the SOT setting, CMV disease refers to either tissue-invasive CMV disease or CMV syndrome, as defined in section III. B. 8., Efficacy Endpoints. In HSCT recipients, CMV disease refers only to tissue-invasive CMV disease.

Options for trial designs for CMV disease treatment trials in either SOT or HSCT recipients include:

- *Superiority Trials.* Trials to demonstrate superiority to SOC therapy, or add-on superiority trials in which subjects are randomized to the investigational drug or placebo added to an SOC therapy (e.g., intravenous ganciclovir or oral valganciclovir), are feasible and appropriate. The primary endpoints would include both resolution or improvement of clinical signs and symptoms of CMV disease and CMV DNAemia below LLOQ (target not detected or target detected).
- *Noninferiority Trials.* No antiviral drugs have been approved for treating CMV disease in SOT or HSCT recipients. Therefore, noninferiority trials are not feasible for this indication unless the treatment effect for the SOC anti-CMV therapy over placebo can be determined for treating CMV disease in these populations to support a noninferiority margin.

- **Treating CMV infections resistant or refractory to CMV antiviral drugs in transplant recipients**

Trials for treating CMV infections resistant or refractory to treatment with available drugs (e.g., ganciclovir/valganciclovir, foscarnet) could include treating CMV disease or CMV viremia. Definitions of resistant and refractory CMV infection for use in trials in this population should be discussed with and agreed upon by DAVP. For trials that include both groups of patients (resistant and refractory to treatment), the sponsor should demonstrate statistical significance in the overall population. Efficacy in the subgroups of patients who are resistant or refractory to CMV antiviral drugs should be consistent with the overall treatment effect.

Trial design options for these populations would include a superiority trial comparing the investigational drug versus SOC therapy or an add-on superiority trial comparing the investigational drug plus SOC versus SOC treatment alone (if the two drugs did not demonstrate antagonism in combination antiviral activity assessments).

2. *Trial Population*

As mentioned, this guidance focuses on treating or preventing CMV disease in SOT and HSCT recipients. Some of the specific issues with regard to trial population for these indications are discussed below:

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- *CMV Prophylaxis in SOT Recipients.* For trials evaluating an investigational drug for CMV prophylaxis in SOT recipients, patients should be high risk based on CMV serostatus (D+/R-).
- *CMV Prophylaxis in HSCT Recipients.* Trials of the investigational drug versus SOC should be conducted in CMV seropositive (R+) HSCT recipients, who are at the highest risk for CMV infection and disease.
- *Preemptive Therapy in SOT or HSCT Recipients.* Preemptive therapy can be studied in any transplant recipient who has evidence of CMV DNAemia at levels above a prespecified threshold.
- *Treating CMV Disease.* Any SOT or HSCT recipient with CMV disease, regardless of CMV serostatus of donor and recipient, could be included in treatment trials. In trials evaluating treatment in SOT recipients, a sufficient number of subjects with tissue-invasive CMV disease should be enrolled (and not just those with CMV syndrome) to support an indication for treating CMV disease.
- *Treating CMV Infections Resistant or Refractory to CMV Antiviral Drugs in Transplant Recipients.* Any SOT or HSCT recipient with CMV infection or disease resistant or refractory to available CMV antiviral drugs could be included in these trials.

3. Entry Criteria

Following are specific considerations for trial entry criteria for CMV treatment or prevention trials:

- *Prophylaxis Trials in SOT or HSCT Recipients.* To be enrolled in a CMV prophylaxis trial, the transplant recipient should have no detectable CMV infection post-transplantation, as documented by CMV DNA testing with PCR in plasma (less than LLOQ, target not detected), within 5 days before initiation of therapy.
- *Preemptive Therapy Trials in SOT or HSCT Recipients.* In clinical practice, virologic thresholds for initiating preemptive therapy in HSCT recipients have been based on preestablished risks for CMV disease (Boeckh and Ljungman 2009). For clinical trials, optimal virologic thresholds for initiating preemptive therapy have not been established. Proposed virologic thresholds for initiating preemptive therapy for CMV viremia in clinical trials should be discussed with and agreed upon by the DAVP.
- *Treatment Trials in SOT or HSCT Recipients with CMV Disease.* To be enrolled in a CMV treatment trial, transplant recipients should have virological evidence of CMV replication with signs and symptoms of CMV syndrome or tissue-invasive CMV disease (SOT recipients) or with clinical evidence of tissue-invasive CMV disease (HSCT recipients).

