Supplemental Data

Brincidofovir for CMV prophylaxis in allogeneic HCT:

A randomized, double-blind, placebo-controlled phase 3 trial

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on behalf of the SUPPRESS Trial Clinical Study Group.

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I. Appendix

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II. Methods

1. Eligibility criteria

Inclusion criteria

Patients must meet all of the following criteria, as applicable, to be eligible to participate in this study:

1. Allogeneic HCT recipient who has prior evidence of CMV exposure before transplantation and who is CMV viremia negative at screening and at any other assessments performed prior to the First Dosing Day (FDD).

   Note: CMV viremia must be reported as negative by the central virology laboratory (i.e., CMV DNA in plasma is "Not Detected" for the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test used by the central virology laboratory) no more than 5 days prior to randomization. In addition, all CMV viremia test results (including CMV PCR, pp65 antigenemia, etc.) performed as part of local standard of care since the qualifying transplant must also be negative.
2. Age ≥ 18 years.

   Note: The minimum acceptable age may be higher depending on local regulations.
3. If male, willing to use an acceptable contraceptive method(s) throughout the duration of his participation in the study, i.e., through Week 24, when engaging in sexual intercourse with a female patient of childbearing potential.
4. If a female of childbearing potential, i.e., not postmenopausal or surgically sterile, willing to use two acceptable contraceptive methods, one of which must be a barrier method, throughout the duration of her participation in the study, i.e., through Week 24, when engaging in sexual intercourse with a non-sterile male partner.

Note: For assessing inclusion criterion 3 or 4, a promise to abstain from sexual intercourse is not an acceptable method of preventing pregnancy for the purposes of this protocol. However, patients who are currently sexually abstinent and who indicate a willingness to use an acceptable contraceptive method(s), as described above, should they begin or resume sexual activity may be enrolled into the study. As applicable, female patients of childbearing potential who discontinue the study prior to Week 24 (e.g., who withdraw consent) should be advised to continue their contraceptive methods with a non- sterile male partner for at least 90 days after the last study drug administration. Male patients who discontinue the study prior to Week 24 should be advised to continue their contraceptive method(s) with a female partner of childbearing potential for at least 90 days after their last study drug administration).

5. Able to begin study drug dosing within 28 days following HCT.
6. Able to comfortably ingest and absorb oral medication (in the judgment of the investigator and based on lack of significant GI events/medical history).

   Note: The use of TPN or NPO (nil per os) is not in and of itself exclusionary as long as the reason would not disqualify the patient based on this criterion.
7. Willing and able to understand and provide written informed consent.

Exclusion criteria

Patients who meet *any* of the following criteria are not eligible to participate in this study:

1. If female, the patient is pregnant or planning to become pregnant during the anticipated duration of her participation in the study (i.e., through Week 24), or nursing a child.
2. Patients who have a positive CMV viremia test (through central or local virology

laboratory) at any time between transplant and the FDD.

3. Patients who weigh ≥ 120 kg (~ 265 lbs.)
4. Patients with hypersensitivity (not renal dysfunction or eye disorder) to cidofovir or to brincidofovir (CMX001) or its excipients.
5. Patients who have received (or who are anticipated to need treatment with) any of the following:

- Ganciclovir, valganciclovir, foscarnet, cidofovir, or any other anti-CMV therapy (including CMV immune globulin, cell-based therapies, and investigational anti-CMV drugs (e.g., leflunomide, letermovir, or maribavir) at any time post-transplant;
- any anti-CMV vaccine at any time;
- any other investigational drug within 14 days prior to the FDD (unless prior approval has been received from the Chimerix Medical Monitor or designee), or
- prior treatment with CMX001 at any time.

Note: An "investigational drug" is defined as any drug that is not approved for any indication by the U.S. FDA (or appropriate regulatory authority).

6. Patients receiving acyclovir orally at > 2,000 mg total daily dose (TDD) or intravenously at > 15 mg/kg TDD, valacyclovir at > 3,000 mg TDD or leflunomide at any dose on the FDD or who are anticipated to receive any of these drugs at the doses described after the FDD.
7. Patients who are receiving digoxin or ketoconazole (other than topical formulations) at the FDD or are anticipated to need treatment with digoxin or ketoconazole during the treatment phase (through Week 14).
8. Patients with possible, probable or definitive CMV disease diagnosed within 6 months

prior to the FDD.

9. Patients who are HIV-infected (based on serology), or who have an active HCV or HBV infection as evidenced by detectable plasma HCV RNA or HBV DNA, respectively.

   Note: Documented results from tests performed up to 6 months prior to the qualifying transplant may be used to satisfy this criterion. Negative results for HBV and HCV PCR tests are required to confirm the absence of active infection(s). If necessary, investigators should contact the Chimerix Medical Monitor for prior approval to randomize a patient who meets all other entry criteria based on the results of negative PCR testing performed at a local laboratory in lieu of pending results from the relevant central laboratory.

10. Patients who have received another allogeneic HCT (i.e., other than the qualifying HCT) within 2 years prior to the FDD.

    Note: Patients who have received one or more autologous transplants, in addition to the qualifying allogeneic HCT, are not excluded from participation in the study.

11. Patients with renal insufficiency, as evidenced by an eGFR < 15 mL/min or requiring renal dialysis.

    Note: Each patient's eGFR will be calculated by the central safety laboratory using MDRD4.

12. Patients with hepatic abnormalities as evidenced by a screening ALT or AST > 5×ULN as reported by the central safety laboratory.

13. Patients with a screening total bilirubin > 2×ULN and direct bilirubin > 1.5×ULN as reported by the central safety laboratory.

    Note: In consultation with the Chimerix Medical Monitor (or designee), patients with laboratory values that meet a disqualifying threshold in either exclusion criterion 12 or 13

may be enrolled based on acceptable repeat test results performed within 28 days post-transplant. One repeat test will be allowed per patient. At the discretion of the Chimerix Medical Monitor (or designee), local laboratory tests results may be assessed in lieu of pending tests results from the central safety laboratory (e.g., where logistical issues would preclude waiting for the central safety laboratory tests results). Blood and urine samples for assessment by the central safety laboratory should be drawn in parallel to the blood and urine samples sent to the local laboratory. For patients for whom serum aminotransferase and/or total or direct bilirubin concentrations drawn prior to the FDD, are subsequently found to be disqualifying, as per exclusion criterion 12 or 13, at the time of FDD, the investigator should immediately contact the Chimerix Medical Monitor (or designee) to discuss continuation of the patient in the study. Patients who meet any of the dose interruption criteria must have study drug interrupted.

14. Patients with active solid tumor malignancies with the exception of basal cell carcinoma or the underlying condition necessitating the stem cell transplant (e.g., lymphomas).
15. Patients with Stage 2 or higher GI-GVHD or any other GI disease that would, in the judgment of the investigator, preclude the patient from taking or absorbing oral medication (e.g., clinically active Crohn's disease, ischemic colitis, moderate or severe ulcerative colitis, small bowel resection, ileus, or any condition expected to require abdominal surgery during the course of study participation).
16. Any other condition, including abnormal laboratory values, that would, in the judgment of the investigator, put the patient at increased risk by participating in the study, or would interfere with the conduct or planned analyses of the study.

2. Virology methods

2.1. CMV DNA PCR testing

Plasma was assessed for the presence of CMV DNA by the designated central virology laboratories (Viracor-IBT Laboratories, Lee's Summit, Missouri, USA, for North American centers; and Eurofins BV, Breda, The Netherlands, for European centers) at all scheduled visits via quantitative PCR testing using the COBAS® AmpliPrep/COBAS® TaqMan® CMV Test (Roche Molecular Systems, Inc., Branchburg, New Jersey, USA). The lower limit of quantification (LLOQ) for the assay was 151 CMV DNA copies per milliliter (= 137 IU per milliliter) and the lower limit of detection was 100 CMV DNA copies/mL (= 91 IU/mL).

2.2. CMV antiviral resistance testing

Conventional PCR followed by DNA sequencing of the UL54 DNA polymerase and UL97 phosphotransferase genes was performed by Viracor-IBT Laboratories (5600 Cytomegalovirus CMV Antiviral Resistance Assay). Sequencing spanned the regions that are known to contain the site of resistance mutations for cidofovir, foscarnet, and ganciclovir. The standard Viracor-IBT Laboratories test evaluates codons from 405 to 613 of the UL97 gene and from codons 301 and 987 of the UL54 gene; however, the standard UL54 assay was expanded to include the entire UL54 gene for this study. A CMV DNA level of ≥400 copies/mL was selected as the threshold for sample selection.

CMV resistance testing was completed for samples collected from 78 brincidofovir-treated patients and 47 placebo-treated patients with CMV viremia ≥ 400 DNA copies/mL at any time during the study. No CMV mutations known to confer phenotypic resistance to cidofovir or

brincidofovir *in vitro* were detected. Three CMV mutations (2 in *UL97*, 1 in *UL54*) associated with resistance to ganciclovir were detected in 2 patient samples.

2.3. CMV glycoprotein B genotyping

Genotyping assays to allow identification and classification of CMV into one of four potential glycoprotein B genotypes (gB1-4) was performed by Viracor-IBT Laboratories. The assay used conventional PCR followed by DNA sequencing of the CMV gB gene and then genotype phylogenetic analysis using the Geneious Bioinformatics Software Suite version 6.1.6 (Biomatters Inc., Newark, NJ) to assign gB type.

Brincidofovir and placebo patients had similar distributions of genotypes ($p = 0.83$, Fisher's Exact Test). Including available data for all patients, the distribution of CMV gB types among subjects treated with brincidofovir was gB1: 50.0%, gB2: 12.8%, gB3: 23.1%, gB4: 11.5%, and undetermined: 2.6%. The distribution of CMV gB types among patients who received placebo was gB1: 39.6%, gB2: 16.7%, gB3: 27.1%, gB4: 14.6%, and undetermined: 2.0%. Similar results were obtained if the analysis population was limited to primary failures or CMV failures. Based on these results, there was no evidence for selective antiviral activity of BCV against any particular CMV gB genotype(s).

3. Pharmacokinetic assessments

Blood samples for pharmacokinetic (PK) assessments were collected on the first dosing day (around 3 hours post-dose) and at each scheduled clinic visit for as long as the patient remained on blinded treatment. The actual date and time of the last study drug administration prior to each blood sample collection (including the timed sample collected on the FDD) were

documented for study drug doses administered in the clinic prior to collection of the blood sample and doses self-administered by the patient prior to arriving at the clinic.

All plasma samples were analyzed by Pyxant Labs (Colorado Springs, Colorado, USA) using Method STM2469. Brincidofovir, cidofovir and the internal standards, stable isotopes, were extracted from 100 µL aliquots of plasma (K_2EDTA) using a protein precipitation procedure. Analysis was performed by liquid chromatography-tandem mass spectroscopy (LC-MS/MS) utilizing electro-spray ionization in the negative ionization mode. The dynamic range of the method was 1.00 to 1,500 ng/mL for brincidofovir and 2.50 to 750 ng/mL for cidofovir.

4. Brincidofovir population pharmacokinetic model development and derivation of exposure measures

Pharmacokinetic (PK) data from study CMX001-301 (SUPPRESS) and five additional studies (CMX001-115, CMX001-201, CMX001-202, CMX001-304, CMX001-350) were utilized to develop a population PK model. The total analysis population consisted of healthy volunteers, adult CMV seropositive allogeneic HCT recipients, adult and pediatric patients with disseminated adenovirus disease or with adenovirus infection and at risk for progression to disseminated adenovirus disease.

A nonlinear mixed effects model was developed using NONMEM software 7.3 (ICON Development Solutions) with first order conditional estimation method with interaction (FOCE+I). One and two compartment models were tested for describing the pharmacokinetics of brincidofovir. Absorption as well as distribution and elimination processes were modeled as first-order processes. Inter-individual variability was added assuming exponential distribution, described by:

$$P_{ij} = TV(P_j) \times e^{\eta ij}$$

where P_{ij} denotes the estimate of the j^{th} pharmacokinetic parameter for the i^{th} individual, TV (P_j) is the typical population value of the j^{th} pharmacokinetic parameter, and η_{ij} is the inter-individual random variable for the i^{th} individual and the j^{th} pharmacokinetic parameter, assumed to be distributed with mean 0 and variance ω^2.

Various residual error structures were tested, including additive, proportional, and combined (additive + proportional) as described by:

$$Y_{ij} = C_{ij}(1 + \varepsilon_{1ij}) + \varepsilon_{2ij}$$

where Y_{ij} is the j^{th} observed concentration for the i^{th} subject, C_{ij} is the corresponding predicted concentration, and ε_{ij} are the residual errors under the assumption that ε N(0, σ^2).

Covariates were selected based clinical relevance and statistical importance. Continuous covariates (e.g., body weight, age) were incorporated using a power function, while the effect of categorical covariates (e.g., sex, diarrhea category) was implemented as proportional or fractional change on the pharmacokinetic parameter.

The PK of brincidofovir was well described by a two-compartment model with zero-order appearance in the depot/absorption compartment, followed by a first order absorption into the central compartment and first-order elimination. The covariate search revealed a correlation between bodyweight and clearance as well as central volume. Concurrent cyclosporine treatment lead to a 30% decrease in clearance, while food and diarrhea negatively influenced bioavailability. Healthy volunteers had approximately two-fold higher clearance compared to patients.

The final population PK model was used to estimate brincidofovir steady state AUC and C_{max} values over one week of brincidofovir administration for each subject included in the population

PK analysis. Initially, each subject's concentration-time profiles was simulated using the individual post hoc parameter estimates. Each profile consisted of predicted concentrations at the following time points relative to administration of brincidofovir: 0, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 72 (time of second dose administration for twice weekly regimens), 72.25, 72.5, 73, 74, 76, 80, 84, 96, 108, 120, 144, and 168 hours. AUC values were estimated by applying the linear trapezoidal rule to each simulated profile; maximum concentration values for each simulated profile provided the estimates for C_{max} during the dose interval. The obtained AUC and C_{max} values were subsequently used as exposure input in the exploratory exposure-response analysis for safety and efficacy.

5. Exploratory Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis

The impact of brincidofovir exposure and dose on safety endpoints in the study CMX001-301 population was characterized by an exploratory PK/PD analysis. The endpoints of interest were: 1) development of diarrhea ≥ CTCAE Grade 2 (defined as increase of ≥ 4 stools per day over baseline) or GVHD ≥ NIH Stage 1 (defined as diarrhea ≥ 500 mL/day), and 2) ALT elevation of ≥ CTCAE Grade 2 (defined as > 3x ULN). End of treatment was defined as the time point of last brincidofovir administration plus seven days.

Correlations between PD endpoints and exposures were tested using univariate logistic regression and localized fit methodologies. The effect of increasing steady-state AUC, steady state C_{max}, and weight-adjusted brincidofovir dose on the above-mentioned endpoints was explored.

For univariate logistic regression, the continuous brincidofovir exposures and weight-normalized doses were converted into quartiles and plotted against the categorical endpoint of interest. All

endpoints were of dichotomous nature; for example, for ALT elevation, subjects were categorized into highest ALT elevation during treatment < Grade 2: yes or no.

A generalized linear model was fitted to mathematically describe the correlation between the PK measure and the endpoint. A PK/PD correlation was considered significant when the calculated p-value was below 0.05. For the localized fit, the PK measures were considered as continuous variable and plotted against the categorical endpoint. A LOESS regression was fitted using the R package 'locfit', designed to allow for LOESS regression for dichotomous data.

6. Anti-CMV immune response

The protocol was amended on 02 September 2014. The amendment included the collection of an additional blood sample to evaluate the potential for reconstitution of the anti-CMV immune response using the T-SPOT.® *CMV* Test (Oxford Immunotec Limited, Abingdon, UK) to be collected at Weeks 5, 9, 14, and 24. These samples were collected from individual study participants where the investigator believed the additional blood loss resulting from the collection of the samples is medically acceptable. For those individuals where the investigator felt that the additional blood loss was not medically acceptable, e.g., because the patient was markedly anemic, then some or all of these samples may have been omitted, as necessary. A collection window of up to +2 weeks from the scheduled collection date was allowed to provide additional flexibility in the collection of these samples.

Given delays in implementing this additional collection procedures, only 104/452 (23%) of patients (64 brincidofovir, 30 placebo) had any samples collected for anti-CMV immune response measurements. No results related to these measurements are presented in this manuscript.

7. Assessments of other double-stranded DNA viruses

Patients were monitored for CMV viremia and CMV disease and for reactivation or infection with other dsDNA viruses (e.g., adenovirus, BK virus, EBV, HHV-6, etc.) throughout the study. Each sign/symptom/condition was graded subjectively (present, improved, stable, worsened) as well as objectively using the CTCAE scale where appropriate.

CMV and other dsDNA virus signs and symptoms (e.g., BKV-associated urinary symptoms, HHV-6-associated CNS symptoms) were assessed at the screening evaluation, prior to dosing on the FDD, at each weekly assessment throughout the treatment phase of the study, and during the posttreatment phase at the visits performed during Weeks 15, 18, 21, and 24.

7.1. BKV-associated urinary symptoms

Patients were assessed for BKV-associated urinary symptoms, such as increased urine frequency during the day, increased nocturia, bladder pain, cystitis, and dysuria, at each visit. The study diary card included a screening question for urine or bladder-related symptoms. Patients reporting viral-related cystitis symptoms were further evaluated according to a cystitis scale. Cystitis and other urinary symptoms not associated with viral infection were assessed using the appropriate CTCAE scale. With prior approval from the Chimerix Medical Monitor (or designee), investigators could request real time analysis of urine samples for patients with known or suspected BK viruria or patients exhibiting signs/symptoms consistent with BKV or adenovirus infection, such as cystitis or renal impairment.

