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

DRAFT GUIDANCE

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

**May 2018
Clinical/Antimicrobial**

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

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**U.S. Department of Health and Human Services
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Cytomegalovirus in Transplantation: Developing Drugs to Treat or Prevent Disease Guidance for Industry¹

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 for the treatment or prevention of cytomegalovirus (CMV) disease in patients who have undergone solid organ (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 biologics to support an indication for the treatment or prevention of CMV disease in post-transplant populations. This draft guidance is intended to serve as a focus for continued discussions among the Division of Antiviral Products (DAVP), pharmaceutical sponsors, the academic community, and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 the prevention or treatment of 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 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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37 *Principles for Clinical Trials and E10 Choice of Control Group and Related Issues in Clinical*
38 *Trials*, respectively.⁴

39
40 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
41 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
42 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
43 the word *should* in Agency guidances means that something is suggested or recommended, but
44 not required.

45

46

47 **II. BACKGROUND**

48

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

60

61 CMV is the single most frequent opportunistic pathogen in transplant recipients. The incidence
62 of CMV infection and disease in this population depends on a number of factors such as
63 transplant type, donor and recipient CMV serostatus, and the level of immunosuppression
64 (Ramanan and Razonable 2013). A transplant recipient is described by nomenclature that first
65 describes the donor’s CMV serostatus followed by the recipient’s CMV serostatus. For example,
66 D+/R- refers to a seronegative individual who has received a transplant from a seropositive
67 donor.⁵ In SOT, observational studies have demonstrated an association between donor and
68 recipient CMV serostatus and risk for CMV disease; D+/R- status is associated with a higher risk
69 (with rates of 50 to 60 percent) for developing CMV disease than CMV seropositive recipients
70 (D+/R+ or D-/R+) who have rates of 10 to 20 percent (Hartmann et al. 2006). The lowest rate of
71 CMV infection (less than 5 percent) occurs in CMV seronegative SOT recipients who received a
72 transplanted organ from a seronegative donor (D-/R-). In HSCT recipients, CMV seropositive
73 recipients (R+) are at the highest risk for development of CMV infection regardless of the
74 donor’s CMV serostatus. Without intervention, approximately 80 percent of CMV seropositive
75 HSCT patients will experience CMV infection (viremia) and approximately 30 percent of
76 patients with CMV viremia will develop CMV disease (Ljungman et al. 2010).

⁴ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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 antibodies to a previously acquired CMV infection and the term *CMV seronegative* denotes that anti-CMV antibodies are absent.

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

84

85 Because of the increased morbidity and mortality associated with CMV infection in transplant
86 recipients, it has been recognized that prevention of CMV disease may be a better strategy than
87 treatment of established CMV disease. Prophylactic therapy (treatment administered to all
88 patients at risk for developing CMV disease) and preemptive therapy (treatment of patients with
89 evidence of CMV replication in blood) are the two major strategies used for prevention (Boeckh
90 and Ljungman 2009; Tomblyn et al. 2009; Razonable et al. 2013; Kotton et al. 2013). Both
91 strategies have been shown to be useful for prevention of CMV disease in SOT and HSCT
92 recipients.

93

94 Although at present no large, randomized, controlled trials have directly compared the two
95 approaches, prophylaxis with oral valganciclovir has emerged as the most commonly used
96 clinical strategy for the prevention of CMV disease in high-risk SOT recipients in part because
97 of the convenient once daily dosing with this drug (Kotton 2013; Razonable et al. 2013). Until
98 recently, preemptive therapy rather than prophylaxis therapy was the preferred strategy in HSCT
99 patients because of the bone marrow toxicities of the available anti-CMV drugs (Boeckh and
100 Ljungman 2009). However, the approval of letermovir in late 2017 for prophylaxis of CMV
101 infection in adult CMV-seropositive recipients of an allogeneic HSCT is anticipated to change
102 the therapeutic approach in these patients (Marty et al. 2017).

103

104 Currently, there are limited therapeutic options for the treatment or prevention of CMV disease
105 in transplant patients. Only five drugs have received FDA approval for systemic use for the
106 treatment or prevention of CMV disease: letermovir, ganciclovir and its prodrug valganciclovir,
107 foscarnet, and cidofovir. Letermovir was approved for CMV prophylaxis in CMV-seropositive
108 recipients of an allogeneic HSCT; ganciclovir and valganciclovir were approved for the
109 prevention of CMV disease in transplant recipients, and for the treatment of CMV retinitis in
110 immunocompromised patients, including patients with AIDS. Foscarnet and cidofovir have
111 received FDA approval only for the treatment of CMV retinitis in AIDS patients. Moreover,
112 most of the existing treatments are associated with significant toxicity. These findings, coupled
113 with the emergence of resistance to available drugs (Lurain and Chou 2010; Komatsu et al.
114 2014), strongly support the urgent need for new therapeutic agents that are effective and less
115 toxic.

116

117 During the past 15 years, all phase 3 studies designed to support marketing applications for CMV
118 drugs were prophylaxis studies in SOT and/or HSCT recipients. The primary endpoint used in
119 these prophylaxis studies in SOT recipients was the incidence of CMV disease, including both
120 symptomatic CMV infection (also called *CMV syndrome*) and/or tissue-invasive CMV disease
121 (e.g., CMV colitis, hepatitis, or pneumonia). CMV syndrome is better defined in SOT than in
122 HSCT patients, mainly because the symptoms associated with CMV syndrome can have several

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123 other causes in the setting of HSCT, including other viral infections. Until recently, the primary
124 endpoint used in prophylaxis studies in HSCT patients was the incidence of tissue-invasive CMV
125 disease.

126
127 However, the results of recent trials revealed that in the current era of preemptive therapy for
128 CMV viremia based on optimized PCR assays, the incidence of tissue-invasive CMV disease in
129 HSCT recipients at 6 months post-transplantation was less than 5 percent (Marty et al. 2011).
130 These results call into question whether trials with tissue-invasive CMV disease as an endpoint
131 in HSCT patients are feasible, considering the sample sizes needed for such trials given the low
132 frequency of CMV disease. The accumulated clinical literature supports the premise that CMV
133 viremia predicts development of CMV disease in transplant patients (Gor et al. 1998; Emery et
134 al. 1999; Emery et al. 2000; Jang et al. 2012; Natori et al. 2018), that prophylaxis or preemptive
135 therapy prevents CMV disease (Green et al. 2016), and that the suppression of viremia is
136 associated with clinical resolution of CMV disease (Åsberg et al. 2007).

137
138 These observations have prompted the FDA to consider CMV viremia (DNAemia) as a
139 sufficiently validated endpoint to be used as a part of a composite endpoint to support traditional
140 approval. Therefore, traditional approval for new drug applications (NDAs) for CMV prophylaxis
141 trials in HSCT recipients can be based on a composite endpoint defined as the occurrence of
142 either CMV tissue-invasive disease or the development of CMV DNAemia above a prespecified
143 threshold. The consideration of CMV DNAemia as a part of a composite endpoint for other
144 indications (e.g., treatment) is also discussed in this guidance.

145

146

III. DEVELOPMENT PROGRAM

147

148

149

A. General Drug Development Considerations

150

151

1. Early Phase Development Considerations

152

153 General considerations pertinent to nonclinical development and early clinical development are
154 outlined in this section. Sponsors considering development of antiviral drugs for the treatment or
155 prevention of CMV disease are encouraged to communicate with the FDA through the pre-
156 investigational new drug application (pre-IND) consultation program.^{6,7} Pre-IND consultation
157 with the FDA is optional, although it may be particularly helpful for sponsors with limited
158 experience in the IND process or to obtain FDA advice in the development of drugs with unique
159 considerations based on mechanistic action, novel treatment approaches, or the use of novel
160 biomarkers.