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- *Treatment Trials in Patients with CMV Infections Resistant or Refractory to CMV Antiviral Drugs.* CMV isolates at baseline should have evidence of resistance to CMV antiviral drugs by genotypic analysis. Patients with CMV disease refractory to treatment can be included, but the inclusion criteria for subjects refractory to therapy should be rigorously defined in the protocol.

4. Randomization, Stratification, and Blinding

Sponsors should conduct randomized, double-blinded trials whenever feasible. For add-on superiority trials of an investigational drug added to SOC therapy compared with SOC therapy alone, subjects randomized to the latter should receive a matching placebo.

Sponsors designing trials in which blinding may be difficult or infeasible should discuss their proposals with the DAVP in advance to review potential modifications that might facilitate blinding and to discuss the potential effect of open-label therapy on interpretation of results.

Sponsors should consider stratifying subjects by important baseline risk factors for CMV infection/disease in HSCT recipients, such as CMV serostatus of donor and recipient and other factors associated with risk of CMV disease. For SOT recipients, sponsors should consider stratifying by CMV serostatus of donor and recipient and the type of transplant (e.g., kidney, liver, lung).

In trials that include both SOT and HSCT recipients, sponsors should consider stratifying by type of transplant (SOT or HSCT).

5. Pediatric Populations

Sponsors are encouraged to begin discussions about their pediatric formulation and clinical development plan early in development because pediatric clinical trials are a required part of the overall drug development program.¹⁷ Under the Pediatric Research Equity Act, sponsors must submit an initial pediatric study plan to the FDA no later than 60 days after the end-of-phase 2 meeting.¹⁸

FDA recommends that inclusion of pediatric patients in clinical trials generally can be initiated after sufficient safety, pharmacokinetic, and efficacy data are available from adults. If clinical trials in adults have demonstrated no significant safety concerns that would preclude study in children, the FDA encourages evaluating adolescents using the adult dose and formulation (Momper et al. 2013). However, sponsors should discuss with the DAVP the initial pediatric pharmacokinetic data and results of available modeling and simulation before selecting doses for

¹⁷ See section 505B(e) of the FD&C Act (21 U.S.C. 355c(e)).

¹⁸ See section 505B(e)(2)(A) of the FD&C Act (21 U.S.C. 355c(e)(2)(A)) and the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (March 2016). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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pediatric treatment trials. Depending on results of the adult clinical trials, and on whether efficacy in adults can be extrapolated to pediatric patients (i.e., if the course of disease and the effect of the drug are sufficiently similar in adults and pediatric patients), either comparative or single-arm trials may be recommended in pediatric subjects.¹⁹ Sponsors' pediatric study plans should include information to support pediatric extrapolation if extrapolation is planned.

6. Dose Selection

To guide optimal dose selection and treatment durations in phase 3 trials, sponsors should consider safety and efficacy results from previous trials and exposure-response relationships for safety and efficacy. For treatment trials, we recommend that sponsors develop a mechanistic model of the kinetics of viral load reduction that can assist with the optimization of dose selection and treatment duration to reduce the risk of selecting for resistant viruses caused by subtherapeutic exposures. Such a model should include a mechanistically appropriate targeted drug effect, components to describe virologic breakthroughs and virologic responses, and relevant covariates for describing differences in response. When applicable, these mechanistic modeling approaches can use viral kinetic model structures and corresponding disease progression-parameter values from the literature.

Sponsors can select a range of doses and treatment durations for phase 3 trials if there are uncertainties about the optimal regimen or if the model indicated a different dose or treatment duration to be better for certain subpopulations, such as patients having CMV with baseline ganciclovir resistance. Sponsors can also consider an adaptive design for the dose selection.