7.2. HHV-6-associated symptoms

Patients were assessed for manifestations associated with HHV-6 infection, such as encephalitis, neurocognitive impairment, and graft failure. The study diary card included a screening question for delirium with a more detailed neurocognitive assessment performed by study personnel based on the responses to those questions. A neurocognitive assessment, such as the MMSE (Folstein test), was to have been implemented for patients with known or suspected HHV-6 infection with CNS involvement.

At selected US study centers, patients were asked to participate in an optional neurocognitive substudy, in which a more detailed assessment of their neurocognitive function was performed using the Brief Test of Adult Cognition by Telephone (BTACT) and Oral Trail Making Test (OTMT-B) instruments. This assessment was performed over the telephone one time only at Week 24 with the subject's responses recorded, for scoring purposes, using audio recording software. Only 23 subjects (12 BCV, 11 placebo) agreed to participate in the substudy. No results related to these measurements are presented in this manuscript.

8. Safety Monitoring and Management Plan (SMMP)

As described previously, the GI effects of CMX001 were first identified in Study CMX001-201. During the dosing of Cohort 4 (200 mg CMX001/placebo BIW) in that study, a cluster of SAEs involving diarrhea as part of the event terms or as part of the symptoms described by the investigators were reported. The onset of these symptoms usually occurred 2 to 4 weeks after the initiation of CMX001/placebo dosing, making it difficult to distinguish drug-related GI events from GVHD of the intestine, which often occurs within 2 to 6 weeks

posttransplant, depending on whether the conditioning therapy was myeloablative or of reduced-intensity.

After reviewing the data from Cohort 4, Chimerix implemented a program-wide SMMP across all CMX001 studies to help identify, characterize, and mitigate GI and hepatic AEs potentially associated with CMX001 treatment, in particular diarrhea and increases in serum aminotransferases, as well as GI events presenting as possible GVHD. The SMMP describes a method for monitoring, characterizing and managing GI and hepatic symptoms or laboratory abnormalities in patients enrolled in CMX001 studies. This guidance was to be used in combination with the investigator's medical judgment in managing the patients enrolled in this study, and is reflected in the following sections detailing the then recommended strategy for managing patients presenting with GI and hepatic AEs. **While the management of AEs was the responsibility of the investigators using their best medical judgment and local standard of care (SoC), the rules for study drug interruption or discontinuation described below had to be adhered to.**

A flow chart summarizing the process for the management of treatment-emergent GI and hepatic toxicities requiring dose interruption is provided in **Figure S3**.

8.1. Diagnosis of causes of gastrointestinal (GI) and hepatic symptoms in patients with severe or serious AEs

Diarrhea is a common symptom in immunocompromised hosts, including HCT recipients posttransplant, resulting from multiple etiologies including infections (e.g., viral, bacterial, such as *Clostridium difficile* [*C. Difficile*], parasitic, and rarely fungal); drug toxicity (including conditioning regimens for HCT and immunosuppressant drugs, such as mycophenolate

mofetil [MMF]); and GVHD after HCT, among other causes).

In animal studies, the dose limiting toxicity of CMX001 was diarrhea related to alteration of the GI tract starting in the small intestine, particularly the ileum. In human studies, GI symptoms have been attributed to CMX001 and were dose-limiting in the CMX001-201 study when administered at 200 mg BIW to HCT patients; therefore, particular attention should be paid to GI-related symptoms and the potential cause(s) should be investigated. Below is guidance on explorations suggested to investigate GI or hepatobiliary signs and symptoms.

I. Diarrhea should be evaluated by measurement of stool volumes and/or number of watery stools per 24 hours; examining a specimen for blood, and evaluation for pathogens, GVHD, and other potential causes.

a. Infectious causes: Except for CMV, all of the common causes of intestinal infection in immune suppressed patients can be found in stool studies. The spectrum of infecting organisms varies with the extent of environmental exposure:

- If the onset of symptoms was in a protected hospital environment, the most useful tests are toxigenic *C. difficile*, AdV DNA, viral culture, CMV DNA (in blood), gut biopsy for immunohistochemistry (IHC) and centrifugation culture
- If symptoms began after hospital discharge, potential exposure to community-acquired organisms should be considered, with tests for rotavirus (EIA), norovirus (RNA), astrovirus (RNA), Giardia antigen, Cryptosporidia PCR, ova and parasites
- If symptoms began after greater exposure to potential pathogens, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Aeromonas*, *E. coli* H7:O157, and fungi should also

be considered.

b. Acute GVHD in its more severe forms causes diarrhea in volumes as high as 8 to 10 L/day, often accompanied by falling serum albumin as a result of gut protein loss, and sometimes accompanied by abdominal pain and pseudo-obstruction.

- The consensus definition listed below may be used to assign a stage for a case of suspected GI GVHD, based upon the severity of GI symptoms and signs. When the exact volume of diarrhea is not recorded, peak daily volumes should be based upon the clinical description.
    - Stage 1, diarrhea 500-999 mL/day or biopsy-proven upper gut involvement
    - Stage 2, diarrhea 1,000-1499 mL/day
    - Stage 3, diarrhea 1,500-1999 mL/day
    - Stage 4, diarrhea ≥ 2,000 mL or severe abdominal pain with or without ileus
- Confirming the diagnosis of GVHD of the intestine depends upon the existence of risk factors, the presence of a drop in serum albumin (which in the setting of diarrhea can be a nonspecific indication of enteropathy), and the endoscopic appearance of the mucosa; histology of mucosal biopsy; and in some cases, intestinal imaging (CT enterography, sonographic ultrasound). The anatomic sites of greatest diagnostic utility for histology are the pyloric gland area in the antrum and the colon; therefore upper GI endoscopy with biopsy should be performed as a first diagnostic method if GVHD is suspected. There is a significant false negative rate in histologic diagnosis of GVHD related to sampling error.
- There are also histologic mimics of GVHD from other causes such as MMF

toxicity.

- CMX001 administration has been associated with diarrhea, typically occurring after 2 or more weeks of dosing. In some cases, decreasing serum albumin concentrations have been noted in patients with persistent, higher volume (Grade 2 to 3) diarrhea. It is unknown at this time whether CMX001 toxicity is associated with histologic changes in the gut or whether it can be differentiated histologically from GVHD. Therefore, in the absence of extra-intestinal signs of GVHD or if the timing/incidence of GVHD is unusual, based on conditioning regimen and risk factors, CMX001 should be considered as a possible cause of diarrhea and, depending upon the severity and persistence of the diarrhea, CMX001 doses should be interrupted before treatment of GVHD is considered (additional guidance is provided below).

c. Medications, other causes: High-volume diarrhea is less likely to be caused by medications and ingestion of disaccharides than GVHD or infections; however, in the presence of diarrhea, oral magnesium supplementation should be interrupted.

II. More severe upper gut symptoms, including anorexia, nausea, vomiting, and early satiety, have a limited differential diagnosis that includes GVHD, herpesvirus infection, medication side effects, and increased intracranial pressure disorders. Endoscopic biopsy for histology and centrifugation culture is the diagnostic method of choice.

III. Severe hepatobiliary problems include cholestatic disorders (cholangitis lenta, GVHD, obstruction) and hepatocellular necrosis (GVHD, DiLI, viral infections, hypoxic hepatitis). Diagnostic methods include hepatobiliary imaging, PCR for relevant viral pathogens, and liver histology in enigmatic cases. Concomitant medications commonly

associated with potential hepatobiliary AEs should also be considered (e.g., azoles, Bactrim®, and isoniazid).

8.2. Management of patients with gastrointestinal AEs

Investigators should pay particular attention to GI signs and symptoms when questioning patients about AEs at every study visit. In particular when a decrease in serum albumin level is noted, investigators should intensify their questioning of patients with respect to symptoms of diarrhea. In order to facilitate this monitoring, serum albumin concentrations that represent a decrease from baseline of ≥ 4g/L (≥ 0.4g/dL) and are ≤ 30 g/L (≤ 3 g/dL) will be systematically flagged by the central safety laboratory on the laboratory report. At each study assessment during the treatment phase, the patient should be specifically asked about GI symptoms.

Any AEs should be graded in accordance with the CTCAE grading scales; additional details regarding the GI symptoms will be collected in the eCRF. For convenience, the CTCAE grading for diarrhea as an AE is listed here:

- Grade 1:
  - Increase of < 4 stools per day over baseline; or mild increase in ostomy output compared to baseline
- Grade 2:
  - Increase of 4 to 6 stools per day over baseline; or moderate increase in ostomy output compared to baseline
- Grade 3:
  - Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization

indicated; or severe increase in ostomy output compared to baseline; limiting self-care activities of daily living (ADL)

- Grade 4:

- Life-threatening consequences; urgent intervention indicated

Please refer to the SRM for the most current version of the CTCAE grading scales.

Management of patients with GI AEs is dependent upon the duration and intensity of signs and symptoms and is described below.

8.2.1. For patients with Grade 1 GI-related AEs:

GI complaints are very frequent in the HCT patient population immediately post transplantation. Nutritional advice should be given to avoid ingesting food and drink that affect intestinal water transport (e.g., caffeine, alcohol, carminative spices, and concentrated sugar syrups). In addition, some patients with intestinal inflammation may develop down-regulation of intestinal disaccharidases (lactase, sucrase-isomaltase), and should avoid lactose- and sucrose- containing drinks. Consideration should be given to adjusting medications associated with GI side effects (e.g., macrolide antibiotics, magnesium sulfate salts, and MMF). Liquid and electrolyte intake should be encouraged to avoid dehydration if renal function is normal.

Symptomatic care may be provided for symptoms as needed (e.g., anti-emetics). Other causes of new GI symptoms should be investigated and treated as appropriate (including infections, GVHD, etc.)

For Grade 1 GI AEs, aggressive treatment of GVHD should be initiated only if the diagnosis is confirmed at another organ site (e.g., skin or liver); anorexia and new onset of lack of

appetite/no pleasure in eating may be used as a potential marker of upper-GI GVHD in addition to biopsy results, if endoscopy was felt to be warranted. Standard first line treatments for aGVHD, including steroids and calcineurin inhibitors, are allowed under this protocol. Details of the diagnostic procedures and risk factors will be captured in the eCRF. In the absence of extra- intestinal involvement and of GVHD risk factors, treatment of GVHD should be delayed if medically feasible for Grade 1 diarrhea.

8.2.2. For patients with Grade 2 GI-related AEs:

In addition to the measures described under Grade 1, institution of loperamide, given at regular intervals rather than PRN (pro re nata), for control of diarrhea should be considered, along with antiemetics for nausea and vomiting.

For patients with diarrhea, oral magnesium supplementation should be interrupted and plasma or blood concentrations of immunosuppressant drugs should be measured.

For intermittent diarrhea symptoms of Grade 2 intensity, no further action on study drug is warranted.

If patients present with more than one Grade 2 GI AE at the same time or Grade 2 diarrhea for more than 3 consecutive days, **consideration should be given to interrupting study drug dosing in consultation with the Chimerix Medical Monitor (or designee)**, particularly if the symptoms are noted 2 to 8 weeks after the initiation of study drug treatment and when a decrease in serum albumin from baseline of ≥ 4 g/L reaching to serum albumin concentrations of ≤ 30 g/L is noted in the absence of other etiology for hypoalbuminemia.

8.2.3. For patients with Grade 3 or higher GI-related AEs:

For patients with more severe AEs (i.e., Grade 3 or higher), the imperative for a diagnosis becomes greater. Study drug administration should be interrupted; and the treatment recommendations described under Grade 1 and 2 above intensified (including measurement of immunosuppressant concentrations).

1. **For patients at high risk of GVHD with evidence of extra-intestinal GVHD** (i.e., liver and/or skin):

- Treatment with steroids or local SoC should be initiated and **study drug administration should be interrupted**.
- If symptoms improve after steroid therapy, study drug should be resumed at the same dose as soon as feasible (see Section 11.5 of the protocol for guidance on resuming dosing after study drug interruption).

2. In the absence of extra-intestinal involvement of GVHD and low risk of GVHD:

- **Study drug administration should be interrupted** and treatment with corticosteroids should be withheld, where medically feasible, for at least 3 days.
- If the signs and symptoms increase in intensity or do not improve after study drug has been withheld for at least 1 dose, then steroid therapy may be introduced if clinically indicated. If symptoms improve on steroid therapy, study drug can be resumed at the same dose as soon as feasible (see Section 11.5 of the protocol for guidance on resuming dosing after study drug interruption).
- If the signs and symptoms improve after study drug interruption without additional intervention, study drug dosing may be resumed but at a reduced dose or dosing frequency, in consultation with the Chimerix Medical Monitor (or designee). In the event of reduced dose, new drug supplies will need to be requested through the

IV/WRS as described in Section 11.5 of the protocol.

- If after 18 days of study drug interruption (with or without steroid therapy), i.e., 4 missed doses, there is no improvement in the GI symptoms (i.e., the symptoms remain Grade 3 or higher), and no other etiology has been identified the patient should be permanently discontinued from study drug. Patients who discontinue study drug should follow the same schedule of assessments through Week 24. If another etiology has been identified it should be treated and dosing with study drug should not be resumed until improvement is noted. If the GI AE improves to Grade 2 or lower after up to 14 days of interruption, the patient may resume dosing with study drug. The choice of resuming at the original dose or with a dose or dosing frequency reduction will be made in consultation with the Chimerix Medical Monitor (or designee).

  Overall, the dose at which study drug may be restarted can be:

- The previously administered dose, if symptoms have improved and an alternate cause for the Grade 3 AE has been identified and treated.
- With a reduced dose or change in dosing frequency if symptoms have improved but no other etiology for the AE has been identified.

  If the GI symptoms return to ≥ Grade 3 after the reintroduction of study drug, study drug should be permanently discontinued. Discontinued patients should remain in the study and should follow the schedule of assessments until resolution of symptoms or study completion, i.e., Week 24, whichever comes later.

8.3. Management of patients with serum elevations in serum aminotransferases

Interruption of treatment with study drug should be considered if any of the following

confirmed abnormalities are met:

1. ALT or AST > 8x ULN and 2x baseline value
2. ALT or AST > 5x ULN for more than 2 weeks and 2x baseline value
3. ALT or AST > 3x ULN (and 2x baseline value) **and** total bilirubin > 2x ULN **or** PT-INR

   > 1.5x ULN
4. ALT or AST > 3x ULN (and 2x baseline value) with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% of total WBC count).

Confirmed abnormalities of the magnitude described above should lead to study drug interruption. These values should be confirmed at the central safety laboratory as soon as feasible, if clinically acceptable. A sample can be drawn in parallel for local laboratory analysis if deemed necessary by the investigator. If awaiting confirmation is not deemed clinically appropriate, then study drug should be interrupted, pending further investigation of the laboratory abnormalities. If confirmed, administration of study drug should be interrupted and the following investigations conducted including, but not limited to, imaging, identification of potential hepatotropic infections, evaluations for GVHD, review of other concomitant medications and possibly liver biopsy, as appropriate. Lactic acidosis should also be ruled out. For patients receiving an azole, interruption of the azole should be considered if criterion 2 is the only criterion met, i.e., there is no bilirubin elevation.

If an alternate reason for the abnormalities is identified and after the abnormalities decrease by one grade below that which triggered the study drug interruption criteria listed above, dosing with study drug may resume at a similar or lower dose after discussion with the

Chimerix Medical Monitor (or designee).

Generally resumption of dosing in patients with ALT or AST elevations remaining at levels > 5x ULN should not be attempted unless an alternative etiology for the aminotransferase elevations is confirmed. Recurrence of the liver abnormalities after reintroduction of study drug should lead to permanent discontinuation of study drug.