161

6

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077776.htm>

7

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077546.htm>

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162 a. Pharmacology/toxicology development considerations
163

164 Pharmacology/toxicology development for CMV antivirals should follow existing guidance for
165 drug development. For detailed recommendations regarding pharmacology/toxicology
166 development for single antiviral drugs and for two or more new investigational drugs to be used
167 in combination, sponsors should consult the following ICH guidance on nonclinical safety
168 studies: For small molecules, see the ICH guidance for industry *M3(R2) Nonclinical Safety
169 Studies for the Conduct of Human Clinical Trials and Marketing Authorization for
170 Pharmaceuticals*; for biologics, see the ICH guidance for industry *S6 Preclinical Safety
171 Evaluation of Biotechnology-Derived Pharmaceuticals*.

172
173 Carcinogenicity studies are recommended if the expected treatment duration, including
174 intermittent use, is 6 months or longer (e.g., prevention indications).⁸ Carcinogenicity studies
175 can be submitted with an initial marketing application (i.e., NDA or biologics license
176 application) or as required postmarketing studies.

177
178 For drugs to be used in combination, ICH M3(R2) includes a discussion of nonclinical safety
179 studies appropriate in a combination drug development setting involving two early stage
180 entities.⁹ ICH M3(R2) defines early stage entities as compounds with limited clinical experience
181 (i.e., phase 2 studies or earlier).

182
183 b. Nonclinical virology development considerations
184

185 Nonclinical virology studies can facilitate initial dose selection, enable the design of a clinical
186 proof-of-concept study, and support an antiviral claim. Studies to support initial human trials
187 should be conducted before submission of an IND. Virology development for CMV treatment or
188 prevention should follow existing guidance for drug development.¹⁰ Additional
189 recommendations for nonclinical and clinical virology assessments specific to the development
190 of drugs for the treatment or prevention of CMV infection are summarized throughout this
191 guidance.

192
193 **Mechanism of action**
194

195 The mechanism by which a drug exhibits anti-CMV activity should be investigated using cell
196 culture, biochemical, structural, and/or genetic studies that include evaluation of the effect of the
197 drug on relevant stages of the virus life cycle and identification of the CMV target protein(s) for
198 direct-acting antivirals. Mechanism of action investigations should include appropriate controls
199 for assessing the specificity of anti-CMV activity, which may include assessments of activity
200 against other CMV proteins, relevant host proteins, other viruses, and/or cells infected with
201 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*.

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

¹⁰ See the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency*.

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

204

Antiviral activity data from cell culture studies

206

207 The antiviral activity of an investigational drug should be characterized in cell culture to identify
208 a target plasma concentration for evaluation in CMV-infected patients. Antiviral activity of
209 investigational drugs should be assessed using CMV laboratory isolates as well as several (more
210 than 20) geographically and temporally distinct isolates, the vast majority of which should be
211 U.S. isolates. The 50 percent and 90 percent effective concentrations (EC₅₀ and EC₉₀ values)
212 should be determined. These studies should include different CMV types (i.e., the four gB
213 (UL55) genotypes (gB1 through gB4) and the two gH (UL75) genotypes (gH1 and gH2)).
214 Additional analyses with worldwide isolates are encouraged. If differences in susceptibility are
215 observed for different clinical isolates, additional genotypic and phenotypic characterizations
216 should be conducted to identify genetic polymorphisms that may affect CMV susceptibility to
217 the investigational drug. Sequestration of the drug by serum proteins should also be assessed and
218 a serum-adjusted EC₅₀ value determined. We recommend evaluation of the drug's antiviral
219 activity at different concentrations of human serum and extrapolation of the EC₅₀ value in the
220 presence of 100 percent human serum.

221

Combination antiviral activity relationships

223

224 Early in development, cell culture combination antiviral activity relationships of the
225 investigational drug and approved drugs for CMV should be characterized to identify any
226 combinations where the antiviral activity is antagonistic if future combination therapy is
227 anticipated. Each component of a drug that contains multiple novel agents (e.g., combinations of
228 monoclonal antibodies) should be assessed individually for antagonism of approved drugs. For
229 all combination antiviral activity assessments, sponsors should provide combination index values
230 when the two agents are combined at their individual EC₅₀ values, and studies should include
231 controls for cytotoxicity. Combination antiviral activity relationships for nucleos(t)ide and
232 deoxynucleos(t)ide CMV investigational drugs should also be assessed with approved
233 nucleos(t)ide and deoxynucleos(t)ide antiviral drugs targeting other viruses (e.g., hepatitis B
234 virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV-1)), as
235 appropriate, before testing combinations of the agents in co-infected patients.

236

Cytotoxicity and mitochondrial toxicity

238

239 The cytotoxic effects of the drug should be quantified directly for the cells used to assess CMV
240 antiviral activity and a 50 percent cytotoxic concentration (CC₅₀) should be determined. The
241 therapeutic index (CC₅₀ value/EC₅₀ value) should be calculated. Cytotoxicity should also be
242 assessed using various human cell lines and primary cells cultured under proliferating conditions
243 for several cell divisions and nonproliferating conditions.

244

245 Mitochondrial toxicity should be assessed in glucose-containing and in galactose-containing
246 medium (Marroquin et al. 2007). In addition for nucleoside analogs, inhibition of mitochondrial
247 ribonucleic acid polymerase should be evaluated (Arnold et al. 2012). Positive controls for

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248 mitochondrial toxicity studies should be relevant to the class of the investigational drug
249 whenever possible.

250
251 These biochemical and cell-based assessments for potential cellular and mitochondrial toxicity
252 should be conducted as a complement to in vivo toxicology assessments and not in lieu of in
253 vivo studies. Results from these studies should be interpreted in the context of the in vivo
254 toxicology, nonclinical, and clinical pharmacokinetic data to help assess clinical risk.

255 256 Considerations for antisense RNA and siRNA candidates

257
258 Knockdown of viral protein expression via antisense RNA and siRNA has shown promise for the
259 development of antiviral drugs. Drugs of this nature, which bind to a nucleic acid target, present
260 potential mismatch issues that could lead to species-specific toxicities not detected in classical
261 toxicity studies. Therefore, we recommend that the following bioinformatic studies be
262 conducted for drugs that target a nucleic acid:

- 263
264 • Potential off-target matches should be identified in the human transcriptome, regardless
265 of tissue expression. For each of these, available information on mouse knockouts and
266 human genetic diseases should be described. A plan for monitoring for significant off-
267 target effects should be included in clinical trial protocols.
- 268
269 • The conservation among the candidate off-target human genes should be determined with
270 their respective mouse genes that are three or fewer mismatched bases different from the
271 drug to determine if these sites are sufficiently conserved in the mouse such that toxicities
272 related to off-target matches would be present in mice.
- 273
274 • Potential off-target matches should be identified in the human mitochondrial
275 transcriptome (e.g., <https://omictools.com/the-mitochondrial-genome-browser-tool> or
276 <http://www.mtodb.igp.uu.se/>, as well as other public sources for mitochondrial genome
277 information).
- 278
279 • The variation within the off-target matches should be determined in the transcriptomes of
280 different populations in the United States to assess whether different populations would
281 be more susceptible to off-target effects than others.
- 282
283 • The effect of different mismatches with respect to off-target effects should be determined
284 (i.e., comparing purine to purine versus other mismatches).