7. Use of Active Comparators

In general, the active comparator in a noninferiority trial should be an FDA-approved drug that is considered the SOC for the specific indication and population being studied. Sponsors should justify proposed noninferiority margins and discuss them with the DAVP. See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016) for additional information on determining noninferiority margins.

8. Efficacy Endpoints

FDA recommends the definitions for CMV infection and disease for use in clinical trials that are advocated by Ljungman and colleagues (Ljungman et al. 2017).

a. CMV prophylaxis trials in SOT recipients

FDA recommends that the primary endpoint for trials of CMV prophylaxis in SOT recipients be a clinical endpoint of CMV disease and includes both CMV syndrome and tissue-invasive CMV disease measured at 6 or 12 months post-transplantation depending on duration of prophylaxis.

¹⁹ For additional information on pediatric extrapolation, see the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014). When final, this guidance will represent the FDA's current thinking on this topic.

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The diagnosis of CMV syndrome and tissue-invasive CMV disease should be confirmed by an independent, blinded, clinical adjudication committee.

FDA recommends that the secondary endpoints in CMV prophylaxis trials for SOT recipients could include but are not limited to the following. However, only a limited number of such endpoints should be considered for testing using appropriate statistical methods for multiplicity:

- The proportion of subjects with CMV disease at time points other than the time point used for the primary endpoint
- The time to development of CMV disease
- The proportion of subjects with investigator-treated CMV disease
- The initiation of other anti-CMV therapy
- The proportion of subjects with CMV DNAemia at different time points
- The time to development of CMV DNAemia
- Survival at different time points
- The proportion of subjects experiencing biopsy-proven acute rejection
- The proportion of subjects with graft loss
- The proportion of subjects with opportunistic infections
- The proportion of subjects developing genotypic changes associated with CMV resistance to the investigational drug

b. CMV prophylaxis trials in HSCT recipients

FDA recommends that the primary endpoint for a phase 3 prophylaxis trial in HSCT recipients be a composite endpoint defined as the occurrence of CMV disease or the initiation of preemptive therapy based on clinically significant CMV DNAemia (as measured by a central virology laboratory) within 6 months post-transplantation.

Viral load thresholds for initiating preemptive therapy should be based on the risks for CMV disease (Boeckh and Ljungman 2009). FDA's recommendations regarding virologic thresholds for initiating preemptive therapy will depend on the assay and specimen (whole blood versus plasma), the risk of CMV infection/disease in the population under study, and individual patient risk factors. Sponsors should agree upon virologic thresholds with the DAVP before initiating trials.

FDA recommends that the secondary endpoints in CMV prophylaxis trials for HSCT recipients could include but are not limited to:

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- The proportion of subjects with tissue-invasive CMV disease
- The proportion of subjects with CMV DNAemia
- The time to onset of CMV infection (DNAemia)/tissue-invasive CMV disease through 6 months or 12 months post-transplantation
- Survival at 6 and 12 months post-transplantation
- The proportion of subjects with opportunistic infections other than CMV infection
- The proportion of subjects developing resistance to the investigational drug

c. CMV preemptive therapy trials in SOT or HSCT recipients

FDA recommends that the primary endpoint for phase 3 trials of preemptive therapy in either SOT or HSCT patients be a composite endpoint defined as the proportion of subjects with CMV DNA less than LLOQ (target not detected or target detected) and absence of CMV disease at a prespecified time point after treatment initiation.

d. Treating CMV disease in SOT or HSCT recipients

FDA recommends that the primary endpoint in a phase 3 trial in either SOT or HSCT recipients with tissue-invasive CMV disease (for SOT or HSCT) or CMV syndrome (for SOT) be the proportion of responders at a prespecified time point after treatment is initiated. Response should include the following elements:

- Substantial improvement/resolution of signs and symptoms of tissue-invasive CMV disease or CMV syndrome
- CMV DNAemia less than LLOQ (target not detected or target detected) in two consecutive tests taken at least 5 to 7 days apart
- No new occurrence of CMV disease at other sites
- No evidence for relapse (CMV disease or DNAemia) within a prespecified time frame after stopping therapy

Specific details regarding the primary endpoint should be discussed with and agreed upon by the DAVP.