III. Supplemental Tables

Table S1. Schedule of study assessments and procedures

Procedure	Screening[a]	Treatment Phase (weeks posttransplant)[b]														Posttreatment Phase[c] (weeks posttransplant)			
		FDD (Baseline)[d]		2	3	4	5	6	7	8	9	10	11	12	13	14	15	18	21	24
Written informed consent[e]	X																			
Review inclusion/exclusion criteria	X	X																		
Medical/medication history, including transplant history[f]	X	X																		
Physical examination[g]	X	X					X				X						X			X
Vital signs measurement[h]	X	X					X				X						X			X
Height/Body weight[i]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory evaluations[j]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[k]	X	X					X				X						X			X
HIV serology/HBV and HCV viral load[l]	X																			
Blood (plasma) for virologic analyses[m]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for analysis of anti-CMV response[n]							X				X					X				X
Lymphocyte subset (CD4+ and CD8+)		X				X		X				X					X			X
Urine for virologic analyses[o]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other samples for virologic analyses (as needed)[p]	<---------- X ---------->																			
Record immunosuppressant(s) concentration[q]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomize patient[r]		X																		
Dispense study drug		X							X[s]											
Study drug dosing[t]		X		X	X	X	X	X	X	X	X	X	X	X	X	X				
Drug accountability				X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Blood (plasma) samples for PK analysis[u]		X		X	X	X	X	X	X	X	X	X	X	X	X	X				
HE/HRQL questionnaires[v]	<---------- X ---------->							X									X			X
Neurocognitive assessments[w]		X						X				X					X			X
Assess CMV/Other dsDNA virus signs and symptoms[x,y]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide/review of study diary card[z]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diarrhea and GVHD assessments[aa]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X[bb]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. All screening procedures do not need to be completed on the same day, but all screening procedures must be completed and the results reviewed prior to initiating treatment on the First Dosing Day (FDD).

b. The duration of the treatment phase will vary for individual patients from 10 to 14 weeks, depending on when treatment is initiated relative to the date of transplant. During the treatment phase, patients will be assessed weekly summarizes which of the Week 2-4 assessments must be completed and which should be omitted based on the FDD to ensure that each patient completes the protocol-specified duration of study treatment, i.e., approximately 100 days posttransplant. If a patient should discontinue study drug (for whatever reason) prior to Week 14, which will be the last week of study drug for all patients, the patient should continue to be assessed on a weekly basis and complete all study procedures and assessments, with the exception of study drug dosing, the collection of blood samples for PK assessments, and study drug accountability, through Week 14.

c. The posttreatment phase (Weeks 15 to 24) is scheduled relative to the transplant date and is fixed for all patients, regardless of whether they complete the study drug.

d. Dosing with study drug (brincidofovir or placebo) will be initiated after transplant as soon as the patient is able to ingest tablet, but no later than Day 28 posttransplant. Other than study drug dosing and the collection of the 3 (± 1) hour postdose PK blood sample, all study procedures should be performed prior to dosing (to serve as baseline measures).

e. Potential patients may be consented for participation in the study before or after transplant. However, patients may only be screened following transplant.

f. If preferred, medical history may be obtained before transplant (and after written informed consent has been obtained) but must be updated following transplant and prior to dosing.

g. A complete physical examination (PE) will be performed at screening and at Week 24; abbreviated PEs, targeted to new signs and symptoms, will be performed at all other assessments.

h. Blood pressure and pulse rate, after the patient has rested quietly for ≥ 5 minutes, and temperature (any measurement site).

i. Height will be captured at screening only.

j. Blood and urine will be collected for testing by the designated central safety laboratory using standard hematology (including PT-INR), serum chemistry, and urinalysis panels. To monitor renal function, eGFR will be calculated by the central safety laboratory using MDRD4. See Table S2 for a list of test parameters.

k. Urine beta-human chorionic gonadotropin (β-hCG) for women of childbearing potential, reflex to serum β-hCG if positive.

l. Pretransplant results may be used to satisfy the protocol entry criteria, if collected within 6 months prior to the qualifying transplant.

m. Blood (plasma) samples will be collected at screening, on the FDD, and weekly throughout the treatment phase and at each posttreatment assessment. Each sample will be divided into aliquots for (1) "real-time" assay of CMV viremia in plasma using the FDA-approved and CE-marked Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test; (2) possible "real-time" testing for other dsDNA viruses (e.g., AdV, BKV, EBV, HHV-6, etc.) in the presence of suggestive clinical symptoms, and (3) one or more storage samples for resistance testing (genotypic and/or phenotypic); additional CMV viremia assessments, based on newly available assays; for retrospective analyses for other dsDNA viruses; and/or for possible testing for biomarkers of GVHD or CMV-specific immunity.

[Note: Plasma CMV viremia must be assessed by the designated central virology laboratory within 5 days prior to randomization; only patients who are determined to be CMV viremia negative on screening assessment (i.e., CMV DNA in plasma is "Not Detected" for the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test used by the central virology laboratory) will be eligible for randomization. In addition, the results of any CMV

viremia testing (including CMV PCR, pp65 antigenemia, etc.) performed as part of local standard of care since the qualifying transplant must also be negative.]

n. A blood sample to evaluate the potential for reconstitution of the anti-CMV immune response using the T-SPOT.® *CMV* Test (Oxford Immunotec Limited, Abingdon, UK) will be collected at Weeks 5, 9, 14, and 24. These samples will be collected from individual study participants where the investigator believes the additional blood loss resulting from the collection of the samples is medically acceptable. For those individuals where the investigator feels that the additional blood loss is not medically acceptable, then some or all of these samples may be omitted, as necessary. A collection window of up to +2 weeks from the scheduled collection date is provided to allow for additional flexibility in the collection of these samples.

o. Urine collected at screening, on the FDD, and weekly throughout the treatment phase and at each posttreatment assessment will be divided into one or more aliquots and stored for possible future analysis, including retrospective analyses of CMV and/or other dsDNA viruses, resistance testing, etc. In consultation with the Chimerix Medical Monitor (or designee), investigators may request real time analysis of the urine samples for patients with known or suspected BK viruria or patients exhibiting signs/symptoms consistent with BKV or AdV infection, such as cystitis or renal impairment.

p. When a dsDNA viral syndrome or disease is suspected, other relevant biological samples (e.g., stool, cerebrospinal fluid [CSF], sputum, bronchoalveolar lavage, skin or nasopharyngeal swab, tissue biopsy, etc., as appropriate) should be sent to the designated central virology laboratory for "real time" analysis and/or storage for possible future analysis. Prior approval is required from the Chimerix Medical Monitor (or designee) for the analysis of any samples other than blood (plasma) for CMV viremia.

q. The following information will be captured for each immunosuppressant: dose, concentration value (most recent value since last study visit if multiple values are available), concentration units, matrix (whole blood, plasma, or serum), date and time of sample collection, and date and time of last dose of immunosuppressant medication prior to sample collection.

r. Patients will be randomized within 1 business day of their scheduled FDD, taking into account normal site logistics, using the IV/WRS. During randomization, patients will be stratified within an investigative center, based on their likelihood for progression to clinically significant CMV infection, i.e., a "lower likelihood" versus a "higher likelihood" of progression. Patients who receive a matched, related, non-T-cell depleted graft (e.g., excluding cord blood), who do not have aGVHD, who have not received ATG or alemtuzumab, and who are not receiving high-dose (≥ 1 mg/kg prednisone equivalent) systemic steroids will be stratified in the "lower likelihood" group. All other patients will be stratified in the "higher likelihood" group.

s. The second card of study drug in each study drug kit should be dispensed to patient at an appropriate time, taking into account the actual duration of the individual patient's treatment, any dose interruptions due to AEs, other missed doses, logistical issues (e.g., public holidays, vacation), etc. If a patient dose reduces in response to a treatment-emergent toxicity, then the dispensing of the new study drug kit can occur at any time during the treatment phase.

t. Patients will be randomized in a 2:1 ratio under double-blind conditions to either 100 mg brincidofovir BIW or placebo BIW. Study drug will be dosed orally, using brincidofovir tablets or matching placebo, and taken with food (as a low-fat meal comprising no more than 20% of its total caloric value from fat) where patients are able to tolerate oral intake. Where possible, at least one of the two weekly doses of study drug will be administered by the investigator or designee; otherwise, study drug will be self-administered by the patient on the protocol-specified day or as close as possible thereto. Doses should be administered at alternating 3- and 4-day intervals (e.g., each Monday and Thursday, each Tuesday and Friday, each Wednesday and Saturday, etc.)

u. A single timed blood sample for analysis of plasma concentrations of brincidofovir and CDV (and possibly other metabolites) will be collected on the FDD at 3 (± 1) hours postdose. In addition, a single PK blood sample for analysis of plasma concentrations of brincidofovir and CDV (and possibly other metabolites) will be collected during each scheduled weekly assessment for as long as the patients remain on blinded study treatment. If the timed blood sample cannot be

collected on the FDD, e.g., due to scheduling or resource issues, it may be collected within the same time window, i.e., at 3 (± 1) hours postdose, following administration of the second dose of study drug.

v. Each patient will complete the EQ-5D-5L and EORTC-QLQ-C30/HDC29 questionnaires during the screening evaluation or prior to study drug administration on the FDD (to establish baseline), then at Week 6, Week 15, and Week 24.

w. A mini-mental state examination (MMSE) will be performed in all patients on the FDD prior to study drug administration (to establish baseline), with subsequent assessments performed at Week 6, Week 10, Week 15, and Week 24. At selected sites, patients may be asked to undergo a more detailed assessment of their neurocognitive function using the validated Brief Test of Adult Cognition by Telephone (BTACT) and Oral Trail Making Test (OTMT-B) instruments. This optional assessment will be performed one time at Week 24. The test will be administered over the telephone and the patient's responses will be recorded, for scoring purposes, using audio recording software. Patients who agree to undergo the more detailed neurocognitive assessment do not have to complete the MMSEs scheduled for Weeks 6, 10, 15, and 24. Additional MMSEs may be performed in individual patients (whether participating in the optional Week 24 assessment or not), when deemed clinically appropriate to do so by the investigator, e.g., based on responses to screening questions on the study diary card.

x. For assessment of the onset of CMV disease and other dsDNA viral syndrome or disease (e.g., assessments for BK urinary symptoms, initiated in patients with increased urine frequency during the day, increased nocturia, or bladder pain or MMSE testing in patients suspected of HHV-6 CNS impairment).

y. Slides from any biopsy performed for the diagnosis of GVHD (regardless of the organ involved), and all GI biopsies or biopsies from any organ conducted to diagnose CMV disease (or other dsDNA viral syndrome or disease), should be sent to the designated central laboratory. Specific guidance with respect to biopsy sampling and handling will be provided in the SRM and/or applicable central laboratory manual.

z. The study diary card will contain dosing information (date and time of dosing, whether the dose was taken with or within 30 minutes after finishing a meal), number of liquid stools per day, urine frequency if > 4-times per day or nocturia, bladder pain and delirium screening questions, contact information for the site when specific criteria are met.

aa. Diarrhea and/or GVHD will be assessed weekly and during any unscheduled assessments where symptoms have changed since the previous assessment.

bb. AEs will be recorded from the time of administration of the first dose of study drug until the patient has completed the study, i.e., following completion of the Week 24 assessment or premature discontinuation from the study, whichever occurs first. In addition, any study procedure-related AE that occurs after study participants have signed the informed consent from (ICF) and prior to administration of the first dose of study drug will be recorded as an AE.

Table S2. Clinical and virologic laboratory evaluations

BIOCHEMISTRY PANEL	HEMATOLOGY PANEL
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Amylase Aspartate aminotransferase (AST) Bilirubin (total and direct) Blood urea nitrogen (BUN) Calcium (ionized) Creatine kinase (CK) Creatinine Electrolyte Panel (Na^+, K^+, Cl^-, HCO_3 [or CO_2]) Gamma-glutamyltransferase (GGT) Globulin, total Glucose Haptoglobin Lactate dehydrogenase (LDH) Lipase Phosphate Protein (total) Uric acid	Absolute neutrophil count (total) Hematocrit Hemoglobin Mean cell hemoglobin (MCH) Mean cell hemoglobin concentration (MCHC) Mean cell volume (MCV) Platelet count (PLT) Red blood count (RBC) RBC morphology (reticulocytes, schistocytes, etc.) White blood count (WBC) with differential (percent and absolute) Lymphocyte subset (percent and total [absolute] CD4+ and CD8+) on the FDD, at Week 4, Week 6, Week 10, Week 15, and Week 24 only
	URINALYSIS PANEL
	Albumin (microalbumin) Blood Glucose Leukocytes (leukocyte esterase) Microscopic analysis, if blood or leukocytes present Protein
MISCELLANEOUS TESTS	**VIROLOGIC EVALUATIONS (dsDNA VIRUSES)**
Coagulation Panel: Prothrombin time-international normalized ratio (PT-INR) **Estimated GFR** (using MDRD4) **Pregnancy Test:** β-human chorionic gonadotropin (β-hCG) in urine **Non-dsDNA Viral Serology/Viral Load:** HBV DNA, HCV RNA, and HIV Ab, as needed[a] **Immune Reconstitution:** Anti-CMV response (using the T-SPOT.® *CMV* Test) at Weeks 5, 9, 14, and Week 24	**Viral Detection:** Routine: CMV in blood (plasma) at all visits Testing for other dsDNA viruses in blood (plasma), urine and/or other biological samples (e.g., stool, CSF, sputum, bronchoalveolar lavage, skin or nasopharyngeal swab, tissue biopsy, etc., as appropriate) at some or all visits (based on signs/symptoms compatible with CMV and/or other dsDNA viral syndrome or disease and with prior approval of the Chimerix Medical Monitor [or designee]) **For storage:** Blood (plasma) and urine (and, where applicable, other biological samples) at all visits for resistance testing and possible future virologic analyses (as well as possible testing for biomarkers of GVHD or CMV-specific immunity).

a. If documented results from viral serology/infection tests performed within 6 months prior to the qualifying transplant are not available.

Central Laboratories used: Covance Central Laboratory Services in Indianapolis, Indiana, USA, for centers in North America; Covance Central Laboratory Services in Geneva, Switzerland for centers in Europe

Table S3. Incident adjudicated dsDNA virus diseases during the trial

dsDNA Virus Disease*	Brincidofovir (N=303)		Placebo (N=149)	
	Week 14	Week 24	Week 14	Week 24
Any non-CMV dsDNA virus disease†	50 (16.5%)	62 (20.5%)	21 (14.1%)	23 (15.4%)
BK polyomavirus disease	40 (13.2%)	45 (14.9%)	14 (9.4%)	17 (11.4%)
Adenovirus disease	3 (1.0%)	5 (1.7%)	2 (1.3%)	2 (1.3%)
EBV disease	3 (1.0%)	4 (1.3%)	2 (1.3%)	3 (2.0%)
Herpes simplex virus disease	4 (1.3%)	9 (3.0%)	3 (2.0%)	5 (3.4%)
HHV-6 disease	2 (0.7%)	3 (1.0%)	4 (2.7%)	4 (2.7%)
Varicella zoster disease	1 (0.3%)	3 (1.0%)	0	2 (1.3%)
JC virus disease	1 (0.3%)	1 (0.3%)	0	0

*See Supplementary Appendix Methods Section 7 for definition and adjudication details.

†Some patients had more than one dsDNA virus disease

Table S4. All-cause mortality through Week 14 and Week 24 according to selected trial subgroups

Group	N	Week 14		Week 24	
		Brincidofovir n/N (%)	Placebo n/N (%)	Brincidofovir n/N (%)	Placebo n/N (%)
Intention-to-treat	452	23/303 (7.6)	8/149 (5.4)	46/303 (15.2)	15/149 (10.1)
CMH OR (95% CI)		1.4 (0.6, 3.3)		1.6 (0.9, 2.8)	
p-value		0.382		0.117	
Higher risk of CMV	332	17/223 (7.6)	7/109 (6.4)	39/223 (17.5)	11/109 (10.1)
CMH OR (95% CI)		1.2 (0.48, 3.03)		1.89 (0.93, 3.85)	
p-value		0.692		0.077	
Lower risk of CMV	120	6/80 (7.5)	1/40 (2.5)	8/80 (10.0)	4/40 (10.0)
CMH OR (95% CI)		3.13 (0.37, 25.0)		1.00 (0.28, 3.57)	
p-value		0.273		1.0	
Myeloablative conditioning	248	14/162 (8.6)	6/86 (7.0)	23/162 (14.2)	12/86 (14.0)
CMH OR (95% CI)		1.27 (0.47, 3.44)		1.02 (0.48, 2.17)	
p-value		0.649		0.965	
Reduced intensity conditioning	204	9/141 (6.4)	2/63 (3.2)	24/141 (17.0)	3/63 (4.8)
CMH OR (95% CI)		2.08 (0.44, 10.0)		4.0 (1.19, 14.3)	
p-value		0.350		0.017	
ATG, alemtuzumab, T-cell depletion	177	7/113 (6.2)	5/64 (7.8)	20/113 (17.7)	7/64 (10.9)
CMH OR (95% CI)		0.78 (0.24, 2.56)		1.75 (0.69, 4.35)	
p-value		0.682		0.231	
No ATG, alemtuzumab, T-cell depletion	275	16/190 (8.4)	3/85 (3.5)	27/190 (14.2)	8/85 (9.4)
CMH OR (95% CI)		2.5 (0.70, 9.09)		1.56 (0.68, 3.57)	
p-value		0.147		0.293	

Table S5. Adverse event summary through Week 15 post-transplantation

Adverse Event Category	BCV (N=303) n (%)	Placebo (N=149) n (%)
Any adverse event	302 (99.7)	146 (98.0)
Any CTCAE Grade ≥3 adverse event	203 (67.0)	56 (37.6)
Any related adverse event	91 (30.0)	23 (15.4)
Any CTCAE Grade ≥3 related adverse event	37 (12.2)	1 (0.7)
Any adverse event with outcome of death	29 (9.6)	6 (4.0)
Any serious adverse event	173 (57.1)	56 (37.6)
Any related serious adverse event	19 (6.3)	1 (0.7)
Any adverse event leading to study drug discontinuation	79 (26.1)	11 (7.4)
Any adverse event leading to study drug interruption, modification, or reduction	136 (44.9)	22 (14.8)

Table S6. Adverse events by system organ class and preferred term reported during study treatment in ≥5% in any treatment group through Week 15 post-transplantation*

System Organ Class Preferred Term	Brincidofovir (N=303) n (%)	Placebo (N=149) n (%)
Any adverse event, all grades	**302 (99.7)**	**146 (98.0)**
Gastrointestinal disorders	**272 (89.8)**	**107 (71.8)**
Diarrhoea	184 (60.7)	54 (36.2)
Abdominal pain	104 (34.3)	26 (17.4)
Nausea	93 (30.7)	29 (19.5)
Vomiting	74 (24.4)	25 (16.8)
Constipation	29 (9.6)	11 (7.4)
Dry mouth	21 (6.9)	13 (8.7)
Abdominal distension	19 (6.3)	10 (6.7)
Dyspepsia	24 (7.9)	4 (2.7)
Metabolism and nutrition disorders	**185 (61.1)**	**64 (43.0)**
Decreased appetite	67 (22.1)	19 (12.8)
Hyperglycaemia	48 (15.8)	11 (7.4)
Hypokalaemia	47 (15.5)	10 (6.7)
Hypomagnesaemia	38 (12.5)	12 (8.1)
Hyponatraemia	21 (6.9)	8 (5.4)
Hyperkalaemia	20 (6.6)	6 (4.0)
Hypoalbuminaemia	21 (6.9)	5 (3.4)
Dehydration	20 (6.6)	5 (3.4)
Hypocalcaemia	19 (6.3)	4 (2.7)
Hypophosphataemia	17 (5.6)	4 (2.7)
General disorders and administration site conditions	**164 (54.1)**	**84 (56.4)**
Fatigue	42 (13.9)	28 (18.8)
Oedema, peripheral	52 (17.2)	18 (12.1)
Pyrexia	42 (13.9)	27 (18.1)
Mucosal inflammation	32 (10.6)	15 (10.1)