285 286 Antiviral activity in animal models

287
288 Demonstration of CMV antiviral activity in an animal model is not required. However, if such
289 studies are conducted and provided as part of nonclinical development, reported data should
290 include the CMV type/subtype used (e.g., four gB (UL55) genotypes and two gH (UL75)
291 genotypes), the EC₅₀ value of the challenge virus, time course plots of viral load data for each
292 animal, and an assessment of resistance development.

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294 **Resistance and cross-resistance**

295
296 The ability of CMV to develop resistance when subjected to drug pressure should be examined
297 in appropriate cell culture models selecting and characterizing genotypically and phenotypically
298 several independent resistant isolates. Amino acid substitutions associated with the development
299 of resistance to the investigational drug should be determined and validated by introducing the
300 changes into the CMV genome (e.g., using bacterial artificial chromosome technology) and
301 determining the fold-shift in susceptibility relative to the parental strain using appropriate cell
302 culture and/or biochemical assays. Results from these studies should be used to: (1) determine
303 whether the genetic barrier for resistance development is high or low; (2) predict whether the
304 genetic barrier for resistance may vary as a function of concentration of the investigational drug;
305 (3) reveal potential resistance pathways and the potential for cross-resistance with other anti-
306 CMV drugs; (4) assess the potential effect of polymorphisms at amino acid positions associated
307 with resistance using available sequence databases; (5) provide preliminary information on
308 assays that may be used in clinical studies; and (6) support the drug's hypothesized mechanism
309 of action. Resistant viruses selected in cell culture can provide important controls for assessing
310 clinical isolates phenotypically.

311
312 Resistance studies should include evaluation of the potential for cross-resistance, both to
313 approved drugs and to drugs in development (when possible), particularly focusing on those in
314 the same drug class and other classes with the same viral target. The antiviral activity of
315 approved drugs against viruses resistant to the investigational drug and the antiviral activity of
316 the investigational drug against viruses resistant to approved drugs should be determined. The
317 resistance and cross-resistance studies may be important to support studies in patients who have
318 developed resistance to approved treatments.

319
320 Some deoxynucleoside analogs for the treatment of CMV have also been found to have antiviral
321 activity against HIV-1 and can select for resistant variants (Tachedjian et al. 1995; McMahon et
322 al. 2008; Lisco et al. 2008). Sponsors of such drugs should determine the cell culture antiviral
323 activity of the active moiety against HIV-1 because these may be used in HIV-positive patients.
324 If the drug demonstrates antiviral activity, development of resistance to the investigational drug
325 should be determined genotypically and phenotypically by selecting resistant HIV-1 variants.
326 Resistance studies should include evaluation of cross-resistance to approved nucleos(t)ide
327 reverse transcriptase inhibitors for HIV-1.

328 329 **Targeting host factors**

330
331 For drugs targeting host factors, polymorphisms in the human population should be assessed to
332 determine if the drug will be more or less effective against different populations. If a nonclinical
333 assay to assess the drug effect is available, multiple samples from each of the key racial groups
334 in the United States should be evaluated to determine whether or not race may be a factor in
335 efficacy. Samples should be collected during clinical trials to determine the genotype of subjects
336 who respond less favorably to treatment. We recommend that drugs targeting host functions be
337 evaluated in animal models to demonstrate activity and assess for the potential for toxicities in
338 infected animals.

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340 **Development of monoclonal antibodies**

341
342 The development of monoclonal antibodies (mAbs) for CMV treatment or prevention should
343 follow the same recommendations described above. In addition, the conservation (identity) at
344 each amino acid position for the mAb binding site in available CMV sequence data for each
345 CMV type/subtype should be assessed as well as the dependence of binding upon the target
346 protein's conformation. The amino acid residues that may affect susceptibility for any isolates
347 showing reduced susceptibility in cell culture studies should be identified. Sponsors developing
348 monoclonal antibodies should evaluate the potential for antibody dependent enhancement of
349 infection (Manley et al. 2011).

350
351 c. General considerations for phase 1 and phase 2 clinical development

352
353 In general, phase 1 trials should be conducted to assess pharmacokinetics and safety of the
354 investigational drug and when possible, antiviral activity. Phase 2 trials should characterize
355 doses of the investigational drug with regard to both antiviral activity and safety for further study
356 in phase 3 trials. Specific study design issues for CMV drug development depend on the
357 intended indication(s) (prevention or treatment of CMV disease) and the intended patient
358 population(s) (SOT or HSCT recipients).

359
360 The following information provides recommendations and examples for potential phase 1 and
361 phase 2 trial designs for CMV antivirals based on the current state of the field.

362
363 **Phase 1a/first-in-human trials**

364
365 For the first-in-human trials, we recommend single- and/or multiple-ascending-dose trials in
366 healthy adult subjects to assess safety, pharmacokinetics, and the ability to achieve target
367 concentrations based on cell culture antiviral activity studies. Single-dose and short-duration
368 multiple-dose pharmacokinetic trials can also be conducted in subjects at risk for CMV disease
369 (e.g., immunocompromised hosts), particularly if nonclinical data indicate that a drug may be
370 genotoxic or otherwise unacceptable for studies in healthy volunteers.

371
372 **Phase 2 proof-of-concept trials**

373
374 For other antiviral drugs (e.g., drugs for treatment of HIV, HBV, or HCV infection), proof of
375 concept for antiviral activity generally is demonstrated via short-term administration of the
376 investigational drug to chronically infected patients with measurable levels of circulating virus.
377 A reduction from baseline in plasma viral load over days or weeks is assessed to establish initial
378 antiviral activity and to evaluate exposure-response relationships. For anti-CMV drugs, proof-
379 of-concept trials may be somewhat more challenging because transplant recipients with CMV
380 DNAemia are typically started immediately on antiviral treatment and generally would not be
381 considered candidates for delaying approved treatments to participate in short-term monotherapy
382 trials of investigational drugs without proven activity in humans.

383
384 Phase 2 trial design options to demonstrate proof of concept could include evaluation of
385 reductions in CMV DNAemia (or by monitoring CMV replication in other compartments) in

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386 patients with measurable virus with or without overt disease. In either category, selection of
387 patients and concomitant treatment are key considerations to avoid situations in which patients
388 would not receive adequate standard of care (SOC). Examples of such designs include:
389

- 390 • Randomized, placebo-controlled, dose-ranging trial in which the investigational drug or
391 placebo is added to SOC treatment (e.g., ganciclovir) or, in some cases, could be directly
392 compared to SOC treatment in patients being treated for CMV viremia. The treatment
393 period would be short (2 to 3 weeks) with a switch to SOC for the remaining duration of
394 therapy. Assessment of antiviral activity is the degree of reduction in plasma CMV
395 DNAemia from baseline after 2 to 3 weeks of treatment, or proportion of patients with
396 undetectable CMV DNAemia (less than the lower limit of quantitation (LLOQ)), at a
397 specified time point, or rate of reduction of CMV DNA. A similar proof-of-concept trial
398 could also be conducted in patients with CMV DNAemia that is resistant to SOC therapy.
399
- 400 • Assessment of antiviral activity in renal transplant patients at low risk for progression to
401 tissue-invasive CMV disease (e.g., D-/R+) with CMV viruria or low-level CMV viremia
402 in a placebo-controlled trial with switch to rescue therapy for progressive viremia above a
403 prespecified threshold may be feasible in some settings.
404
- 405 • Randomized, placebo-controlled, dose-ranging trial to measure reductions in CMV
406 shedding in semen or in urine in asymptomatic patients with underlying immune
407 suppression such as HIV infection who generally would not be treated for asymptomatic
408 CMV infection.
409