FDA recommends that the secondary endpoints could include but are not limited to:

- The time to CMV DNA less than LLOQ (target not detected or target detected)

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- The time to resolution of signs and symptoms of tissue-invasive CMV disease or CMV syndrome
- Patient survival
- The development of opportunistic infections, graft rejection or failure
- The development of antiviral resistance

9. Trial Procedures and Timing of Assessments

For trials of investigational drugs for treating or preventing CMV disease in the post-transplant setting, rescue therapy for developing CMV disease or CMV viremia should be included in the protocol. Quantitative CMV DNA should be measured frequently during clinical trials. Treatment of CMV disease should continue at least until CMV DNAemia is less than LLOQ (target not detected or target detected) for at least two consecutive measurements performed at a prespecified interval, and treatment duration should be recorded. Sponsors should consider longer treatment based on the kinetics of viral load reduction because several logs of CMV may be present when an assay reports less than LLOQ (target detected). In prophylaxis trials, CMV DNA should be monitored routinely during the trial and subjects should be monitored for development of signs and symptoms of CMV disease. In treatment trials (including preemptive therapy), frequent monitoring of CMV DNA should continue after discontinuation of therapy to detect relapse of CMV viremia during the risk period.

10. Endpoint Adjudication

Determination of tissue-invasive CMV disease and CMV syndrome endpoints should be adjudicated by an independent endpoint-assessment committee conducting a blinded review of clinical source data (Ljungman et al. 2017).

11. Statistical Considerations

In general, sponsors should submit a detailed statistical analysis plan stating the trial hypotheses and analysis methods before initiating the trial. Statistical analysis methods and issues are discussed in detail in the guidances for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* and *Non-Inferiority Clinical Trials to Establish Effectiveness* and the article “Statistical Considerations on Subgroup Analysis in Clinical Trials” (Alosh et al. 2015).

a. Analysis populations

Generally, sponsors should include in the primary efficacy analysis all subjects who are randomized and receive at least one dose of assigned therapy during the trial. However, if a substantial proportion of randomized subjects do not receive treatment in either or both arms, then FDA may recommend additional analyses.

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b. Efficacy analyses

The primary efficacy analyses in prophylaxis trials in SOT recipients should compare the incidence of CMV disease within 6 or 12 months post-transplantation across treatment arms.

The primary efficacy analyses in prophylaxis trials in HSCT recipients should compare the incidence of tissue-invasive CMV disease and clinically significant CMV DNAemia requiring initiation of preemptive therapy within 6 months post-transplantation across treatment arms.

The primary efficacy analyses in preemptive therapy trials should compare the proportion of SOT recipients or HSCT recipients with CMV DNAemia below LLOQ (target not detected or target detected) in the absence of CMV disease at a prespecified time point across treatment arms.

For subgroups, the analysis of the primary efficacy endpoint should be performed for important demographic and baseline characteristics (e.g., geographic region (United States, non-United States), sex, race, age group, high- versus low-risk group, donor CMV serostatus (D+ or D-), recipient CMV serostatus (R- or R+)). The purpose of these analyses is to explore the consistency of the primary efficacy endpoint result across these subgroups.

c. Handling of missing data

Sponsors should make every attempt to limit loss of subjects from the trial. We recommend that sponsors collect detailed data on reasons for trial discontinuation (e.g., opportunity to enter another trial offering a promising new treatment, death or events leading to death, disease progression, adverse events, loss to follow-up, withdrawal of consent, noncompliance, pregnancy, protocol violations, not discontinued or not known to be discontinued but data were missing at the final visit). For subjects who discontinue treatment early, sponsors should determine if these subjects switched treatments or added additional therapy.

Analyses excluding subjects with missing data or other post-treatment outcomes can be biased because subjects who do not complete the trial may differ substantially in both measured and unmeasured ways from subjects who remain in the trial. The method of how missing data will be handled should be prespecified in the protocol or the statistical analysis plan. FDA may recommend sensitivity analyses to demonstrate that the primary analysis results are robust to the assumptions regarding missing data.