Asthenia	29 (9.6)	6 (4.0)
Immune system disorders	**174 (57.4)**	**54 (36.2)**
Acute graft-versus-host disease	173 (57.1)	48 (32.2)
Hypogammaglobulinaemia	16 (5.3)	6 (4.0)
Infections and infestations	**147 (48.5)**	**49 (32.9)**
BK virus infection	24 (7.9)	7 (4.7)
Clostridium difficile colitis	27 (8.9)	3 (2.0)
Cystitis, viral	17 (5.6)	4 (2.7)
Investigations	**142 (46.9)**	**48 (32.2)**
Alanine aminotransferase increased	34 (11.2)	9 (6.0)
Aspartate aminotransferase increased	29 (9.6)	8 (5.4)
Blood creatinine increased	24 (7.9)	12 (8.1)
Weight decreased	24 (7.9)	2 (1.3)
Skin and subcutaneous tissue disorders	**124 (40.9)**	**62 (41.6)**
Rash	43 (14.2)	28 (18.8)
Pruritus	29 (9.6)	13 (8.7)
Dry skin	27 (8.9)	8 (5.4)
Erythema	16 (5.3)	4 (2.7)
Nervous system disorders	**112 (37.0)**	**55 (36.9)**
Headache	31 (10.2)	21 (14.1)
Dizziness	22 (7.3)	13 (8.7)
Tremor	20 (6.6)	10 (6.7)
Dysgeusia	18 (5.9)	9 (6.0)
Respiratory, thoracic and mediastinal disorders	**108 (35.6)**	**46 (30.9)**
Cough	31 (10.2)	20 (13.4)
Oropharyngeal pain	20 (6.6)	7 (4.7)
Dyspnoea	16 (5.3)	8 (5.4)
Epistaxis	15 (5.0)	9 (6.0)
Rhinorrhoea	10 (3.3)	8 (5.4)

Musculoskeletal and connective tissue disorders	**93 (30.7)**	**54 (36.2)**
Pain in extremity	26 (8.6)	8 (5.4)
Back pain	22 (7.3)	10 (6.7)
Arthralgia	13 (4.3)	12 (8.1)
Myalgia	9 (3.0)	8 (5.4)
Renal and urinary disorders	**98 (32.3)**	**45 (30.2)**
Acute kidney injury	30 (9.9)	10 (6.7)
Pollakiuria	20 (6.6)	10 (6.7)
Dysuria	17 (5.6)	10 (6.7)
Psychiatric disorders	**76 (25.1)**	**35 (23.5)**
Insomnia	31 (10.2)	12 (8.1)
Depression	20 (6.6)	6 (4.0)
Anxiety	14 (4.6)	10 (6.7)
Vascular disorders	**83 (27.4)**	**28 (18.8)**
Hypertension	33 (10.9)	16 (10.7)
Hypotension	32 (10.6)	6 (4.0)
Blood and lymphatic system disorders	**76 (25.1)**	**31 (20.8)**
Febrile neutropenia	19 (6.3)	11 (7.4)
Anaemia	18 (5.9)	7 (4.7)
Neutropenia	16 (5.3)	8 (5.4)
Thrombocytopenia	16 (5.3)	3 (2.0)
Eye Disorders	**55 (18.2)**	**26 (17.4)**
Dry eye	15 (5.0)	11 (7.4)
Cardiac disorders	**47 (15.5)**	**12 (8.1)**
Tachycardia	18 (5.9)	4 (2.7)
Injury, poisoning and procedural complications	**39 (12.9)**	**16 (10.7)**

Fall	14 (4.6)	2 (1.3)
Neoplasms benign, malignant and unspecified	**24 (7.9)**	**12 (8.1)**
Acute myeloid leukaemia, recurrent	8 (2.6)	4 (2.7)
Reproductive system and breast disorders	**21 (6.9)**	**11 (7.4)**
Vulvovaginal discomfort	3 (1.0)	1 (0.7)
Hepatobiliary disorders	**23 (7.6)**	**5 (3.4)**
Hyperbilirubinaemia	12 (4.0)	1 (0.7)
Ear and labyrinth disorders	**9 (3.0)**	**11 (7.4)**
Deafness	0 (0.0)	3 (2.0)

*Adverse events during treatment were captured beginning on or after the first dose of study drug up to 7 days after the last dose. Adverse events were coded using MedDRA dictionary 18.0. For system organ classes with aggregate number of events ≥5%, but with no individual adverse event ≥5%, the most common adverse event is reported. Patients are only counted once for each system organ class and preferred term regardless of how many events they experienced.

Table S7. Adverse events CTCAE grade ≥3 by system organ class and preferred term reported during study treatment in ≥1% in any treatment group through Week 15 post-transplantation*

System Organ Class Preferred Term	Brincidofovir (N=303) n (%)	Placebo (N=149) n (%)
Any grade ≥3 adverse event	**203 (67.0)**	**56 (37.6)**
Immune system disorders	**89 (29.4)**	**10 (6.7)**
Acute graft-versus-host disease	89 (29.4)	9 (6.0)
Investigations	**62 (20.5)**	**9 (6.0)**
Alanine aminotransferase increased	15 (5.0)	2 (1.3)
Aspartate aminotransferase increased	6 (2.0)	1 (0.7)
Blood creatinine increased	24 (7.9)	12 (8.1)
Weight decreased	24 (7.9)	2 (1.3)
Platelet Count Decreased	6 (2.0)	1 (0.7)
Polyomavirus Test Positive	4 (1.3)	2 (1.3)
Liver Function Test Abnormal	5 (1.7)	0 (0.0)
Neutrophil Count Decreased	4 (1.3)	1 (0.7)
Weight Decreased	5 (1.7)	0 (0.0)
Gamma-Glutamyltransferase Increased	3 (1.0)	1 (0.7)
Hepatic Enzyme Increased	3 (1.0)	0 (0.0)
Lymphocyte Count Decreased	3 (1.0)	0 (0.0)
Metabolism and nutrition disorders	**50 (16.5)**	**9 (6.0)**
Decreased appetite	18 (5.9)	1 (0.7)
Hyperglycaemia	10 (3.3)	1 (0.7)
Hypokalaemia	8 (2.6)	4 (2.7)
Hypoalbuminaemia	9 (3.0)	1 (0.7)
Hypophosphataemia	7 (2.3)	2 (1.3)
Hyponatraemia	5 (1.7)	1 (0.7)
Hypomagnesaemia	3 (1.0)	1 (0.7)
Malnutrition	3 (1.0)	1 (0.7)
Dehydration	3 (1.0)	0 (0.0)

Gastrointestinal disorders	**51 (16.8)**	**5 (3.4)**
Diarrhoea	30 (9.9)	2 (1.3)
Abdominal pain	6 (2.0)	0 (0.0)
Nausea	6 (2.0)	0 (0.0)
Lower gastrointestinal haemorrhage	2 (0.7)	2 (1.3)
Infections and infestations	**41 (13.5)**	**15 (10.1)**
Clostridium difficile colitis	7 (2.3)	0 (0.0)
Pneumonia	4 (1.3)	2 (1.3)
BK virus infection	2 (0.7)	3 (2.0)
Urinary Tract Infection Enterococcal	3 (1.0)	0 (0.0)
Viral Haemorrhagic Cystitis	1 (0.3)	2 (1.3)
Blood and lymphatic system disorders	**36 (11.9)**	**12 (8.1)**
Anaemia	12 (4.0)	5 (3.4)
Febrile neutropenia	9 (3.0)	3 (2.0)
Thrombocytopenia	11 (3.6)	1 (0.7)
Neutropenia	7 (2.3)	4 (2.7)
General Disorders and administration site conditions	**25 (8.3)**	**9 (6.0)**
Mucosal Inflammation	10 (3.3)	3 (2.0)
Fatigue	5 (1.7)	2 (1.3)
Multi-Organ Failure	4 (1.3)	1 (0.7)
Asthenia	4 (1.3)	0 (0.0)
Pyrexia	1 (0.3)	2 (1.3)
Respiratory, thoracic and mediastinal disorders	**19 (6.3)**	**7 (4.7)**
Hypoxia	6 (2.0)	2 (1.3)
Pulmonary Embolism	3 (1.0)	1 (0.7)
Respiratory Failure	2 (0.7)	2 (1.3)
Hypoxia	6 (2.0)	2 (1.3)
Neoplasms benign, malignant and unspecified	**14 (4.6)**	**8 (5.4)**

Acute myeloid leukaemia, recurrent	6 (2.0)	3 (2.0)
Renal and urinary disorders	**15 (5.0)**	**5 (3.4)**
Acute kidney injury	10 (3.3)	4 (2.7)
Vascular disorders	**15 (5.0)**	**3 (2.0)**
Hypotension	6 (2.0)	1 (0.7)
Hypertension	2 (0.7)	2 (1.3)
Cardiac disorders	**14 (4.6)**	**3 (2.0)**
Atrial Fibrillation	4 (1.3)	2 (1.3)
Cardiac Failure Congestive	5 (1.7)	0 (0.0)
Pulseless Electrical Activity	3 (1.0)	0 (0.0)
Supraventricular Tachycardia	3 (1.0)	0 (0.0)
Nervous system disorders	**11 (3.6)**	**5 (3.4)**
Headache	2 (0.7)	2 (1.3)
Syncope	3 (1.0)	1 (0.7)
Musculoskeletal and connective tissue disorders	**13 (4.3)**	**2 (1.3)**
Pain in extremity	4 (1.3)	1 (0.7)
Injury, poisoning and procedural complications	**8 (2.6)**	**4 (2.7)**
Fall	3 (1.0)	1 (0.7)
Transplant Failure	2 (0.7)	2 (1.3)
Hepatobiliary disorders	**9 (3.0)**	**1 (0.7)**
Hyperbilirubinaemia	3 (1.0)	0 (0.0)
Psychiatric disorders	**6 (2.0)**	**2 (1.3)**
Insomnia	4 (1.3)	0 (0.0)
Ear and labyrinth disorders	**0 (0.0)**	**2 (1.3)**
Deafness	0 (0.0)	2 (1.3)

Table S8. Serious adverse events by system organ class and preferred term reported during study treatment in >1 patient in any treatment group through Week 15 post-transplantation*

System Organ Class Preferred Term	Brincidofovir (N=303) n (%)	Placebo (N=149) n (%)
Any Serious Adverse Event	**173 (57.1)**	**56 (37.6)**
Immune system disorders	**99 (32.7)**	**9 (6.0)**
Acute graft-versus-host disease	98 (32.3)	9 (6.0)
Infections and infestations	**41 (13.5)**	**18 (12.1)**
Clostridium difficile colitis	11 (3.7)	0 (0.0)
Pneumonia	5 (1.7)	4 (2.7)
Cellulitis	3 (1.0)	1 (0.7)
BK virus infection	2 (0.7)	1 (0.7)
Coronavirus Infection	2 (0.7)	0 (0.0)
Septic shock	2 (0.7)	0 (0.0)
Staphylococcal infection	0 (0.0)	2 (1.3)
Toxoplasmosis	2 (0.7)	0 (0.0)
Gastrointestinal disorders	**35 (11.6)**	**7 (4.7)**
Diarrhoea	21 (6.9)	4 (2.7)
Nausea	5 (1.7)	1 (0.7)
Abdominal pain	5 (1.7)	0 (0.0)
Vomiting	3 (1.0)	1 (0.7)
Enteritis	2 (0.7)	0 (0.0)
General disorders and administration site conditions	**15 (5.0)**	**11 (7.4)**
Pyrexia	9 (3.0)	8 (5.4)
Multi-organ failure	4 (1.3)	1 (0.7)
Investigations	**17 (5.6)**	**8 (5.4)**
Alanine aminotransferase increased	6 (2.0)	1 (0.7)
Aspartate aminotransferase increased	4 (1.3)	1 (0.7)

Klebsiella test positive	2 (0.7)	1 (0.7)
Polyomavirus test positive	2 (0.7)	1 (0.7)
Bacterial test positive	0 (0.0)	2 (1.3)
Respiratory, thoracic and mediastinal disorders	**12 (4.0)**	**5 (3.4)**
Hypoxia	3 (1.0)	1 (0.7)
Pulmonary embolism	2 (0.7)	1 (0.7)
Neoplasms benign, malignant and unspecified	**11 (3.6)**	**5 (3.4)**
Acute myeloid leukaemia, recurrent	6 (2.0)	3 (2.0)
Metabolism and nutrition disorders	**13 (4.3)**	**2 (1.3)**
Decreased appetite	5 (1.7)	0 (0.0)
Dehydration	3 (1.0)	0 (0.0)
Renal and urinary disorders	**11 (3.6)**	**4 (2.7)**
Acute kidney injury	9 (3.0)	4 (2.7)
Vascular disorders	**12 (4.0)**	**3 (2.0)**
Hypotension	3 (1.0)	1 (0.7)
Deep vein thrombosis	3 (1.0)	0 (0.0)
Jugular vein thrombosis	2 (0.7)	0 (0.0)
Blood and lymphatic system disorders	**9 (3.0)**	**5 (3.4)**
Febrile neutropenia	6 (2.0)	1 (0.7)
Cardiac disorders	**11 (3.6)**	**3 (2.0)**
Cardiac failure, congestive	4 (1.3)	0 (0.0)
Supraventricular tachycardia	3 (1.0)	0 (0.0)
Injury, poisoning and procedural complications	**9 (3.0)**	**5 (3.4)**
Fall	4 (1.3)	1 (0.7)
Transplant failure	2 (0.7)	2 (1.3)

Nervous system disorders	**9 (3.0)**	**4 (2.7)**
Headache	3 (1.0)	0 (0.0)
Syncope	2 (0.7)	1 (0.7)
Musculoskeletal and connective tissue disorders	**7 (2.3)**	**3 (2.0)**
Back pain	2 (0.7)	1 (0.7)
Myopathy	2 (0.7)	0 (0.0)
Psychiatric disorders	**4 (1.3)**	**1 (0.7)**
Mental status changes	4 (1.3)	0 (0.0)
Hepatobiliary disorders	**4 (1.3)**	**0 (0.0)**
Venoocclusive liver disease	2 (0.7)	0 (0.0)

Table S9. Summary of acute graft-versus-host disease (GVHD) events as adjudicated by the blinded GAC, intention-to-treat population

	Brincidofovir (N = 303) n (%)	Placebo (N = 149) n (%)
GVHD likelihood adjudicated as:		
Likely	141 (46.5)	33 (22.1)
Presumptive	60 (19.8)	36 (24.2)
Unlikely	12 (4.0)	6 (4.0)
Not reviewed*	90 (29.7)	74 (49.7)
GVHD severity adjudicated as:		
Grade I	25 (8.3)	25 (16.8)
Grade II	89 (29.4)	33 (22.1)
Grade III	78 (25.7)	8 (5.4)
Grade IV	12 (4.0)	5 (3.4)

*Includes patients for whom adjudicators determined the maximum grade/stage to be prior to the first dose of study drug.