410 Before adding the investigational drug to other approved therapies, the potential for drug-drug
411 interactions should be assessed and drug interaction trials may be needed if there is a likelihood
412 of a pharmacokinetic interaction. Doses selected for early phase 2 trials should be predicted to
413 provide plasma and/or tissue drug exposures that exceed by several-fold the protein binding-
414 adjusted, cell culture EC₅₀ value of the drug. The doses evaluated should also take into account
415 any safety margins previously identified in animal toxicology studies and in trials conducted in
416 healthy volunteers.
417

418 Results from proof-of-concept antiviral activity trials can be used to guide dose selection for
419 subsequent phase 2b or phase 3 trials in which anti-CMV therapy is studied for longer durations.
420

Phase 2b trials

421 The same trial designs discussed for phase 3 (section III.B., Phase 3 Efficacy Trial
422 Considerations) could be used for phase 2b; however, phase 2b trials generally should include
423 more doses and fewer subjects per arm compared with the phase 3 trials. The primary goal in
424 phase 2b trials is to determine doses and durations based on safety and efficacy considerations
425 for further evaluation in phase 3 trials. Further dose discrimination for efficacy and safety can be
426 evaluated in phase 3 trials with greater statistical power to detect smaller differences.
427
428

429 Trial randomization should be stratified according to baseline characteristics predicted to have a
430 significant effect on treatment outcome (e.g., donor and recipient CMV serostatus). Initial trials
431

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432 should include frequent CMV virologic monitoring and individual and study stopping rules for
433 poor virologic outcomes (e.g., virologic breakthrough or relapse or progression to CMV disease).
434 Protocols should include opportunities for patients with virologic failure or clinical progression
435 to receive appropriate therapeutic *rescue* regimens. Final efficacy outcome data from all
436 subjects, including those who received therapeutic *rescue* regimen(s), should be collected and
437 reported in final trial reports and/or other appropriate regulatory submissions, as these data could
438 be informative for future clinical trials. As safer and more tolerable and efficacious drugs
439 become available, we anticipate that the risk-benefit considerations for patient populations will
440 evolve.

441

442 Specific information recommended to support phase 3 trials includes:

443

- 444 • Single- and multiple-dose pharmacokinetics and safety in healthy subjects or other
445 populations, as appropriate.
- 446
- 447 • Antiviral (anti-CMV) activity data from phase 2 clinical trials.
- 448
- 449 • Human safety data in approximately 100 patients for the highest dose that will be
450 evaluated further in phase 3 trials.
- 451
- 452 • Data from clinical trials or other sources indicating that doses and duration of dosing
453 chosen for study are likely to provide anti-CMV activity. Dose selection should take into
454 consideration the potential for overlapping toxicities with other drugs likely to be used in
455 the proposed patient population.
- 456
- 457 • Drug-drug interaction data if in vitro and in vivo study results suggest potential for a drug
458 interaction with other drugs likely to be used concomitantly in phase 3 trials.
- 459

460

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

464

2. *Drug Development Population*

465

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

468

- 469 • HSCT recipients
- 470 • SOT recipients, including kidney, liver, heart, lung, pancreas, and other SOT recipients
- 471

472

473 Supportive data may be needed before trials in specific subgroups to define safety and
474 pharmacokinetics. This may include data from hepatic or renal impairment trials and drug-drug
475 interaction trials (e.g., drug-drug interaction trials with immunosuppressants used post-
476 transplantation).

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

484 485 3. *Efficacy Considerations* 486

487 Sponsors can submit a marketing application to gain approval of a drug for a single indication
488 (prophylaxis or treatment) in one or more populations, or can submit a marketing application for
489 multiple indications. Generally, applications should include at least two adequate and well-
490 controlled trials. However, two trials may not be needed for every indication and population.
491 Trials for different indications (prophylaxis or treatment) and in different populations (HSCT or
492 SOT recipients) generally would be considered supportive of each other. Sponsors should
493 consult existing guidance regarding circumstances in which one phase 3 clinical trial may be
494 supportive of approval.¹¹

495
496 Because CMV disease in transplant recipients is considered serious and life-threatening and
497 currently available treatments have limitations in terms of efficacy and safety, CMV
498 investigational drugs may be eligible for fast track, priority review, or breakthrough therapy
499 designation.

500 501 4. *Safety Considerations* 502

503 The FDA recommends that sponsors engage in early discussions with the DAVP on trial designs
504 as well as on the proposed size of the safety database that depends upon the patient population
505 and proposed indication. Because CMV disease is serious and life-threatening in
506 immunocompromised patients, a safety database of 300 to 500 patients who received the
507 proposed dose and duration (or greater) of the drug generally should be sufficient to assess risk-
508 benefit for an initial marketing application. Flexibility in the size of the recommended safety
509 database potentially could be considered for investigational drugs that demonstrate substantial
510 improvement in efficacy and safety compared to currently available therapeutic options. On
511 occasion, specific findings from nonclinical or clinical development may indicate the need for a
512 larger safety database to adequately evaluate potential drug toxicity. If significant safety signals
513 emerge during drug development, the safety database may need to be increased or specific safety
514 studies may need to be conducted.

515
516 For marketing applications containing trials evaluating treatment of CMV disease in patients
517 who have failed or developed resistance to approved treatments, a safety database of
518 approximately 300 patients may be appropriate.
519

¹¹ See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

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

525

B. Phase 3 Efficacy Trial Considerations

526

527

528

1. Trial Design

529

530

531

532

533

534

Phase 3 trial design depends on the proposed indication(s) and the intended population(s) for use. The following are examples of trial designs that could be considered for evaluation of CMV antiviral therapy in transplant patients. All trial designs should include considerations for rescue therapy in case of treatment or prophylaxis failure.

535

a. Prevention of CMV disease

536

537

538

539

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541

542

Prevention of CMV in transplant recipients includes both prophylaxis (administration of anti-CMV drug to at-risk subjects with no evidence for CMV DNAemia or CMV disease) and preemptive therapy (prevention of CMV disease by treatment of subjects with CMV DNAemia). The following sections discuss trial designs for CMV prophylaxis or preemptive therapy in SOT or HSCT populations.

543

CMV prophylaxis trials in SOT recipients

544

545

546

547

The following clinical trial designs can be considered for evaluation of CMV prophylaxis in SOT recipients:

548

549

550

551

552

553

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558

- *Noninferiority Trials.* In a randomized, double-blinded, active-controlled trial, high-risk (D+/R-) SOT recipients would be randomized to receive the SOC regimen (currently valganciclovir) 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 need to be followed for an adequate time to ensure they are not at increased risk for late-onset CMV disease. Longer term follow-up potentially could be performed as a part of a postmarketing commitment.

559

560

561

562

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564

565

The size of the noninferiority margin depends 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 study 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.