12. Accelerated Approval Considerations

As explained above, FDA considers CMV viremia (DNAemia) a validated surrogate endpoint for use as part of a composite endpoint that includes a clinical component to support traditional approval; therefore, accelerated approval regulations generally are not applicable for CMV treatment and prevention indications.

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C. Other Considerations

1. Clinical Virology Considerations

Sponsors should use an FDA-approved assay to quantify CMV DNA in plasma. We recommend that CMV DNA in whole blood also be quantified for short-term monotherapy studies because this may improve sensitivity to detect antiviral activity. Additionally, plasma CMV DNA has been shown to be highly fragmented, so care should be taken when interpreting the CMV DNA levels (Boom et al. 2002). Virology analyses should be conducted at a central virology laboratory.

Proof-of-concept and efficacy trials should assess the development of CMV genotypic resistance to the investigational drug. In prophylaxis trials, resistance testing should be performed for subjects who have detectable CMV DNA at any time point or confirmed diagnosis of CMV disease, regardless of viral load. Observations of particular interest that should be reported include multiple occurrences of substitutions from the reference sequence or sequences at highly conserved amino acid residues, substitutions at positions identified in cell culture selection studies and treatment trials, and multiple occurrences of unusual substitutions at polymorphic residues.

In treatment trials, sponsors should perform resistance testing for subjects who demonstrate virologic breakthrough (defined as a greater than or equal to 1 log₁₀ increase in CMV DNA above nadir, or detectable CMV DNA, while on treatment, after an initial drop to undetectable), an incomplete antiviral response (e.g., detectable CMV DNA at end of treatment or slower rate of decline than the average response), a decline to a plateau viral load decay phase, or virologic relapse after treatment cessation. Sponsors should include a proposal of the subjects to be evaluated for resistance in their resistance analysis plans. Any amino acid changes, including mixtures, in the coding sequence of the targeted genome region present in on-treatment or follow-up samples, but not in the baseline sample, should be reported as having developed during therapy. In addition, sponsors should analyze baseline samples to identify CMV genetic polymorphisms that are associated with differential antiviral activity with the new investigational drug.

Sponsors should consider genotyping regions outside the direct CMV genome target depending on the characteristics of the antiviral drug and interactions of the target with other viral proteins or whole genome sequencing, if viral loads are adequate. In cases when resistance is suspected based on viral DNA kinetics but genotypic evidence of resistance is not detected, sponsors should also consider performing additional genotypic analyses using a method sufficiently sensitive to detect minority variants (e.g., next-generation sequencing). Ganciclovir/valganciclovir resistance-associated substitutions have been detected in specific compartments exclusively and not in blood. Therefore, sponsors should also consider genotyping samples collected from specific compartments.

Viral resistance-associated substitutions and baseline polymorphisms affecting response observed in clinical trials but not identified and characterized in nonclinical virology experiments should be evaluated phenotypically by introducing the changes into the CMV genome and

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determining the conferred fold-shift in susceptibility to the drug using appropriate cell culture and/or biochemical assays. In addition, sponsors should perform phenotypic analyses using baseline and on-treatment clinical isolates from a subset of trial subjects representative of the CMV genetic diversity and virologic responses observed in clinical trials. Phenotypic assays should include wild-type reference virus and resistant virus (initially from cell culture selection studies) controls.

For quantification of CMV DNA, we recommend that sponsors use an FDA-approved PCR assay or assays using a central laboratory. Sponsors should collect results from local laboratory tests, identifying the assay or assays used. If investigational assays are used, performance characteristics with geographically and temporally distinct isolates should be provided. Sponsors should report values that are less than LLOQ as “less than LLOQ, target not detected” or “less than LLOQ, target detected,” as appropriate.

The FDA performs independent assessments of virologic and resistance data. Before submitting virology datasets, sponsors should consult with the DAVP to obtain information on the most recent format and, in the case of next-generation sequence analysis, the procedure for submitting FASTQ files.