Table S10. Maximum organ stage of acute GVHD events as adjudicated by the blinded GAC, intention-to-treat population

	BCV (N = 303)			Placebo (N = 149)		
	Skin n (%)	Liver n (%)	Gut n (%)	Skin n (%)	Liver n (%)	Gut n (%)
Stage 1	49 (16.2)	9 (3.0)	88 (29.0)	24 (16.1)	1 (0.7)	28 (18.8)
Stage 2	42 (13.9)	14 (4.6)	40 (13.2)	18 (12.1)	0	7 (4.7)
Stage 3	22 (7.3)	7 (2.3)	33 (10.9)	8 (5.4)	3 (2.0)	2 (1.3)
Stage 4	0	6 (2.0)	13 (4.3)	3 (2.0)	3 (2.0)	3 (2.0)

IV. Figures

Figure S1. SUPPRESS Trial (CMX001-301) study schema

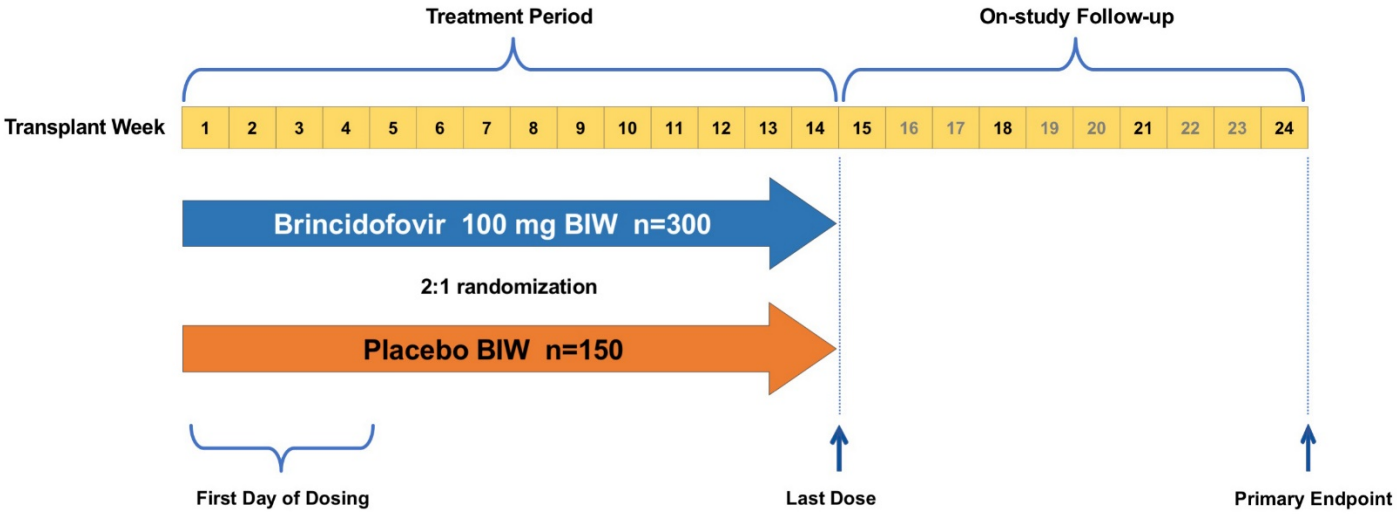


Figure S2. Flow chart to guide initiation of preemptive therapy for CMV

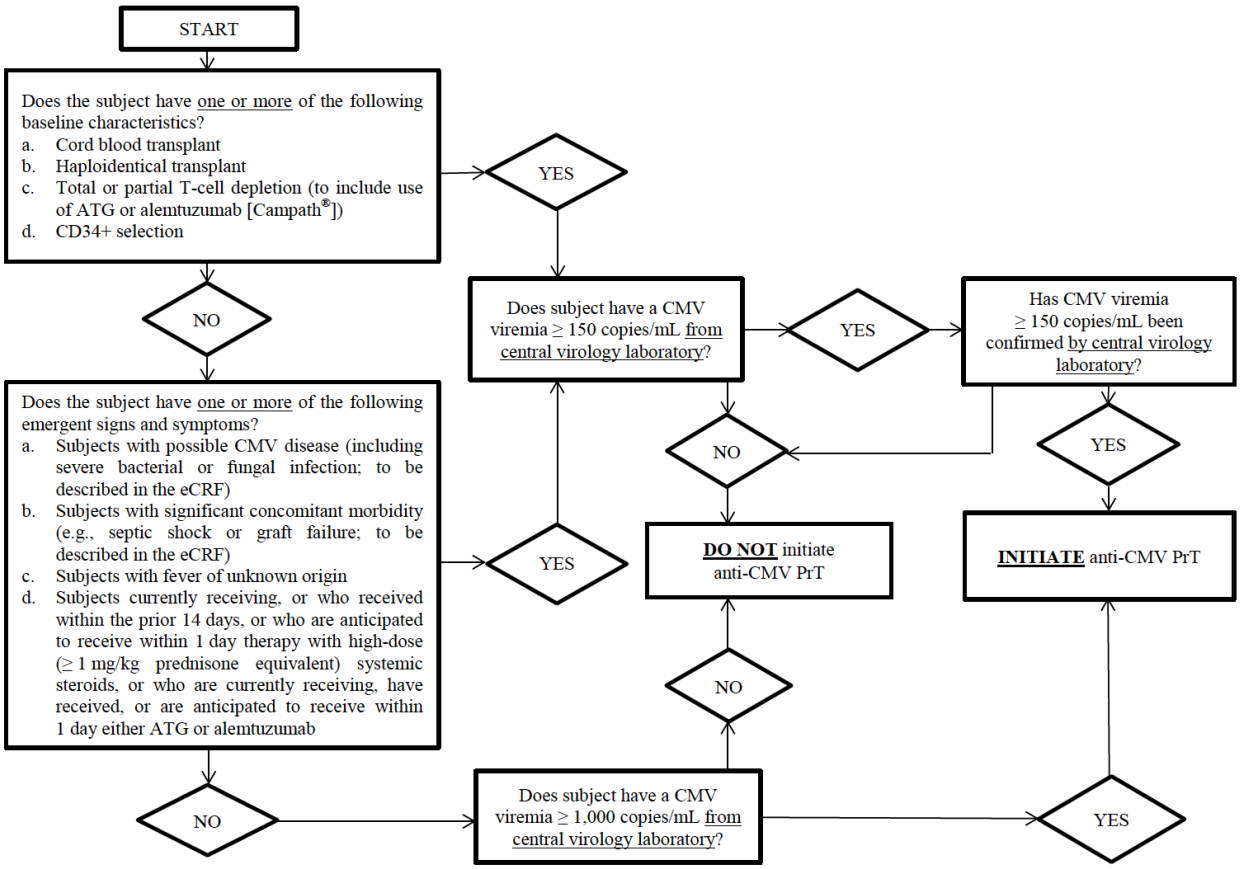
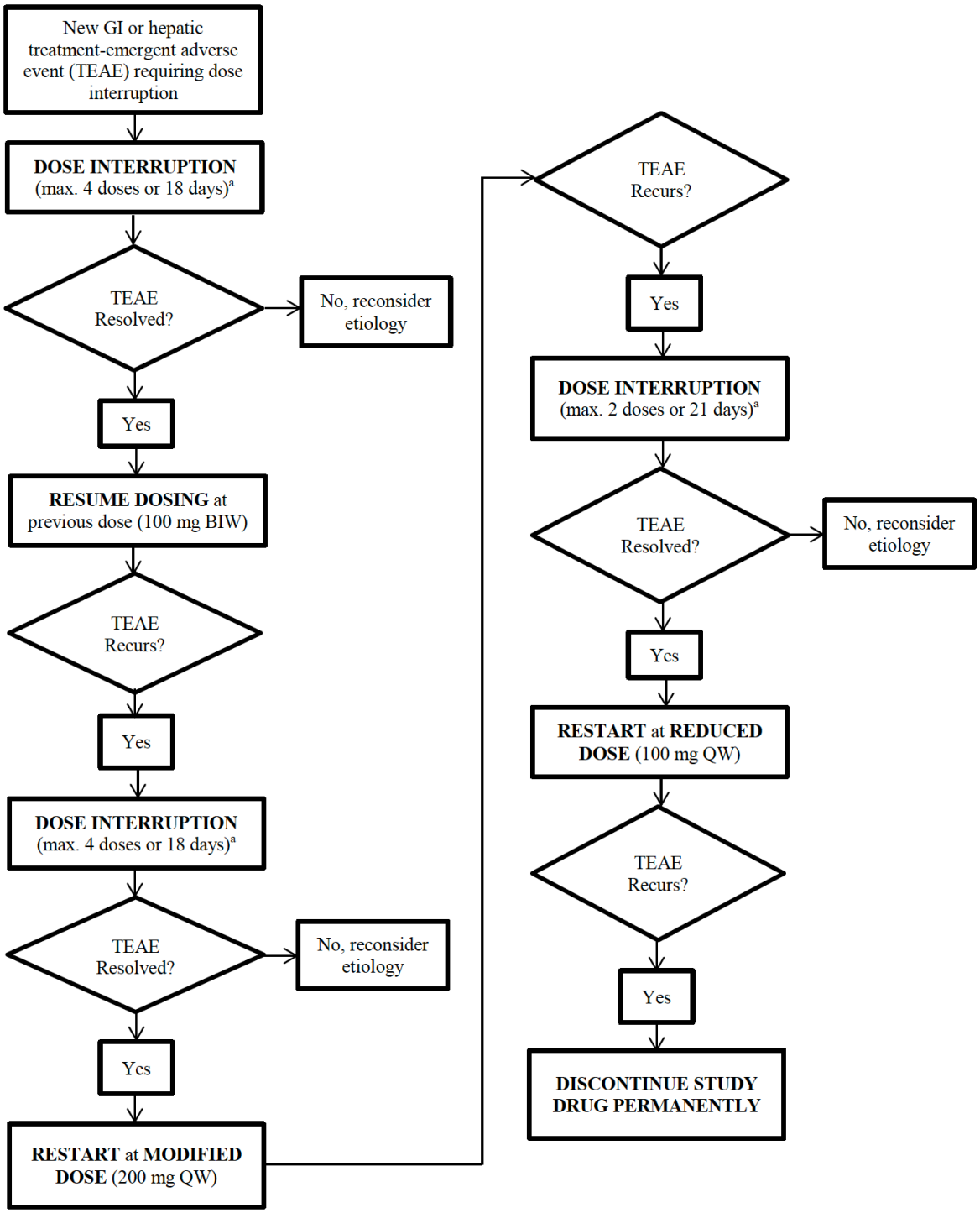
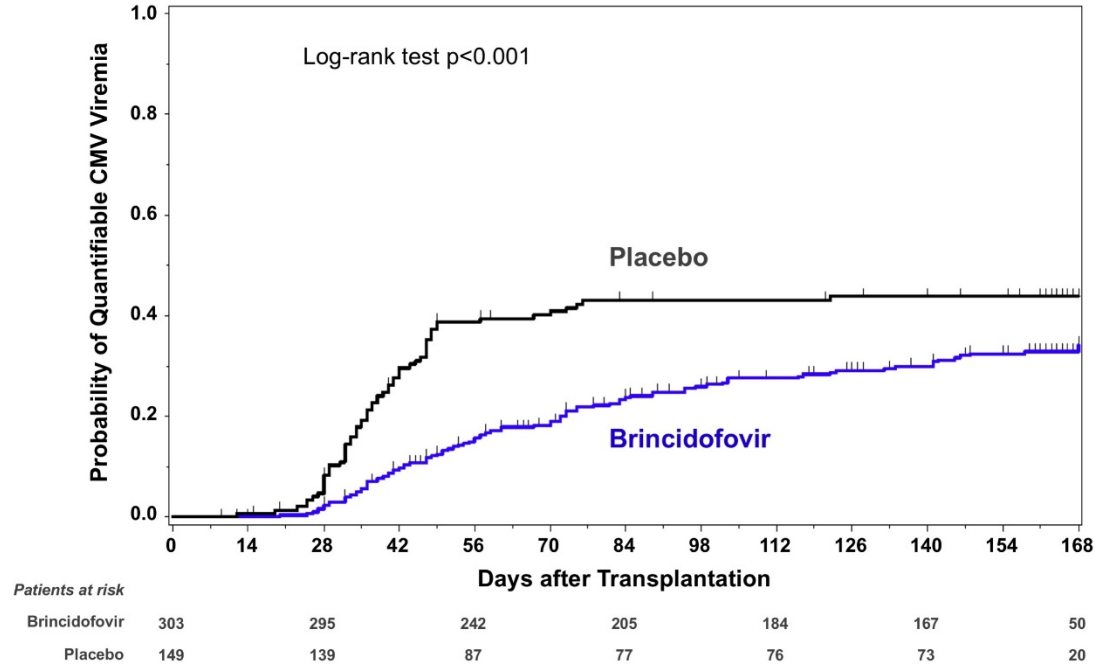


Figure S3. Flow chart for the management of treatment-emergent gastrointestinal and hepatic toxicities that require study drug interruption



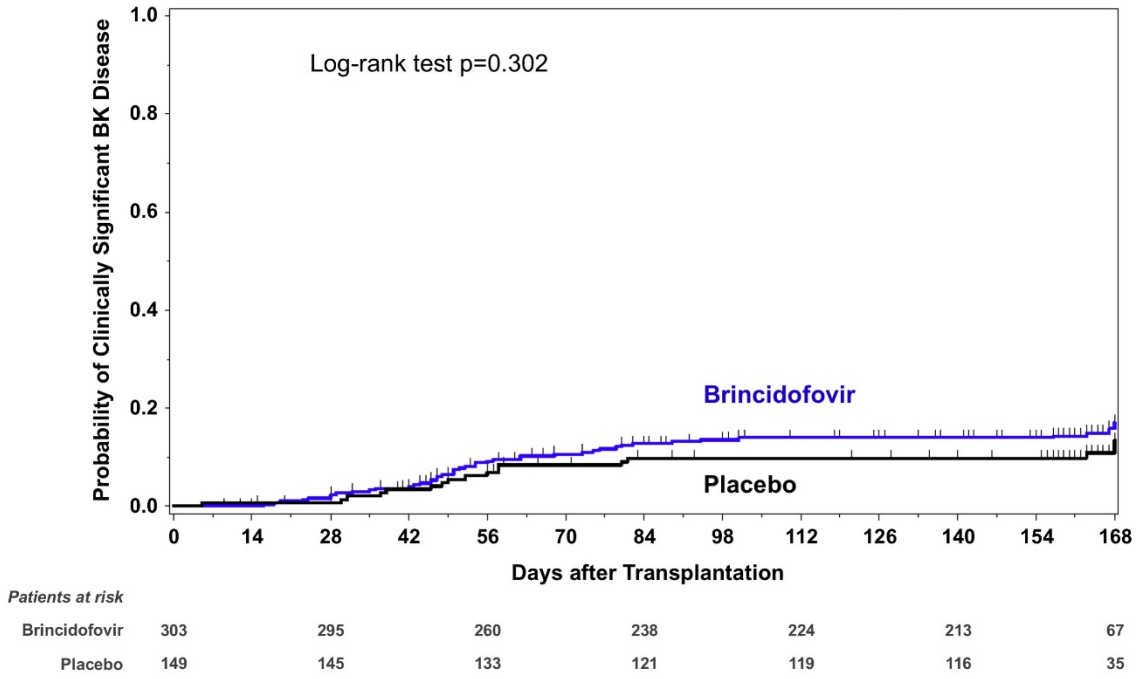
[a] Any subject who misses a cumulative total of 4 weeks of study drug (i.e., 8 doses of a BIW regimen or 4 doses of a QW regimen following dose modification/reduction) should be discontinued from study treatment.

Figure S4. Time to first quantifiable CMV viremia (≥151 DNA copies/mL [≥137 IU/mL) since transplant, intention-to-treat population



Subjects without CMV viremia ≥151 copies/mL are censored at the end of study date or 24 weeks (+2 week window), whichever is earlier.

Figure S5. Time to adjudicated BK polyomavirus disease, intention to treat population.

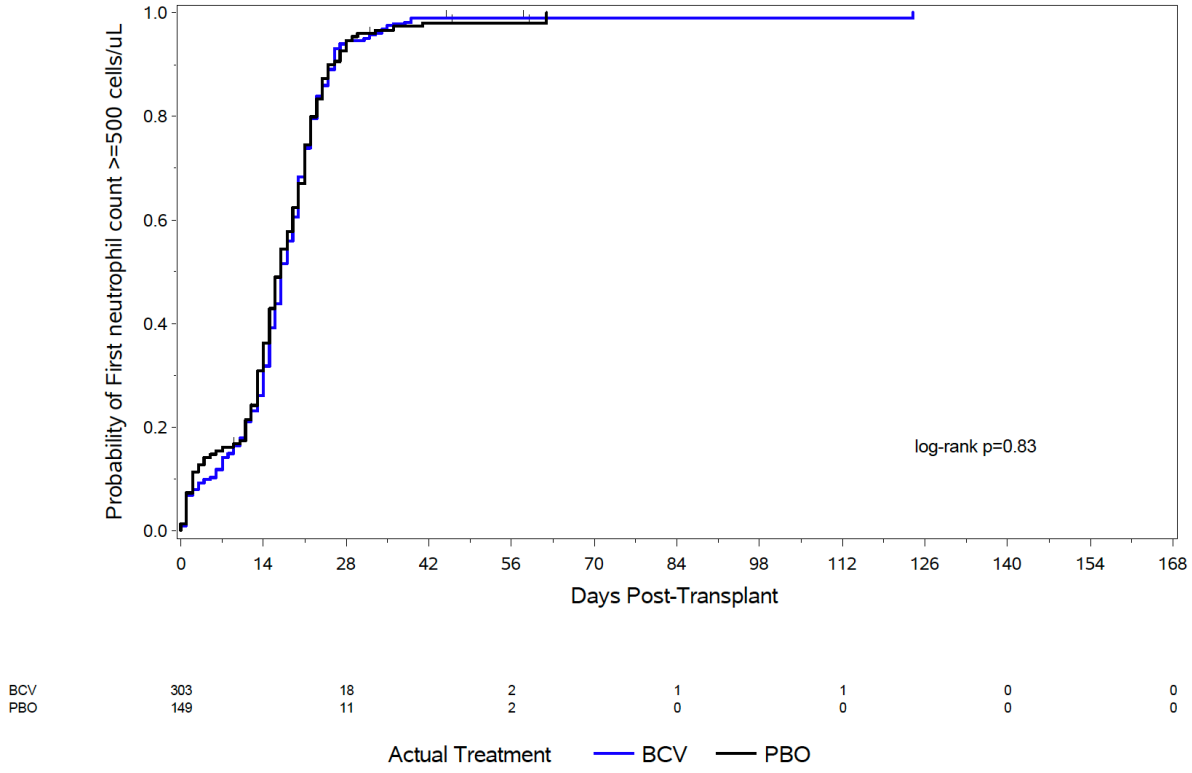


Patients at risk

Brincidofovir	303	295	260	238	224	213	67
Placebo	149	145	133	121	119	116	35

Subjects who do not develop BK polyomavirus disease are censored at the end of study date or 24 weeks (+2 week window), whichever is earlier.