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- 566
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- 568
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- 570
- 571
- *Superiority Trials.* In a randomized, double-blinded, superiority trial, valganciclovir (or other drug considered SOC for the indication) would be used as comparator. Alternatively, in an add-on superiority trial, transplant recipients would be randomized to receive the investigational drug plus valganciclovir versus valganciclovir alone. The primary endpoint would be the incidence of CMV disease (CMV syndrome or tissue-invasive CMV disease).

572

CMV prophylaxis trials in HSCT recipients

573

574

575 The following clinical trial designs can be considered for evaluation of CMV prophylaxis in

576 HSCT recipients:

577

- 578
- 579
- 580
- 581
- 582
- 583
- 584
- 585
- 586
- *Noninferiority Trials:* In a randomized, double-blinded, active-controlled trial, high-risk (CMV seropositive) HSCT recipients would be randomized to receive the SOC regimen (currently letermovir) 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 development of CMV DNAemia above a prespecified threshold. It is expected that the endpoint will be driven by the incidence of CMV DNAemia. The FDA considers CMV viremia (DNAemia) as a sufficiently validated endpoint to grant traditional approval for NDAs for prophylaxis trials in HSCT recipients.

587

- 588
- 589
- 590
- 591
- 592
- 593
- *Superiority Trials:* A superiority trial of the investigational drug in a blinded comparison against the SOC may be appropriate in CMV seropositive HSCT recipients. Enrolled patients should 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.¹² The primary endpoint would be a composite endpoint, as defined above.

594

595 A dose-ranging or duration of prophylaxis superiority trial in which shorter and longer

596 duration of prophylaxis or a range of doses are compared may also be appropriate in this

597 population. Efficacy is supported by demonstrating superiority of the longer duration

598 over the shorter duration or of the higher dose over the lower dose.

599

Preemptive therapy in SOT or HSCT recipients

600

601

602 Preemptive therapy (antiviral therapy initiated when CMV DNAemia is detected at a level above

603 a predetermined threshold without evidence of tissue-invasive CMV disease or CMV syndrome)

604 depends on frequent and regular monitoring for CMV DNAemia. The goal of preemptive

605 therapy is to prevent tissue-invasive CMV disease. In the past, establishing universal

606 quantitative viral thresholds for initiation of preemptive therapy has been difficult because of

607 differences in assay performance and source (whole blood versus plasma), but may now be

¹² Other treatment durations may be proposed based on scientific rationale.

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608 feasible with the publication of the World Health Organization standard for CMV DNA
609 quantification (Fryer et al. 2010) and with the availability of approved assays.¹³

610
611 Some examples of preemptive therapy study designs that could be used in these populations
612 include:

613
614 • *Superiority Trials.* Superiority trials of the investigational drug versus intravenous
615 ganciclovir or oral valganciclovir, or add-on superiority trial in which subjects are
616 randomized to the investigational drug or placebo added to an SOC background therapy
617 (e.g., intravenous ganciclovir or oral valganciclovir) may be feasible. In superiority trials
618 for this indication, efficacy can be assessed using the clinical endpoint of the occurrence
619 of CMV disease (tissue-invasive disease or CMV syndrome in SOT recipients or tissue-
620 invasive CMV disease in HSCT recipients) or by using a composite endpoint
621 (undetectability of CMV DNAemia at a specific time point, or time to undetectability of
622 CMV DNAemia and absence of CMV disease).

623
624 Other trial design considerations could include duration of treatment or dose-ranging
625 superiority trials in which shorter and longer durations of treatment or higher versus
626 lower doses are compared. Superiority of the longer duration or of the higher dose
627 demonstrates efficacy of the investigational drug.

628
629 • *Noninferiority Trials.* For a noninferiority trial, the treatment effect of the SOC
630 comparator, ganciclovir or valganciclovir, over placebo should be determined to support
631 an appropriate noninferiority margin for this indication. Detailed justification should be
632 provided for proposed noninferiority margins, and proposals should be discussed with the
633 DAVP.

634
635 b. Treatment of CMV disease

636
637 The following section discusses considerations for clinical trial design for treatment of CMV
638 disease in SOT or HSCT recipients, including treatment of CMV infections resistant or
639 refractory to current SOC therapy.

640 **Treatment of CMV disease in SOT and HSCT recipients**

641
642 In the SOT setting, CMV disease refers to either tissue-invasive disease or CMV syndrome, as
643 defined in section III.B.8., Efficacy Endpoints. In HSCT recipients, CMV disease refers only to
644 tissue-invasive CMV disease.

645
646 Options for trial designs for CMV disease treatment trials in either SOT or in HSCT recipients
647 include:

648
649 • *Superiority Trials.* Trials to demonstrate superiority to SOC therapy, or add-on
650 superiority trials in which subjects are randomized to the investigational drug or placebo
651

¹³ <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm330711.htm>

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652 added to an SOC therapy (e.g., intravenous ganciclovir or oral valganciclovir) are
653 feasible and appropriate. The primary endpoints should include both resolution or
654 improvement of clinical signs and symptoms of CMV disease and undetectable CMV
655 DNAemia.

656

- 657 • *Noninferiority Trials.* No antiviral drugs have been approved for the treatment of CMV
658 disease in SOT or HSCT recipients. Therefore, noninferiority trials are not feasible for
659 this indication unless the treatment effect for the SOC anti-CMV therapy over placebo
660 can be determined for treatment of CMV disease in these populations to support a
661 noninferiority margin.

662

Treatment of CMV infections resistant or refractory to CMV antiviral drugs in transplant recipients

664

665
666 Trials for treatment of CMV infections resistant or refractory to treatment with available drugs
667 (i.e., ganciclovir/valganciclovir, foscarnet) could include treatment of CMV disease or treatment
668 of CMV viremia. The term *resistant* refers to CMV infection having documented resistance-
669 associated amino acid substitutions and documented failure to achieve greater than 1 log₁₀
670 decline in CMV DNA level in plasma after an interval of at least 2 weeks of treatment. The term
671 *refractory* refers to CMV infection that has documented failure to achieve greater than 1 log₁₀
672 decline in CMV DNA level in plasma after an interval of at least 2 weeks of treatment despite
673 the absence of documented resistance-associated amino acid substitutions to SOC drugs. It
674 should be noted for trials that include both groups of patients (resistant and refractory to
675 treatment) that statistical significance should be demonstrated in the overall population. Efficacy
676 in the key subgroups of patients who are refractory or resistant to CMV antiviral drugs should be
677 consistent with the overall treatment effect.

678

679 Trial design options for these populations can include superiority trial versus SOC therapy or
680 add-on superiority trial comparing the investigational drug plus SOC versus SOC treatment alone
681 (if the two drugs did not demonstrate antagonism in combination antiviral activity assessments).
682 Rescue therapy options for subjects failing therapy should be proposed as part of the protocol.

683

2. Trial Population

684

685
686 As mentioned, this guidance focuses on treatment or prevention of CMV disease in SOT and
687 HSCT recipients. Some of the specific issues with regard to trial population for these indications
688 are discussed below.

689

- 690 • *CMV Prophylaxis in SOT Recipients.* For trials evaluating an investigational drug for
691 CMV prophylaxis in SOT recipients, patients should be high risk based on CMV
692 serostatus (D+/R-).
- 693 • *CMV Prophylaxis in HSCT Recipients.* Trials of investigational drug versus SOC should
694 be conducted in CMV seropositive (R+) HSCT recipients who are at the highest risk for
695 CMV infection and disease.