2. Pharmacokinetic/Pharmacodynamic Considerations

Sponsors should assess pharmacokinetics and the relationship between systemic drug exposure and virologic or clinical endpoints and safety. Virologic or clinical endpoints to be used for analyses depend on the proposed indication and trial designs.

Sponsors can use a combination of intensive and sparse blood sampling throughout development to characterize the pharmacokinetics of the investigational drug. An intensive sampling schedule is recommended in early-phase trials. In longer-term/late phase trials, however, an intensive blood sampling schedule might not be feasible or may be feasible only in a subset of subjects or over a limited period of time. Sponsors should obtain sparse pharmacokinetic samples from as many subjects in longer-term/late phase duration trials as possible and can combine the pharmacokinetic data from these trials with intensive pharmacokinetic data from earlier trials for analysis.

Sponsors can use pharmacokinetics and the relationship between systemic drug exposure and virologic or clinical responses in early-phase trials (i.e., proof-of-concept studies) to aid the design of phase 2b or phase 3 trials (e.g., dose selection and treatment duration). When sufficient efficacy and pharmacokinetic data are available, sponsors can use a simplified analysis relating proportion of subjects with treatment failure and appropriate exposure variable (e.g., trough concentration or area under the plasma drug concentration versus time curve) to support evidence of effectiveness of different dosage regimens. Sponsors should also perform analyses of the exposure-safety relationships using similar approaches to assist in evaluating the balance between effectiveness and safety toxicity of different dosage regimens.

GLOSSARY OF ACRONYMS

AIDS	acquired immunodeficiency syndrome
CC	cytotoxic concentration
CMV	cytomegalovirus
DAVP	the Division of Antiviral Products
DNA	deoxyribonucleic acid
EC	effective concentration
FDA	Food and Drug Administration
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
IND	investigational new drug application
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
NDA	new drug application
PCR	polymerase chain reaction
pre-IND	pre-investigational new drug application
SOC	standard of care
SOT	solid organ transplantation

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APPENDIX

**CLINICAL TRIAL DESIGN CONSIDERATIONS FOR CMV PROPHYLAXIS
IN LIVER TRANSPLANT RECIPIENTS**

At this time, FDA does not recommend a noninferiority trial with valganciclovir as comparator to evaluate efficacy in liver transplant recipients as the sole population in the trial because the efficacy of valganciclovir in this population has not been adequately demonstrated. In a randomized controlled trial in solid organ transplant recipients submitted for marketing authorization, valganciclovir was noninferior to oral ganciclovir in the overall trial population for preventing cytomegalovirus (CMV) disease (CMV syndrome and tissue-invasive CMV disease) post-transplantation.²⁰ However, among liver transplant recipients, who made up the largest subgroup (approximately 50 percent of patients enrolled), almost five times more tissue-invasive CMV disease (as determined by an adjudication committee) was reported with valganciclovir than with oral ganciclovir as prophylaxis (valganciclovir package insert).

These findings remain unexplained, and currently no antiviral drugs other than oral ganciclovir have been approved in the United States for CMV prophylaxis in liver transplant recipients. However, because valganciclovir generally is considered the standard of care in this population (Levitsky et al. 2008; Kotton et al. 2018) and because oral ganciclovir currently is not available in the United States, FDA may recommend that valganciclovir be used as a comparator in a superiority trial. Additionally, FDA may recommend that a noninferiority trial including recipients of different types of organ transplants (e.g., liver, heart, kidney, kidney-pancreas) using valganciclovir as comparator may be appropriate to demonstrate efficacy in liver transplant recipients if noninferiority is demonstrated for the overall trial population and the rate of CMV disease is similar between the liver transplant recipients and the other subpopulations for both the new treatment and the valganciclovir comparator. However, if the rate of tissue-invasive CMV disease is higher for liver transplant recipients than for other organ transplant recipients in the valganciclovir comparator arm, then noninferiority could not be concluded for liver transplant recipients.

²⁰ In a placebo-controlled trial, oral ganciclovir was shown to decrease the incidence of CMV disease in liver transplant recipients during the first 6 months post-transplantation (ganciclovir capsules package insert). However, oral ganciclovir is currently not available in the United States.