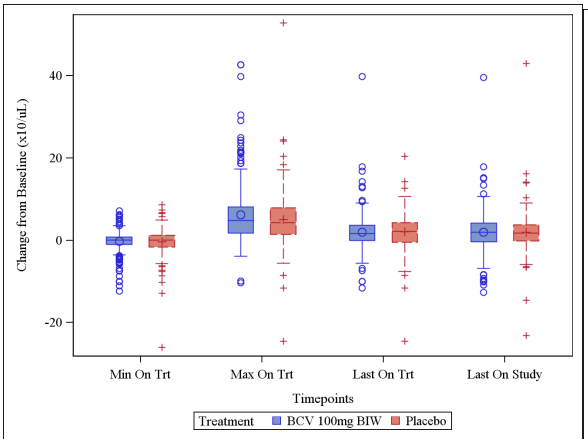
Figure S6. Time to engraftment (first absolute neutrophil count ≥500 cells/μL) by study treatment group.



BCV, brincidofovir; PBO, placebo

Figure S7. Boxplots of change from baseline for (A) white blood cell count, (B) absolute lymphocyte Count, (C) absolute neutrophil count, (D) platelet count, (E) hemoglobin, (F) alanine aminotransferase, (G) aspartate aminotransferase, (H) bilirubin, (I) creatinine, and (J) eGFR-CKD EPI

A



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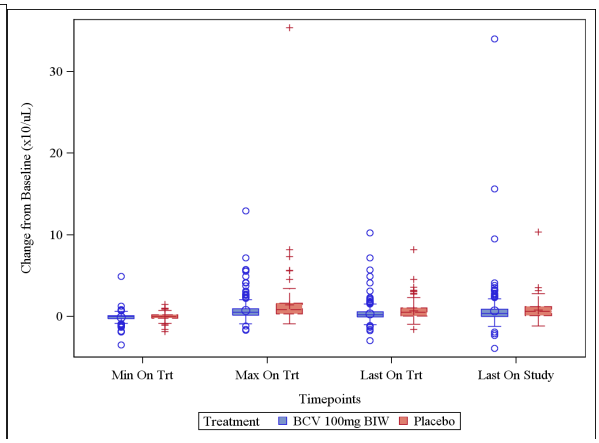

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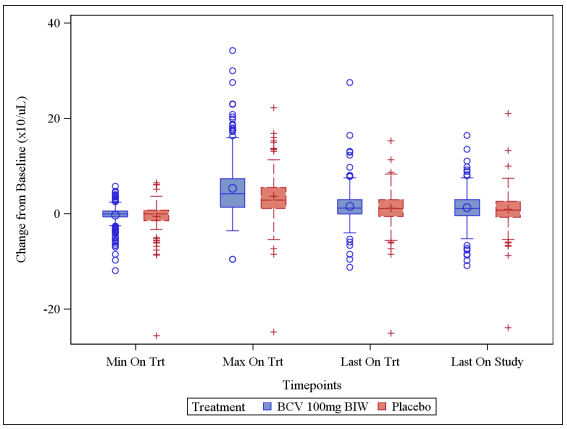

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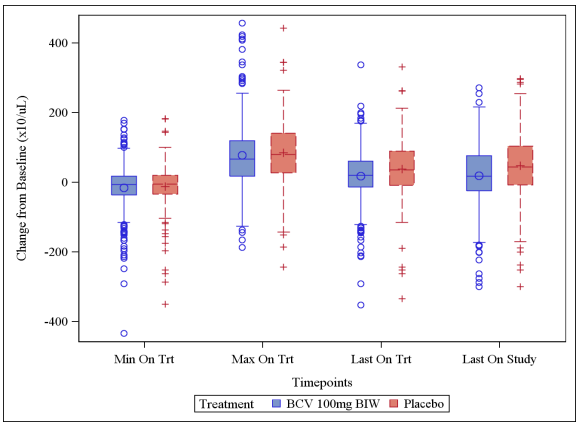

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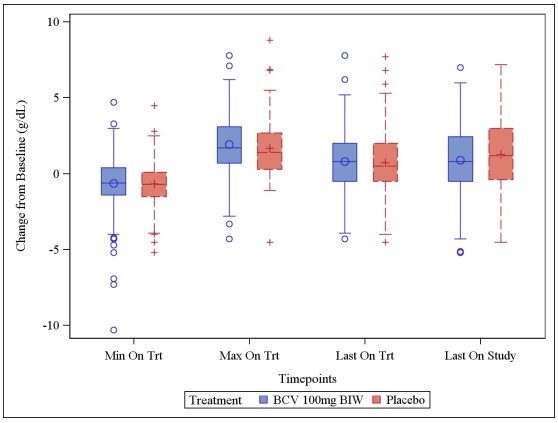

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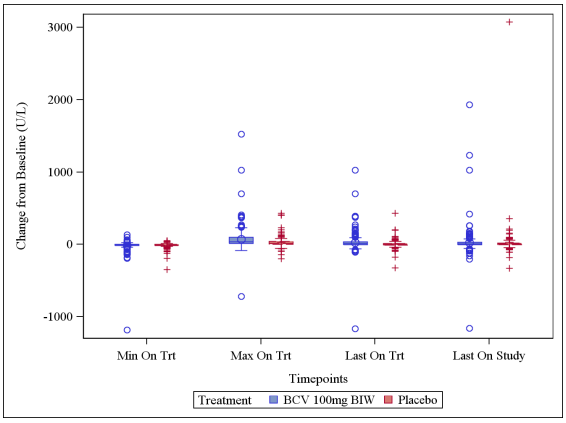

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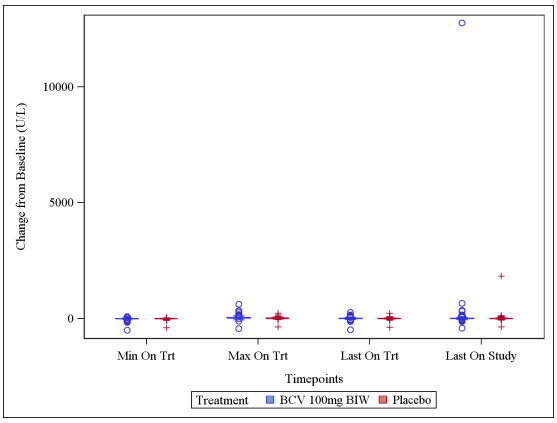

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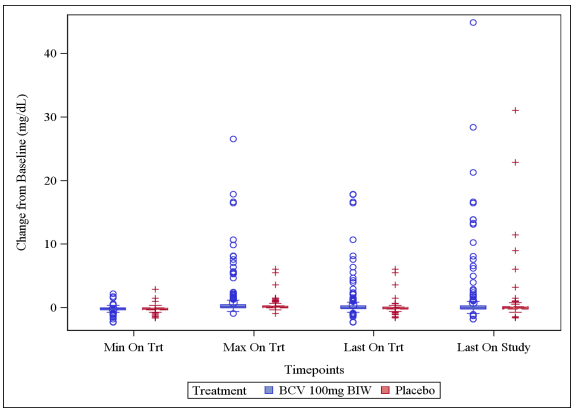

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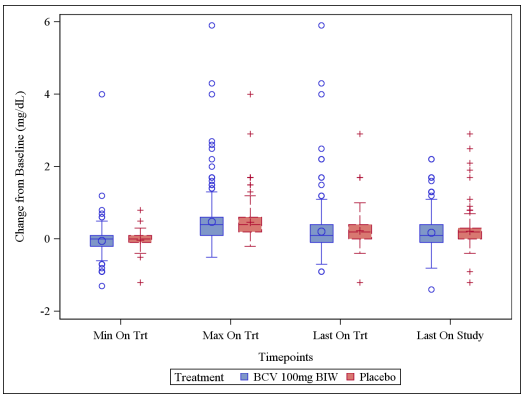
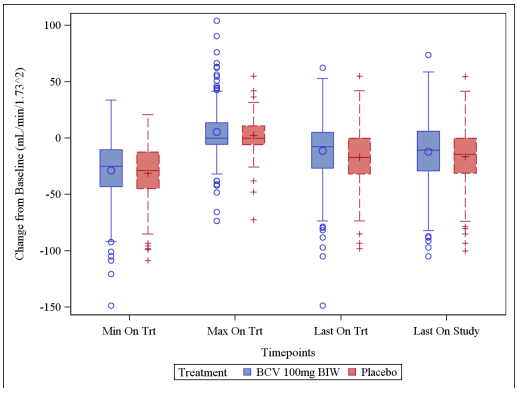
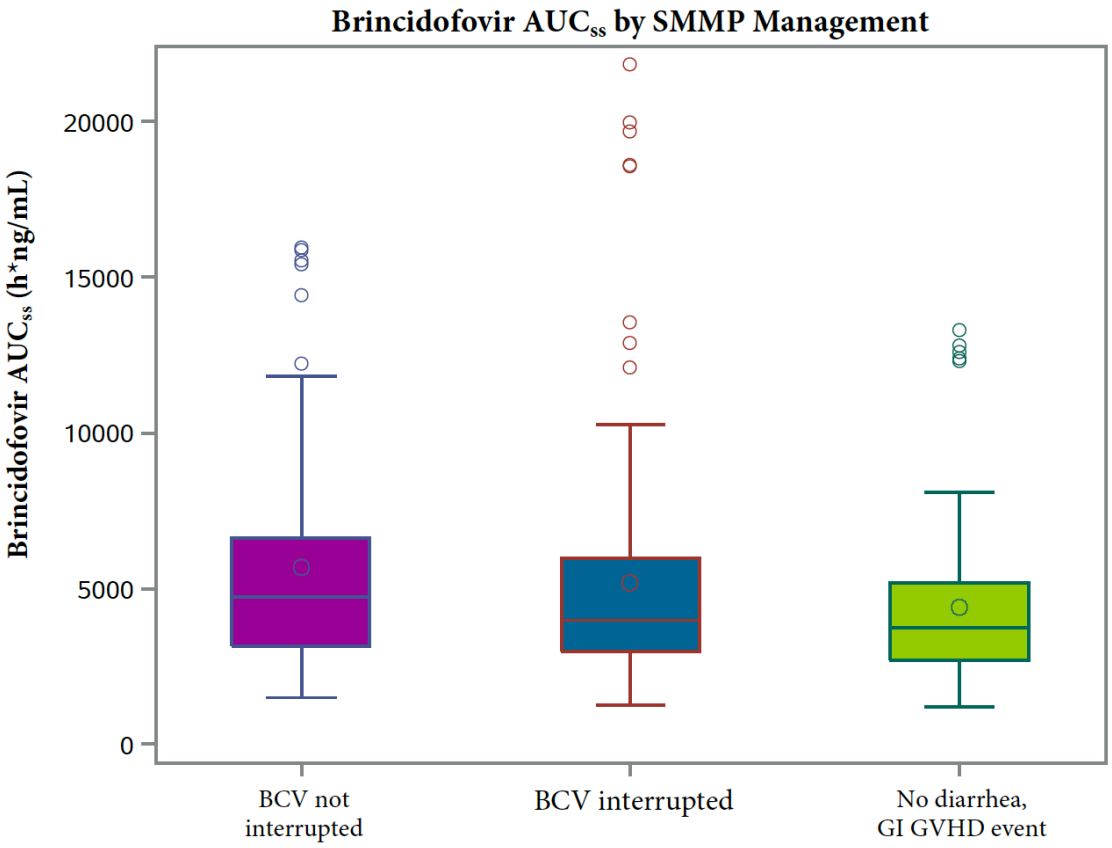


J



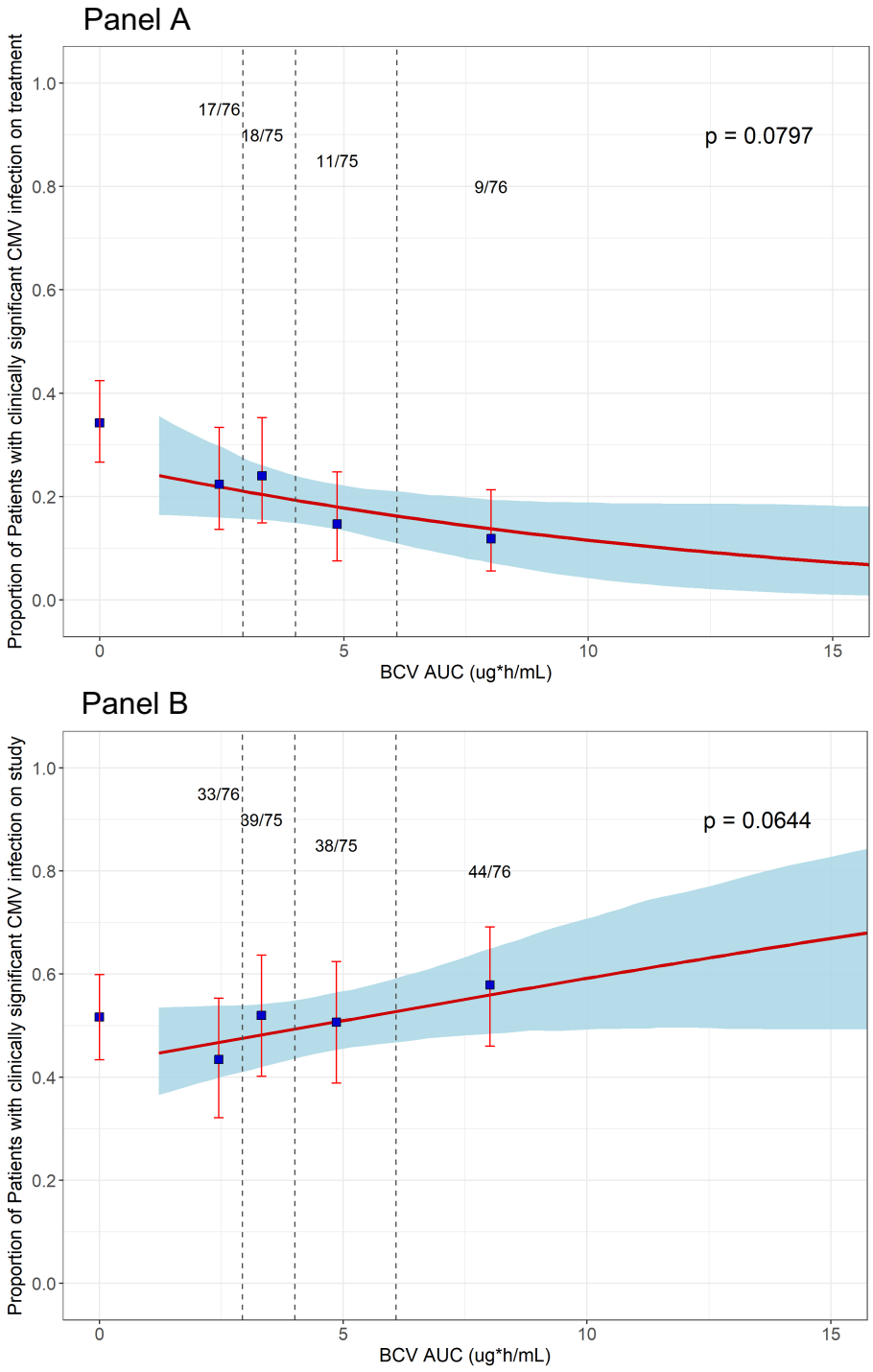
Box plots showing maximum on-treatment, minimum on-treatment, last-on treatment and last on-study for (A) white blood cell count (x10^6/µL), (B) absolute lymphocyte count (x10^3/µL), (C) absolute neutrophil count (x10^3/µL), (D) platelet count (x10^3/µL), and (E) hemoglobin (g/dL), (F) ALT (U/L), (G) AST (U/L), (H) total bilirubin (mg/dL), (I) creatinine (mg/dL), and (J) eGFR-CKD EPI (mL/min/1.73 m^2). BCV, brincidofovir; PBO, placebo

Figure S8. Brincidofovir (BCV) AUC_{ss} according to adherence to the Safety Monitoring and Management Plan (SMMP) for gastrointestinal events



Includes all BCV subjects with no GI aGvHD and no Grade 2 or higher diarrhea at Baseline
Subjects with GI aGvHD or Grade 2 or higher diarrhea during treatment are counted as having an event 10 such subjects with unknown management are included in the No Event group

Figure S9. Probability of clinically-significant CMV infection according to brincidofovir (BCV) AUC_{ss} exposure during (A) study treatment, and (B) by the end of study, HCT Week 24.



Box plots represent quartiles of brincidofovir exposure, leftmost box plot represents placebo patients (brincidofovir exposure = 0). Fractions above each brincidofovir exposure quartile box plot present the number of clinically-significant CMV events.

1. TITLE PAGE

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study of the Safety, Tolerability, and Efficacy of CMX001 for the Prevention of Cytomegalovirus (CMV) Infection in CMV-seropositive (R+) Hematopoietic Stem Cell Transplant Recipients

PROTOCOL No. CMX001-301

Protocol Version/Date: Amendment 1 (final): 02 September 2014

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SPONSOR'S SIGNATURE PAGE

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study of the Safety, Tolerability, and Efficacy of CMX001 for the Prevention of Cytomegalovirus (CMV) Infection in CMV-seropositive (R+) Hematopoietic Stem Cell Transplant Recipients

PROTOCOL No. CMX001-301

Protocol Version/Date: Amendment 1 (final), dated 02 September 2014

This protocol has been approved by Chimerix, Inc. The following signature documents this approval.