696

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- 698
- *Preemptive Therapy in SOT or HSCT Recipients.* Preemptive therapy can be studied in
699 any transplant recipient who has evidence of CMV DNAemia at levels above a
700 prespecified threshold.
 - *Treatment of CMV Disease.* Any SOT or HSCT recipient with CMV disease, regardless
702 of CMV serostatus of donor and recipient, could be included in treatment trials.
703 However, in trials evaluating treatment in SOT recipients, a sufficient number of subjects
704 with tissue-invasive CMV disease should be enrolled (and not just those with CMV
705 syndrome) to support an indication for treatment of CMV disease.
 - *Treatment of CMV Infections Resistant or Refractory to CMV Antiviral Drugs in
707 Transplant Recipients.* Any SOT or HSCT recipient with CMV infection resistant or
708 refractory to available CMV antiviral drugs could be included in these trials.

3. *Entry Criteria*

712

713

714 The following are specific considerations for trial entry criteria for CMV treatment or prevention
715 trials:

- 716
- *Prophylaxis Trials in SOT or HSCT Recipients.* To be enrolled in a CMV prophylaxis
717 trial, the patient should have no detectable CMV infection post-transplantation as
718 documented by CMV DNA testing with PCR in plasma (less than LLOQ), within 5 days
719 before initiation of therapy.
 - *Preemptive Therapy Trials in SOT or HSCT Recipients.* In clinical practice, virologic
722 thresholds for initiation of preemptive therapy in HSCT recipients have been based on
723 preestablished risks for CMV disease (Boeckh and Ljungman 2009). For clinical trials,
724 optimal virologic thresholds for initiation of preemptive therapy have not been
725 established. Proposed virologic thresholds for initiation of preemptive therapy for CMV
726 viremia in clinical trials should be discussed and agreed upon with the DAVP.
 - *Treatment Trials in SOT or HSCT Recipients.* To be enrolled in a CMV treatment trial,
728 transplant recipients should have virological evidence of CMV replication with signs and
729 symptoms of CMV syndrome or tissue-invasive CMV disease (SOT recipients) or with
730 clinical evidence of tissue-invasive CMV disease (HSCT recipients).
 - *Treatment Trials in Patients With CMV Infections Resistant or Refractory to CMV
733 Antiviral Drugs.* CMV isolates at baseline should have evidence of resistance to CMV
734 antiviral drugs by genotypic analysis. Patients with CMV disease refractory to treatment
735 can be included, but the inclusion criteria for subjects refractory to therapy should be
736 rigorously defined in the protocol.
- 737
- 738
- 739

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740 4. *Randomization, Stratification, and Blinding*

741

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

745

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

749

750 Sponsors should consider stratification of subjects by important baseline risk factors for CMV
751 infection/disease in HSCT recipients, such as CMV serostatus of donor and recipient and other
752 factors associated with risk of CMV disease. For SOT recipients, consideration should be given
753 to stratification by CMV serostatus of donor and recipient and the type of transplant (e.g.,
754 kidney, liver, lung).

755

756 In trials that include both SOT and HSCT recipients, stratification by type of transplant (SOT or
757 HSCT) should be considered.

758

759 5. *Pediatric Populations*

760

761 Sponsors are encouraged to begin discussions about their pediatric formulation and clinical
762 development plan early in development because pediatric clinical trials are a required part of the
763 overall drug development program. Under the Pediatric Research Equity Act, sponsors must
764 submit an initial pediatric study plan to the FDA no later than 60 days after the end-of-phase 2
765 meeting.¹⁴

766

767 Inclusion of pediatric patients in clinical trials generally can be initiated after sufficient safety,
768 pharmacokinetic, and efficacy data are available from adults. If clinical trials in adults have
769 demonstrated no significant safety concern that would preclude study in children, evaluation of
770 adolescents using the adult dose and formulation is encouraged (Momper et al. 2013). However,
771 initial pediatric pharmacokinetic data and results of available modeling and simulation should be
772 discussed with the DAVP before dose selection for pediatric treatment trials. Depending on
773 results of the adult clinical trials, and on whether efficacy in adults can be extrapolated to
774 pediatric patients (i.e., if the course of disease and the effect of the drug are sufficiently similar in
775 adults and pediatric patients), either comparative or single-arm trials may be appropriate in
776 pediatric subjects.¹⁵ The sponsor's pediatric study plan should include information to support
777 pediatric extrapolation, as needed.

778

¹⁴ See the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

¹⁵ For additional information on pediatric extrapolation, see the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic.

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779 6. *Dose Selection*

780
781 To guide optimal selection of doses and treatment durations in phase 3 trials, sponsors should
782 consider safety and efficacy results from previous trials and exposure-response relationships for
783 safety and efficacy. For treatment studies, we recommend that sponsors develop a mechanistic
784 model of the kinetics of viral load reduction that can assist the optimization of dose and
785 treatment duration, and reduce the risk of selecting for resistant virus caused by subtherapeutic
786 exposures. Such a model should include a mechanistically appropriate targeted drug effect,
787 components to describe virologic breakthrough and virologic response, and contain relevant
788 covariates for describing differences in response. When applicable, these mechanistic modeling
789 approaches can use viral kinetic model structures and corresponding disease progression
790 parameter values from the literature.

791
792 A range of doses and treatment durations can be selected for phase 3 trials if there are
793 uncertainties on the optimal regimen or the model indicated a different dose or treatment
794 duration to be better for certain subpopulations such as patients having CMV with baseline
795 ganciclovir resistance. An adaptive design for the dose selection can also be considered.

796
797 7. *Use of Active Comparators*

798
799 In general, the active comparator in a noninferiority trial should be an FDA-approved drug that is
800 considered the SOC for the specific indication and population being studied. Proposed
801 noninferiority margins should be justified and discussed with the DAVP. See the guidance for
802 industry *Non-Inferiority Clinical Trials to Establish Effectiveness* for additional information on
803 determining noninferiority margins.

804
805 8. *Efficacy Endpoints*

806
807 The preferred definitions for CMV infection and disease for use in clinical trials are those
808 advocated by Ljungman and colleagues (Ljungman et al. 2017).

809
810 a. CMV prophylaxis trials in SOT recipients

811
812 The recommended primary endpoint for trials of CMV prophylaxis in SOT recipients is a clinical
813 endpoint of CMV disease, and includes both CMV syndrome and tissue-invasive CMV disease
814 measured at 6 or 12 months post-transplantation depending on duration of prophylaxis. The
815 diagnosis of CMV syndrome and tissue-invasive CMV disease should be confirmed by an
816 independent, blinded, clinical adjudication committee.

817
818 Secondary endpoints in CMV prophylaxis trials for SOT recipients could include some of the
819 following. However, only a limited number of such endpoint(s) should be considered for testing
820 using appropriate statistical methods for multiplicity:

- 821
822 • The proportion of subjects with CMV disease at time points other than the time point
823 used for the primary endpoint

824

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- 825 • The time to development of CMV disease
- 826
- 827 • The proportion of subjects with investigator-determined CMV disease
- 828
- 829 • The initiation of other anti-CMV therapy
- 830
- 831 • The proportion of subjects with CMV DNAemia at different time points
- 832
- 833 • The time to development of CMV DNAemia
- 834
- 835 • Survival at different time points
- 836
- 837 • The proportion of subjects experiencing biopsy-proven acute rejection
- 838
- 839 • The proportion of subjects with graft loss
- 840
- 841 • The proportion of subjects with opportunistic infections
- 842
- 843 • The proportion of subjects developing genotypic changes associated with CMV resistance
- 844 to investigational drug

b. CMV prophylaxis trials in HSCT recipients

845

846

847

848 The recommended primary endpoint for a phase 3 prophylaxis trial in HSCT recipients is the

849 incidence of CMV infection or disease within 6 months post-transplantation. This is a composite

850 endpoint that includes both a clinical component (tissue-invasive CMV disease) and a surrogate

851 endpoint (CMV DNAemia).