_____

Printed Name of Chimerix Medical Officer

_____

Signature of Chimerix Medical Officer

_____

Date

INVESTIGATOR'S AGREEMENT

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study of the Safety, Tolerability, and Efficacy of CMX001 for the Prevention of Cytomegalovirus (CMV) Infection in CMV-seropositive (R+) Hematopoietic Stem Cell Transplant Recipients

PROTOCOL No. CMX001-301

Protocol Version/Date: Amendment 1 (final), dated 02 September 2014

I have received and carefully read the Investigator's Brochure for CMX001. I have carefully read this study protocol and the Safety Monitoring and Management Plan (SMMP) for CMX001, and agree to conduct the CMX001-301 study in accordance with this study protocol, International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines, and all applicable local laws and regulations pertaining to the conduct of clinical trials.

I will ensure that all subinvestigators and all other staff members involved with the conduct of the study read and understand all aspects of this study protocol.

I have received and read all study-related information provided to me.

I agree to maintain the confidentiality of all information received or developed in connection with this study protocol.

All rights of publication of the results reside with Chimerix, Inc. unless made in a separate agreement.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTACTS IN CASE OF EMERGENCY

Relevant medical/emergency contacts are provided in the following table. Any updates to the contact information will be provided in the study reference manual (SRM).

Table 1: Emergency Contact Information

Chimerix Chief Medical Officer	M. Michelle Berrey, MD, MPH Chief Medical Officer Chimerix, Inc. 2505 Meridian Parkway, Suite 340 Durham, North Carolina 27713 USA Tel: +1 919-806-1074, ext. 155 Fax: +1 919-806-1146 Email: mberrey@chimerix.com
Chimerix Senior Medical Reviewer	Hervé Momméja-Marin, MD Vice President, Clinical Research Chimerix, Inc. 2505 Meridian Parkway, Suite 340 Durham, North Carolina 27713 USA Tel: +1 919-806-1074, ext. 128 Cell: +1 919-597-9381 Fax: +1 919-806-1146 Email: hmommeja-marin@chimerix.com
Chimerix Medical Monitor	Marion E. Morrison, MD Senior Medical Director Chimerix, Inc. 2505 Meridian Parkway, Suite 340 Durham, North Carolina 27713 USA Tel: +1 919-313-2977 Cell: +1 919-886-0830 Fax: +1 919-313-6797 Email: mmorrison@chimerix.com

Table 1: Emergency Contact Information (Continued)

Serious adverse events (SAEs) and other adverse events of special interest (AEOSIs) that are judged to be related to study drug must be reported within 24 hours of learning of the event to Theorem Global Safety Advantage[SM]. SAEs and AEOSIs that are judged to be not related to study drug may be reported up to the end of the next business day after learning of the event (where permitted by local regulations, otherwise unrelated SAEs and AEOSIs should also be reported within 24 hours of learning of the event). See also Section 12.5.3.	<u>For reporting in USA and Canada</u>: Theorem Clinical Research Global Safety Advantage 1016 West Ninth Avenue King of Prussia, PA 19406 USA SAE Phone: +1 877-324-8200 SAE Fax: +1 866-869-1551 SAE email: drugsafety@theoremclinical.com <u>For reporting in European Union</u>: Theorem Clinical Research Global Safety Advantage Methuen Park South Bath Road Chippenham, Wiltshire SN14 0GT United Kingdom SAE Phone: +44 7980 265917 SAE Fax: 00-800-6666-6660 SAE email: drugsafety@theoremclinical.com

2. SYNOPSIS

Name of Sponsor/Company: Chimerix, Inc.

Name of Investigational Product: CMX001; hexadecyloxypropyl-cidofovir

Name of Active Ingredient: Phosphonic acid, [[(S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]mono[3-(hexadecyloxy)propyl] ester

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study of the Safety, Tolerability, and Efficacy of CMX001 for the Prevention of Cytomegalovirus (CMV) Infection in CMV-seropositive (R+) Hematopoietic Stem Cell Transplant Recipients

Study Center(s): The study will be conducted at multiple study centers in the USA, Canada, and Europe. Additional countries may be added, as necessary.

Phase of Development: Three (3)

Objectives:

The primary objectives of this study are:

- To compare the efficacy of CMX001 to placebo for the prevention of clinically significant CMV infection in R+ allogeneic hematopoietic stem cell transplant (HSCT) recipients
- To compare the safety and tolerability of CMX001 to placebo for the prevention of clinically significant CMV infection in R+ allogeneic HSCT recipients

The secondary objectives of this study are:

- To describe the effect of CMX001 versus placebo on all-cause mortality, non-relapse mortality, mortality attributed to CMV, and graft failure
- To evaluate the virologic response for subjects treated with CMX001 who are CMV viremic on the first dose day (FDD) and the emergence of resistance for subjects treated with CMX001 compared to placebo
- To characterize the effect of CMX001 in preventing clinical manifestations associated with non-CMV double-stranded deoxyribonucleic acid (dsDNA) viruses, including: manifestations associated with BK virus (BKV) infections (e.g., bladder and kidney infections, and renal insufficiency); manifestations associated with human herpes virus type 6 (HHV-6) infections (e.g., encephalitis, graft failure, and neurocognitive impairment), and manifestations associated with infections with herpes simplex virus type 1 or 2 (HSV-1/2), varicella-zoster virus (VZV), adenoviruses (AdV), and Epstein-Barr virus (EBV), separately and in aggregate
- To describe plasma concentrations of CMX001 and cidofovir (CDV) in R+ allogeneic HSCT recipients
- To compare health economic (HE) and health-related quality-of-life (HRQL) outcome parameters between CMX001- and placebo-treated subjects
- To compare reconstitution of the anti-CMV immunological response between CMX001- and placebo-treated subjects and the impact of anti-CMV preemptive therapy (PrT) on the observed responses

Methodology:

This is a randomized, double-blind, placebo-controlled, parallel group, multicenter study of CMX001 in CMV-seropositive subjects who have undergone allogeneic HSCT. The study will comprise a screening evaluation, a treatment phase of 10 to 14 weeks' duration (through Week 14), followed by a 10-week posttreatment phase (to Week 24), which are described as follows:

Screening: Potential subjects may be consented for participation in the study before or after transplant. Subjects providing written informed consent will be screened following transplant as soon as the subject can ingest tablets. As part of the screening procedures, CMV viremia (i.e., the measurement of CMV deoxyribonucleic acid [DNA] in plasma by polymerase chain reaction [PCR] assay) must be assessed by the designated central virology laboratory within 5 days prior to randomization and only those subjects who are determined to be CMV viremia negative at screening (i.e., CMV DNA in plasma is "Not Detected" for the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test used by the central virology laboratory) will be eligible for randomization. In addition, the results of any CMV viremia testing (including CMV PCR, pp65 antigenemia, etc.) performed as part of local standard of care (SoC) since the qualifying transplant must also be negative. Subjects who were CMV viremia negative at screening, but who are subsequently found to have been CMV viremic at baseline (i.e., at the predose assessment on the first dose day [FDD]) will be continued in the study.

Randomization: Subjects who meet all applicable eligibility criteria will be randomized to one of the following two treatment arms in a 2:1 ratio using an automated integrated voice/web response system (IV/WRS):

- Treatment 1: 100 mg CMX001 twice weekly (BIW)
- Treatment 2: placebo BIW

Both treatments will be administered under double-blind conditions (i.e., neither the subject nor the investigator and clinic staff will be aware of the individual subject treatment assignment). During randomization, subjects will be stratified within an investigative center, based on their likelihood for progression to clinically significant CMV infection, defined as a "lower likelihood" versus a "higher likelihood" of progression. Subjects who receive a matched, related, non-T-cell depleted graft (e.g., excluding cord blood), who do not have acute graft versus host disease (aGVHD), who have not received anti-thymocyte globulin (ATG) or alemtuzumab, and who are not receiving high-dose (≥ 1 mg/kg prednisone equivalent) systemic steroids will be stratified in the "lower likelihood" group. All other subjects will be stratified in the "higher likelihood" group. Following randomization, subjects must begin study drug (CMX001 or placebo) within 1 business day.

Treatment Phase (FDD to Week 14): Dosing for all subjects will be initiated after transplant as soon as subjects can ingest tablets, but no later than Day 28 posttransplant, and will continue through Week 14. The first dose of blinded study drug (CMX001 or placebo) will be administered after completion of all predose (baseline) clinic and laboratory assessments on the FDD, with subsequent doses administered at alternating 3- and 4-day intervals through Week 14. Following randomization, all subjects will undergo weekly assessments through Week 14, before transitioning to the posttreatment phase. Thus, the planned duration of the treatment phase will vary for individual subjects from a minimum of 10 weeks, up to a maximum of 14 weeks, depending on when treatment is initiated relative to the date of transplant. Subjects who initiate treatment during the first week after transplant will complete the longest period of treatment at 14 weeks, while subjects who initiate treatment in the fourth week after transplant will complete the shortest period of treatment at 10 weeks.

Posttreatment Phase (Week 15 to Week 24): All randomized subjects will follow the same schedule of assessments through Week 24. Subjects will undergo a first assessment during Week 15, with additional assessments at Weeks 18, 21, and 24.

During the posttreatment phase (Week 15 to Week 24), any supplemental CMV viremia assessments (i.e., in addition to the scheduled assessments by the central virology laboratory at Weeks 15, 18, 21, and 24) may be guided by local SoC, but should be conducted at the central virology laboratory. If this is not medically feasible, any positive CMV PCR result performed at the local virology laboratory should have a confirmatory PCR test performed in parallel at the central virology laboratory.

Early Study Drug Discontinuation: If study drug is discontinued for safety, tolerability, or due to efficacy failure, subjects must remain on the schedule of assessments and complete all protocol-scheduled assessments at each visit through Week 24 except those related to study drug dosing, study drug accountability, or the collection of blood samples for PK analysis.

It is expected that all subjects should complete all study assessments, up to and including Week 15, at their designated study center. For those subjects who are unable to return to the transplant center after being discharged from the clinic, site personnel should make other arrangements for subjects to complete all assessments through Week 24. For subjects who do not return to their transplant centers during the posttreatment phase the following assessments must be completed at a minimum:

- CMV viremia as assessed by the central virology laboratory;
- urine and plasma for storage at the central virology laboratory, and
- safety laboratory assessments as performed by the designated central safety laboratory.

Additionally, a telephone contact (supported by copies of local medical records) between study personnel and the local physician will be performed to assess:

- emergence of CMV infection or disease requiring anti-CMV PrT,
- cause of death, where applicable; and
- the follow-up of any ongoing adverse events (AEs), including serious adverse events (SAEs), and the reporting of new (S)AEs.

Number of Subjects (Planned):

Approximately 450 eligible subjects will be randomized between the two treatment arms in a ratio of 2:1 to CMX001 or placebo, i.e., approximately 300 subjects will be randomized to Treatment 1 (CMX001) and approximately 150 subjects will be randomized to Treatment 2 (placebo).

Diagnosis and Main Criteria for Inclusion:

Subjects must be able to understand and provide written informed consent and be willing to participate in all required study activities for the entire duration of the study (i.e., through Week 24).

Subjects will be adult allogeneic HSCT recipients aged ≥ 18 years-old (or as applicable, per local law) who were CMV seropositive before transplant (i.e., R+) and are CMV viremia negative after transplant.

Subjects will be eligible for treatment if they are ≤ 28 days posttransplant and they are able to ingest tablets. Subjects should initiate treatment after transplant as soon as ingesting tablets is possible.

Investigational Product, Dosage and Mode of Administration:

Subjects randomized to the CMX001 treatment arm will receive the following:

- Treatment 1: 100 mg CMX001, administered orally as one 100 mg tablet, BIW

All doses should be given with or within 30 minutes after finishing a low-fat meal. [Note: For the purposes of this study, a low-fat meal is any meal comprising no more than 20% of its total caloric value from fat.] The study drug doses should be administered at alternating 3- and 4-day intervals.

Reference Therapy, Dosage and Mode of Administration:

Subjects randomized to the placebo treatment arm will receive the following:

- Treatment 2: placebo, administered orally as one tablet, BIW

Each placebo dose will be administered under the same conditions described above for the investigational product.

Duration of Treatment/Study/Long-term Follow-up:

HSCT recipients who are CMV-seropositive pretransplant are considered at risk of CMV infection/reactivation posttransplant and are, therefore, managed under the care of their transplant team according to local SoC for approximately 100 days posttransplant, which is when patients usually return to the care of their local oncologist at many centers in the United States. Following screening, study drug administration will begin no later than Day 28 posttransplant, and will continue through Week 14, which approximates the end of the 100-day posttransplant period. Subjects completing the entire treatment phase of the study will receive 10 to 14 weeks of study drug.

All randomized subjects will be followed in this study until Week 24, regardless of whether the subject remains on study drug through Week 14. Thus, each subject's participation in the study will range from approximately 20 to 24 weeks, depending when treatment is initiated relative to the date of transplant.

Each subject enrolled into this study will be asked to additionally participate in the 'Chimerix Registry for Former CMX001 Study Participants' (Protocol No. CMX001-333) to assess the long-term impact of CMX001 administration on carcinogenicity, late CMV-associated events, and survival. While participation in the Registry is encouraged, a subject will not be required to participate in the Registry in order to participate in this study.

Criteria for Evaluation:

Efficacy:

Blood (plasma) and urine for virologic evaluations will be collected at screening, predose on the FDD and throughout the treatment and posttreatment phases of the study and sent to the designated central virology laboratory(ies) for analysis.

Blood (plasma) samples will be divided into aliquots for:

- "real-time" assay of CMV viremia in plasma using the US Food and Drug Administration (FDA)-approved and CE (Conformité Européene)-marked Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test;
- possible "real-time" testing for other dsDNA viruses (e.g., AdV, BKV, EBV, HHV-6, etc.) in the presence of suggestive clinical symptoms, and
- one or more storage samples for CMV and/or other dsDNA virus resistance testing (genotypic and/or phenotypic); additional CMV viremia assessments, based on newly available assays; for retrospective analyses for other non-CMV dsDNA viruses; and/or for testing for possible biomarkers of graft versus host disease (GVHD) or CMV-specific immunity.

Urine will be divided into one or more aliquots and stored for possible future analysis, including retrospective analyses of CMV and/or other dsDNA viruses, resistance testing, etc. In consultation with the Chimerix Medical Monitor (or designee), investigators may request real-time analysis of the urine samples for subjects with known or suspected BK viruria or subjects exhibiting signs/symptoms consistent with BKV or AdV infection, such as cystitis or renal impairment.

In addition, when a dsDNA viral syndrome or disease is suspected, other relevant biological samples (e.g., stool, cerebrospinal fluid, sputum, bronchoalveolar lavage, skin or nasopharyngeal swab, tissue biopsy etc., as appropriate) should be collected and sent to the central virology laboratory for "real-time" analysis and/or storage for possible future analysis.

Prior approval is required from the Chimerix Medical Monitor (or designee) for the analysis of any samples other than blood (plasma) for CMV viremia.

Stored samples will not be used for human genomic analyses or any other purposes other than virology/immunology testing for the viruses of interest (i.e., CMV and other dsDNA viruses), possible analysis of biomarkers of GVHD or CMV-specific immunity, and/or additional testing to measure concentrations of CMX001 and its metabolites.

A blood sample to evaluate the potential for reconstitution of the anti-CMV immune response using the T-SPOT.® *CMV* Test (Oxford Immunotec Limited, Abingdon, UK) will be collected at Weeks 5, 9, 14, and 24. These samples will be collected from individual study participants where the investigator believes the additional blood loss resulting from the collection of the samples is medically acceptable. For those individuals where the investigator feels that the additional blood loss is not medically acceptable, then some or all of these samples may be omitted, as necessary. A collection window of up to +2 weeks from the scheduled collection date is provided to allow for additional flexibility in the collection of these samples.

The emergence of antiviral-resistant CMV will be defined by virologic failure and/or retrospective genotypic and phenotypic analyses (with the definitions of virologic failure following the Virology Plan for Monitoring the Selection of Resistant Viruses in Clinical Studies of CMV with CMX001).

Slides from gastrointestinal (GI) or other biopsies obtained to diagnose CMV disease or other dsDNA viral syndrome or disease should be sent to the designated central laboratory. Specific guidance with respect to biopsy sampling and handling will be provided in the SRM and/or applicable central laboratory manual. Suspected CMV end-organ disease will be adjudicated by a blinded Endpoint Adjudicating Committee (EAC) according to the definitions/procedures described by Ljungman et al (Ljungman 2002).

If anti-CMV PrT is required, information on the use of ganciclovir (GCV), valganciclovir (vGCV), foscarnet (FOS), CDV and other anti-CMV therapies (including dose and duration) through Week 24 will be recorded.

Safety:

Safety will be assessed through physical examination findings, vital signs measurements, reported AEs, mortality, and clinical laboratory results (analyzed by the central safety laboratory) determined at periodic intervals throughout the treatment and posttreatment phases of the study.

Diarrhea and GVHD will be captured on the AE page in the electronic case report form (eCRF) and assessed in more detail on separate eCRF modules designed to capture individual events. For diarrhea, the frequency, estimated volume (where available from subjects who are inpatient), the severity (as defined by the National Institutes of Health/National Cancer Institute [NIH/NCI] Common Terminology Criteria for Adverse Events [CTCAE]), and any diagnostic procedures performed will be recorded at each visit, in addition to specific dates of worsening and/or improvement. For GVHD, organ stage and overall grade, and any diagnostic procedures performed will be recorded at each visit and more frequently if GVHD events persist or require additional, unscheduled visits. Medications administered for GVHD will be specifically recorded, including indication (prophylaxis, presumptive use, or treatment), dose, duration of therapy, and dose adjustments, as applicable. Treatment interruptions/dose modification/dose reductions for diarrhea, serum aminotransferase abnormalities and/or GVHD will be recorded. Correlation of diarrhea to GVHD of the intestine (GI-GVHD) will be assessed by the responsible investigator and a blinded GVHD Adjudication Committee (GAC). Slides from any biopsy performed for the diagnosis of GVHD (regardless of the organ involved) should be sent to the designated central safety laboratory. The results from any analyses of slides from GVHD biopsies will only be shared with the GAC and, if requested, the FDA. These results will not be provided to individual investigators. Specific guidance with respect to biopsy sampling and handling will be provided in the SRM and/or applicable central laboratory manual.