852

853 Initiation of anti-CMV preemptive treatment in prophylaxis trials should be based on

854 documented CMV DNAemia (as measured by a central virology laboratory). Viral load

855 thresholds for initiation of preemptive therapy should be based on the risks for CMV disease

856 (Boeckh and Ljungman 2009). Virologic thresholds for initiation of preemptive therapy will

857 depend on the assay and specimen (whole blood versus plasma), as well as the risk of CMV

858 infection/disease in the population under study, and individual patient risk factors. Virologic

859 thresholds should be agreed upon with the DAVP before trial initiation.

860

861 Secondary endpoints in CMV prophylaxis trials in HSCT recipients could include, but are not

862 limited to:

- 863
- 864 • The proportion of subjects with tissue-invasive CMV disease
- 865
- 866 • The proportion of subjects with CMV DNAemia
- 867
- 868 • The time to onset of CMV infection (DNAemia)/tissue-invasive disease through
- 869 6 months or 12 months post-transplantation
- 870

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- 871 • Survival at 6 and 12 months post-transplantation
872
873 • The proportion of subjects with opportunistic infections other than CMV infection
874
875 • The proportion of subjects developing resistance to the investigational drug
876

877 c. CMV preemptive therapy trials in SOT or HSCT recipients
878

879 The recommended primary endpoint for phase 3 trials of preemptive therapy in either SOT or
880 HSCT patients is the proportion of subjects with undetectable CMV DNA (less than LLOQ)
881 without evidence of CMV disease at a prespecified time point after treatment initiation.
882

883 d. Treatment of CMV disease in SOT or HSCT recipients
884

885 The recommended primary endpoint in a phase 3 trial in either SOT or HSCT recipients with
886 tissue invasive CMV disease (for SOT or HSCT) or CMV syndrome (for SOT) is the proportion
887 of responders at a prespecified time point after treatment initiation. Response should include the
888 following elements:
889

- 890 • Substantial improvement/resolution of signs and symptoms of tissue-invasive CMV
891 disease or CMV syndrome
892
893 • Undetectable CMV DNAemia (defined as two consecutive negative tests taken at least
894 5 to 7 days apart)
895
896 • No new occurrence of CMV disease at other sites
897
898 • No evidence for relapse (CMV disease or DNAemia) within a prespecified time frame
899 after stopping therapy
900

901 Specific details regarding the primary endpoint should be discussed with and agreed upon by the
902 DAVP.
903

904 Secondary endpoints can include, but are not limited to:

- 905 • The time to undetectable CMV DNA (less than LLOQ)
906
907 • The time to resolution of signs and symptoms of tissue-invasive disease or CMV
908 syndrome
909
910 • Survival
911
912 • The development of opportunistic infections, graft rejection, or failure
913
914 • The development of antiviral resistance
915
916

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917 9. *Trial Procedures and Timing of Assessments*

918
919 For trials of investigational drugs for treatment or prophylaxis of CMV in the post-transplant
920 setting, rescue therapy for development of CMV disease or CMV viremia should be included in
921 the protocol. Quantitative CMV DNA should be measured frequently during clinical trials. For
922 treatment of CMV disease, treatment should continue at least until CMV DNAemia is less than
923 LLOQ for at least two consecutive measurements performed at a prespecified interval, and
924 duration of treatment should be recorded. Sponsors should consider longer treatment based on
925 the kinetics of viral load reduction because several logs of CMV may be present when an assay
926 reports less than LLOQ. In prophylaxis trials, CMV DNA should be monitored routinely during
927 the trial and subjects should be monitored for development of signs and symptoms of CMV
928 disease. In treatment trials (including preemptive therapy), frequent monitoring of CMV DNA
929 should continue after discontinuation of therapy to detect relapse of CMV viremia during the risk
930 period.

931 10. *Endpoint Adjudication*

932
933 Determination of CMV tissue-invasive disease and CMV syndrome endpoints should be
934 adjudicated by an independent endpoint assessment committee conducting a blinded review of
935 clinical source data (Ljungman et al. 2017).

937 11. *Statistical Considerations*

938
939 In general, a detailed statistical analysis plan stating the trial hypotheses and analysis methods
940 should be submitted before trial initiation. Statistical analysis topics and issues are discussed in
941 detail in the guidances for industry *Providing Clinical Evidence of Effectiveness for Human*
942 *Drug and Biological Products* and *Non-Inferiority Clinical Trials to Establish Effectiveness* and
943 the FDA white paper “Statistical Considerations on Subgroup Analysis in Clinical Trials” (Alosh
944 et al. 2015).

946 a. Analysis populations

947
948 All subjects who are randomized and receive at least one dose of assigned therapy during the
949 trial generally should be included in the primary efficacy analysis. However, if a substantial
950 proportion of randomized subjects do not receive treatment in either or both arms, then
951 additional analyses may be needed.

953 b. Efficacy analyses

954
955 The primary efficacy analyses in prophylaxis trials in SOT recipients should compare the
956 incidence of CMV disease within 6 or 12 months post-transplantation across treatment arms.

957
958 The primary efficacy analyses in prophylaxis trials in HSCT recipients should compare the
959 incidence of tissue-invasive CMV disease and CMV DNAemia above a prespecified threshold
960 within 6 months post-transplantation across treatment arms.

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963 The primary efficacy analyses in preemptive therapy trials should compare the proportion of
964 SOT recipients or HSCT recipients with undetectable CMV DNA in the absence of CMV disease
965 at a prespecified time point across treatment arms.
966

967 For subgroup analyses, the analysis of the primary efficacy endpoint should be performed within
968 important demographic and baseline characteristics (e.g., geographic region (United States, non-
969 United States), sex, race, age group, high- versus low-risk group, donor CMV serostatus (D+ or
970 D-), recipient CMV serostatus (R- or R+)). The purpose of these analyses is to explore the
971 consistency of the primary efficacy endpoint result across these subgroups.
972

c. Handling of missing data

973
974
975 Sponsors should make every attempt to limit loss of subjects from the trial. We recommend that
976 sponsors collect detailed data on reasons for trial discontinuation (e.g., opportunity to enter
977 another trial offering a promising new treatment, death or events leading to death, disease
978 progression, adverse events, loss to follow-up, withdrawal of consent, noncompliance,
979 pregnancy, protocol violations, not discontinued or not known to be discontinued but data were
980 missing at the final visit). For subjects who discontinue treatment early, investigators should
981 determine if these subjects switched treatments or added additional therapy.
982

983 Analyses excluding subjects with missing data or other post-treatment outcomes can be biased
984 because subjects who do not complete the trial may differ substantially in both measured and
985 unmeasured ways from subjects who remain in the trial. The method of how missing data will
986 be handled should be prespecified in the protocol or the statistical analysis plan. Sensitivity
987 analyses may be needed to demonstrate that the primary analysis results are robust to the
988 assumptions regarding missing data.
989

12. *Accelerated Approval (Subpart H/E) Considerations*

990
991
992 CMV viremia (DNAemia) is considered a sufficiently validated endpoint for use as part of a
993 composite endpoint that includes a clinical component to support traditional approval; therefore,
994 accelerated approval regulations generally are not applicable for CMV treatment and prevention
995 indications.
996

C. Other Considerations

1. Clinical Virology Considerations

1000
1001 An FDA-approved assay should be used to quantify CMV DNA in plasma. We recommend that
1002 CMV DNA in whole blood also be quantified for short-term monotherapy studies because this
1003 may improve sensitivity to detect antiviral activity. Additionally, plasma CMV DNA has been
1004 shown to be highly fragmented, so care should be taken when interpreting the CMV DNA levels
1005 (Boom et al. 2002). Virology analyses should be conducted at a central virology laboratory.
1006

1007 Proof-of-concept and efficacy trials should assess the development of CMV genotypic resistance
1008 to the investigational drug. In prophylaxis studies, resistance testing should be performed for

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1009 subjects who have detectable CMV DNA at any time point or confirmed diagnosis of CMV
1010 disease, regardless of viral load. Observations of particular interest that should be reported
1011 include multiple occurrences of substitutions from the reference sequence(s) at highly conserved
1012 amino acid residues, substitutions at positions identified in cell culture selection studies and
1013 treatment studies, and multiple occurrences of unusual substitutions at polymorphic residues.
1014

1015 In treatment studies, resistance testing should be performed for subjects who demonstrate
1016 virologic breakthrough (defined as a greater than or equal to 1 log₁₀ increase in CMV DNA
1017 above nadir, or detectable CMV DNA, while on treatment, after an initial drop to undetectable),
1018 an incomplete antiviral response (e.g., detectable CMV DNA at end of treatment or slower rate
1019 of decline than the average response), decline to a plateau viral load decay phase, or virologic
1020 relapse after treatment cessation. Sponsors should include a proposal of the subjects to be
1021 evaluated for resistance in their resistance analysis plans. Any amino acid changes, including
1022 mixtures, in the coding sequence of the targeted genome region present in on-treatment or
1023 follow-up samples, but not in the baseline sample, should be reported as having developed
1024 during therapy. In addition, baseline samples should be analyzed to identify CMV genetic
1025 polymorphisms that are associated with differential antiviral activity with the new investigational
1026 drug.
1027

1028 Sponsors should consider genotyping regions outside the direct CMV genome target depending
1029 on the characteristics of the antiviral drug and interactions of the target with other viral proteins
1030 or whole genome sequencing, if viral loads are adequate. In cases when resistance is suspected
1031 based on viral DNA kinetics, but genotypic evidence of resistance is not detected, sponsors
1032 should also consider performing additional genotypic analyses using a method sufficiently
1033 sensitive to detect minority variants (e.g., next generation sequencing). GCV/vGCV resistance-
1034 associated substitutions have been detected in specific compartments exclusively and not in
1035 blood. Therefore, sponsors should also consider genotyping samples collected from specific
1036 compartments.
1037

1038 Viral resistance-associated substitutions and baseline polymorphisms affecting response
1039 observed in clinical trials but not identified and characterized in nonclinical virology experiments
1040 should be evaluated phenotypically by introducing the changes into the CMV genome, and
1041 determining the conferred fold-shift in susceptibility to the drug using appropriate cell culture
1042 and/or biochemical assays. In addition, phenotypic analyses should be performed using baseline
1043 and on-treatment clinical isolates from a subset of trial subjects representative of the CMV
1044 genetic diversity and virologic responses observed in clinical trials. Phenotypic assays should
1045 include wild-type reference virus and resistant virus (initially from cell culture selection studies)
1046 controls.
1047

1048 For quantification of CMV DNA, we recommend that sponsors use an FDA-approved PCR
1049 assay(s) using a central laboratory. Sponsors should collect results from local laboratory tests,
1050 identifying the assay(s) used. If investigational assays are used, performance characteristics with
1051 geographically and temporally distinct isolates should be provided. Values that are less than
1052 LLOQ should be reported as “less than LLOQ, target not detected” or “less than LLOQ, target
1053 detected,” as appropriate.
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1055 The FDA performs independent assessments of virologic and resistance data. Before submitting
1056 virology datasets, sponsors should consult with the DAVP to obtain information on the most
1057 recent format and, in the case of Next Generation Sequence analysis, the procedure for
1058 submitting FASTQ files.

1059

1060 2. *Pharmacokinetic/Pharmacodynamic Considerations*

1061

1062 Pharmacokinetics and the relationship between exposure and virologic or clinical endpoints and
1063 toxicity should be assessed. Virologic or clinical endpoints to be used for analyses depend on
1064 the proposed indication and study designs.

1065

1066 Sponsors can use a combination of intensive and sparse sampling throughout development to
1067 characterize the pharmacokinetics of the investigational drug. An intensive sampling schedule is
1068 recommended in early phase trials. In longer term trials, however, an intensive sampling
1069 schedule might not be feasible, or may be feasible only in a subset of subjects or over a limited
1070 period of time. Sparse pharmacokinetic samples should be obtained from as many subjects in
1071 longer duration trials as possible, and the pharmacokinetic samples from these trials can be
1072 combined with intensive pharmacokinetic data from earlier trials for analysis.

1073

1074 Pharmacokinetics and the relationship between exposure and virologic or clinical responses in
1075 early phase trials (i.e., proof-of-concept studies) can be used to aid the design of phase 2b or
1076 phase 3 trials (e.g., dose selection and treatment duration). When sufficient efficacy and
1077 pharmacokinetic data are available, a simplified analysis relating proportion of subjects with
1078 treatment failure and appropriate exposure variable (e.g., minimum concentration or area under
1079 the plasma drug concentration versus time curve) can be used to support evidence of
1080 effectiveness of different dosage regimens. Analyses of the exposure-safety relationship(s) using
1081 similar approaches also should be performed to assist in evaluating the balance between
1082 effectiveness and toxicity of different dosage regimens.

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GLOSSARY OF ACRONYMS

1083		
1084		
1085	AIDS	acquired immune deficiency syndrome
1086	CC	cytotoxic concentration
1087	CMV	cytomegalovirus
1088	DAVP	the Division of Antiviral Products
1089	DNA	deoxyribonucleic acid
1090	EC	effective concentration
1091	FDA	the Food and Drug Administration
1092	HBV	hepatitis B virus
1093	HCV	hepatitis C virus
1094	HIV	human immunodeficiency virus
1095	HSCT	hematopoietic stem cell transplantation
1096	LLOQ	lower limit of quantitation
1097	mAb	monoclonal antibody
1098	NDA	new drug application
1099	PCR	polymerase chain reaction
1100	pre-IND	pre-investigational new drug application
1101	SOC	standard of care
1102	SOT	solid organ transplantation
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APPENDIX:

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

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At this time, a noninferiority trial with valganciclovir as comparator cannot be used 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 prevention of cytomegalovirus (CMV) disease (CMV syndrome and tissue-invasive CMV disease) post-transplantation.¹⁶ However, among liver transplant recipients who made up the largest subgroup (approximately 50 percent of patients enrolled), approximately three 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. 2013) and because oral ganciclovir currently is not available in the United States, valganciclovir could be used as a comparator in a superiority trial. Additionally, 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. Definitions for success in subpopulations in this type of study design should be defined in the statistical analysis plan. 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.

¹⁶ 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.