Pharmacokinetics:

All subjects will have a single timed blood sample for analysis of plasma concentrations of CMX001 and CDV (and possibly other metabolites) collected on the FDD at 3 (± 1) hours postdose. In addition, a single blood sample for analysis of plasma concentrations of CMX001 and CDV (and possibly other metabolites) will be collected from all subjects during each scheduled weekly assessment during the treatment phase for as long as the subject remains on study drug. If the timed

blood sample cannot be collected on the FDD, e.g., due to scheduling or resource issues, it may be collected within the same time window, i.e., at 3 (± 1) hours postdose, following administration of the second dose of study drug. The actual date and time of the last study drug administration prior to each blood sample collection (including the timed sample collected on the FDD) should be documented.

Other Clinical Endpoints:

The clinical impact of treatment with CMX001, as compared to treatment with placebo will be assessed by reported AEs, SAEs, number and duration of hospitalizations (i.e., initial and subsequent hospitalizations), receipt of and duration of relevant concomitant therapies (e.g., transfusions, receipt of hematopoietic growth factors, anti-infective medications, calcineurin inhibitors, and other immunosuppressive agents of interest, etc.), and number of diagnostic or therapeutic procedures not related to the primary HSCT (e.g., invasive GI procedures, such as endoscopies, biopsies, renal dialysis, bladder irrigations, etc.) collected through Week 24.

Health Economic/Health-related Quality of Life Assessments:

HE/HRQL outcomes will be assessed based on subject responses to the EQ-5D™ (EuroQol Health Utility Index 5D) and the EORTC-QLQ-C30 questionnaire (European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30) with treatment-specific HDC29 module (high-dose chemotherapy 29).

Each subject will complete the EQ-5D-5L and EORTC-QLQ-C30/HDC29 questionnaires during the screening evaluation or prior to the first study drug administration on the FDD to establish baseline, and at Week 6, Week 15, and Week 24.

Safety Monitoring and Safety Reviews:

During the treatment phase of the study, treatment-emergent adverse events (TEAEs) will be managed according to the Safety Monitoring and Management Plan (SMMP) for CMX001.

For subjects who experience TEAEs during the study, the investigator will have the option of interrupting dosing (for up to 4 doses or 18 consecutive days) and resuming dosing once the AE has improved.

Study drug may be interrupted for:

- Persistent diarrhea, defined as Grade 2 diarrhea for more than 3 consecutive days, if no other etiology has been identified, particularly if the symptoms are noted 2 to 8 weeks after the initiation of blinded study drug and when a decrease in serum albumin from baseline of ≥ 4 g/L (≥ 0.4 g/dL) reaching to serum albumin concentrations of ≤ 30 g/L (≤ 3.0 g/dL) is noted in the absence of other etiology for hypoalbuminemia

Study drug will be interrupted for:

- Grade 3 or higher diarrhea;
- Confirmed increase in serum aminotransferases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) that is 1) > 8x upper limit of the normal reference range (ULN) and 2x baseline; 2) > 5x ULN for at least 2 weeks and 2x baseline; 3) > 3x ULN (and 2x baseline) and with a total bilirubin > 2x ULN or prothrombin time-international normalized ratio (PT-INR) > 1.5x ULN, or 4) > 3x ULN (and 2x baseline) with the appearance of clinically relevant signs/symptoms of liver injury, including fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia (> 5% of total white blood cell count), or
- Stage 3 or higher GI-GVHD that is unresponsive to SoC therapy.

In certain circumstances, a change in dose frequency ("dose modification") may be an appropriate course of action in response to a TEAE, followed by a reduction in dose ("dose reduction"), as necessary.

For the purposes of this protocol, "dose modification" describes administering the same total weekly dose, but changing the dose frequency from BIW to once-weekly (QW), i.e.:

- from 100 mg CMX001 BIW to 200 mg CMX001 QW

"Dose reduction" describes reducing the previously modified dose, while keeping the QW administration, i.e.:

- from 200 mg CMX001 QW to 100 mg CMX001 QW

When a dose modification, or subsequent dose reduction, is being considered, the investigator must first contact the Chimerix Medical Monitor (or designee) to discuss the proposed change before initiating the dose modification or reduction. Once a subject "dose modifies" or "dose reduces", the subject cannot return to the previous dosing regimen.

Subjects who meet any of the following criteria after initiating study drug will be required to discontinue study drug (but will continue to be followed in the study): (1) onset of CMV end-organ disease; (2) require treatment with, or requirement for treatment with, an excluded medication, including subjects who develop clinically significant CMV infection or disease requiring anti-CMV PrT during the treatment phase; (3) persistent neutropenia, as defined by the investigator using standard site definitions, as applicable, and without an alternative explanation); (4) decrease in eGFR to < 15 mL/min or a new or persistent requirement for dialysis, if the eGFR change or the requirement for dialysis is considered to be study drug-related, and (5) pregnancy in a female subject.

For subjects with an on-treatment decrease in eGFR to < 15 mL/min that is not related to study drug, then study drug treatment may be continued if dialysis or other renal replacement therapy (RRT) is initiated. RRT must be continued for as long as the subject's eGFR remains < 15 mL/min and the subject remains on study drug.

If the female partner of a male subject becomes pregnant, the investigator will contact the Chimerix medical monitor (or designee) to discuss the most appropriate course of action, up to and including withdrawal of study drug.

In addition, if any of the following criteria are met, study drug may be discontinued at the discretion of the investigator, in consultation with the Chimerix Medical Monitor (or designee): (1) development of an exclusionary condition other than CMV infection/disease; (2) unacceptable toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest; (3) request of the primary care provider if (s)/he believes that the study is no longer in the best interest of the subject; (4) subject request to discontinue for any reason; (5) subject is not compliant with the protocol (i.e., significant protocol deviation), and (6) discontinuation of the study at the request of Chimerix, Inc., a regulatory agency, or the governing institutional review board (IRB), research ethics board (REB), or independent ethics committee (IEC), as applicable.

A Data and Safety Monitoring Board (DSMB) will monitor safety for this study, reviewing unblinded safety data on an ongoing basis on a schedule determined by the DSMB and detailed in the DSMB charter with the following caveats: 1) once the first subject has dosed, the DSMB must meet at least once every three months; 2) the meetings must be more frequent if unexpected safety issues arise (e.g., unexpectedly high rate of ≥ Grade 3 AEs and/or SAEs), and 3) the DSMB Chair will be allowed to convene ad-hoc meetings, as necessary.

Study Endpoints:

Primary Efficacy Endpoint:

The primary efficacy endpoint of this study will be the incidence of clinically significant CMV infection through Week 24, defined as the occurrence of either of the following outcomes:

- Onset of CMV end-organ disease, or
- Initiation of anti-CMV specific PrT based on documented CMV viremia as measured by the central virology laboratory and the clinical condition of the subject as described in the following table:

Category	Risk Factor(s)	CMV Viremia Threshold for Initiation of Anti-CMV PrT
Aggressive CMV viremia management	Does subject have one or more of the following baseline characteristics? 1. Cord blood transplant 2. Haploidentical transplant 3. Total or partial T-cell depletion (to include use of ATG or alemtuzumab [Campath®]) 4. CD34+ selection **- OR -** Does subject have one or more of the following clinical conditions? 1. Possible CMV disease (including severe bacterial or fungal infection; to be described in the eCRF) 2. Significant concomitant morbidity (e.g., septic shock or graft failure; to be described in eCRF) 3. Fever of unknown origin 4. Currently receiving, have received within the prior 14 days, or are anticipated to receive within 1 day therapy with high-dose (≥ 1 mg/kg prednisone equivalent) systemic steroids, or are currently receiving, have received, or are anticipated to receive within 1 day either ATG or alemtuzumab	Confirmed CMV viremia level ≥ 150 copies/mL post-FDD as measured by the central virology laboratory (for both the initial and confirmatory sample)
Standard CMV viremia management	If subject has none of the baseline characteristics or clinical conditions described above	One CMV viremia result ≥ 1,000 copies/mL post-FDD as measured by the central virology laboratory

CMV viremia testing at the central virology laboratory should occur once weekly from FDD through Week 14 posttransplant; however, more frequent monitoring can be implemented by the investigator, as clinically appropriate. If and when samples are collected for CMV viremia testing in the local virology laboratory, including any unscheduled CMV viremia assessments performed per local SoC, samples should be collected and sent to the central virology laboratory for analysis in parallel.

To ensure a standardized approach between investigators at different institutions, the CMV viral threshold for stopping study drug treatment and initiating anti-CMV PrT is one CMV viremia result ≥ 1,000 copies/mL post-FDD based on PCR assays performed only by the central virology laboratory, unless the clinical condition of the subject meets the prespecified criteria based on the baseline characteristics and emergent signs and symptoms for aggressive CMV viremia management. If the

clinical condition of the subject meets the prespecified criteria for aggressive CMV viremia management, then the CMV viral threshold for initiating anti-CMV PrT is a confirmed CMV viremia level ≥ 150 copies/mL (i.e., ≥ LLOQ) post-FDD performed only by the central virology laboratory. While two samples (initial and confirmatory) should be collected and sent to the central virology laboratory prior to the initiation of PrT, the decision to await the second, confirmatory result will be left to the investigator's discretion, depending on the subject's clinical condition. Alternatively, in order to not delay the initiation of anti-CMV PrT, the confirmatory sample should still be drawn and submitted to the central virology laboratory prior to administration of the first dose of anti-CMV PrT and if the result is not confirmed, and no more than 48 hours of dosing with anti-CMV PrT has been completed, then the PrT may be discontinued and will be considered as having been initiated prematurely. In either case, a decision regarding the initiation of anti-CMV therapy should be made as soon as practicable in the circumstances, and preferably no more than 4 days after the initial CMV viremia result ≥ 150 copies/mL.

The same criteria for initiating anti-CMV PrT will apply throughout the treatment and posttreatment phases of the study.

During the treatment phase, subjects who meet either of the above outcomes (i.e., onset of CMV end-organ disease or initiation of anti-CMV specific PrT) must discontinue treatment with study drug, but will continue to be followed in the study until Week 24. In circumstances where PrT is initiated prematurely (as described above, or based on local virology laboratory results that have not been confirmed by the central virology laboratory), subjects will be authorized to resume study drug if the duration of the PrT was ≤ 48 hours. Such allowance can only be for a single episode during each subject's study participation. If the duration of the PrT is > 48 hours, then the subject may not resume study drug. If PrT is initiated for a second time, the subject must permanently discontinue study drug.

[Note: PrT therapy will not be supplied by Chimerix, Inc. and must be sourced by the investigator or treating physician in accordance with standard institutional practice.]

Secondary Efficacy Endpoints:

- Incidence of and time to all-cause mortality through Week 14 and through Week 24
- Incidence of and time to non-relapse mortality (i.e., mortality not associated with the relapse of the underlying malignancy) through Week 14 and through Week 24
- Incidence of and time to mortality attributed to CMV through Week 14 and through Week 24
- Incidence of and time to graft failure through Week 14 and through Week 24
- Incidence of clinically significant CMV infection through Week 14
- Time to clinically significant CMV infection through Week 14 and through Week 24
- Incidence of clinically significant CMV infection during the posttreatment phase (i.e., from Week 15 through Week 24). The analysis will adjust for subject characteristics existing at Week 15 [e.g., the presence of GVHD of Grades II to IV severity, use of high-dose (≥ 1 mg/kg prednisone equivalent) steroids, persistent lymphopenia, the presence or absence of CMV-specific cellular immunity, etc.]
- Incidence, time to initiation and number of anti-CMV PrT courses (e.g., GCV, vGCV, FOS, or CDV) through Week 14 and through Week 24
- Incidence of and time to CMV end-organ disease, as adjudicated by the blinded EAC according to the definitions/procedures described by Ljungman et al (Ljungman 2002), through Week 14 and through Week 24
- Incidence of BKV end-organ disease during study drug administration (through last dose of study drug +7 days, through Week 14, and through Week 24), defined as symptoms associated with BKV-associated cystitis (e.g., increased frequency of urination, bladder pain, hematuria, clots, etc.) or a decrease in renal function (as measured by estimated glomerular

filtration rate [eGFR] using the Chronic Kidney Disease Epidemiology equation [CKD-EPI]) to a value < 60 mL/min/1.73 m^2 and a ≥ 30% decrease from baseline

- Incidence of and time to CMV viremia ≥ 150 copies/mL (≥ LLOQ) through Week 14 and through Week 24
- Incidence of and time to virologic breakthrough and emergence of CMV mutations associated with phenotypic resistance to CMX001
- Incidence of and time to emergence of clinical and laboratory events associated with other dsDNA viruses, including AdV, BKV, EBV, HSV-1/2, HHV-6, and VZV, through Week 14 and through Week 24
- Incidence of emergence of anti-CMV immune response (as measured by the T-SPOT.® *CMV* Test) through Weeks 5, 9, 14, and 24

Safety Endpoints:

- Incidence of and time to discontinuation from study drug due to AEs
- Incidence of TEAEs, in particular TEAEs of ≥ Grade 3 severity, as defined by the NIH/NCI CTCAE
- Incidence and severity of treatment-related TEAEs
- Incidence, severity, and worsening of GI-related events, in particular diarrhea
- Incidence, severity, and worsening of aGVHD, in particular GI-GVHD, as adjudicated by the blinded GAC
- Incidence, severity, and worsening of hepatobiliary events, in particular liver-related laboratory abnormalities
- Incidence of TEAEs leading to dose interruption, dose reduction, or dose discontinuation

Pharmacokinetic Endpoints:

- Plasma concentrations of CMX001 and CDV

Other Clinical Endpoints:

- Total number and duration of hospitalizations and the use of transfusions, hematopoietic growth factors, and anti-infective medications through Week 14 and through Week 24
- Incidence and severity of non-CMV infections (i.e., bacterial, protozoal, fungal, or viral) through Week 14 and through Week 24
- Incidence and severity of new onset (i.e., post-FDD) renal dysfunction through Week 14 and through Week 24
- Frequency of diagnostic or therapeutic procedures not related to the primary HSCT (e.g., endoscopies, imaging, biopsies and related procedures) through Week 24

Health Economic/Health-related Quality of Life Endpoints:

- Subject responses to EQ-5D-5L and EORTC-QLQ-C30/HDC29 questionnaires

Statistical Methods:

General Considerations: Statistical analyses will be reported using summary tables, figures, and data listings. Continuous variables will be summarized using the mean, standard deviation, median, quartiles (Q1, Q3), minimum, and maximum by treatment group. Categorical variables will be summarized by numbers and percentages of subjects in corresponding categories by treatment group. Time-to-event endpoints will be summarized by Kaplan-Meier plots, with treatment groups compared via log-rank tests. All data collected will be included in listings.

Unless otherwise stated, all statistical tests will be two-sided, with a p-value of < 0.05 considered statistically significant, and values for missing data will not be imputed.

Analysis Sets: The Intent-to-Treat (ITT) analysis set will include all subjects who receive at least one dose of study drug. This analysis set will be used to summarize all endpoints and will be used for the primary inferential efficacy analysis. The Modified Intent-to-Treat (mITT) analysis set will include all subjects in the ITT who are CMV viremia negative at baseline, i.e., excluding subjects subsequently found to have been CMV viremic at baseline. The Per Protocol (PP) analysis set will include all subjects in the mITT analysis set who complete the study through Week 24 (or die on study) and do not have any major protocol deviations (defined as significant inclusion/exclusion criteria violation, study drug noncompliance, or the use of a prohibited concomitant medication unless initiated as anti-CMV PrT post-FDD per protocol). The mITT and PP analysis sets will be determined prior to unblinding the study. All analyses will use the actual treatment received by the subject. In the event that a meaningful number of subjects (e.g., $\geq 3\%$) are either (a) randomized and not treated, or (b) first treated with the incorrect study drug, the primary endpoint will be analyzed with all randomized subjects and using randomized treatment to assess the impact on the results. The PK analysis set will include all randomized subjects who take at least one dose of CMX001 and have at least one blood sample collected for analysis of plasma CMX001/CDV concentrations.

Sample Size: Approximately 450 subjects will be enrolled into this study. Sample size calculations were based on the primary endpoint, i.e., the development of clinically significant CMV infection. Prior data indicate that the proportion of placebo subjects developing clinically significant CMV infection is at least 0.30. A clinically meaningful relative risk for CMX001 subjects relative to placebo is 0.5 (i.e., a 50% reduction). A two group continuity corrected chi-squared test with a 0.05 two-sided significance level will have > 85% power to detect the difference between a CMX001 proportion of 0.15 and a placebo proportion of 0.30 when 360 subjects are allocated 2:1 between the two treatment groups (CMX001:placebo). In order to account for an estimated 20% dropout rate, 300 subjects will be randomized to CMX001 and 150 subjects will be randomized to placebo, i.e., a total of 450 subjects.

Primary Efficacy Endpoint: The primary efficacy endpoint is a composite endpoint for the development of clinically significant CMV infection measured through Week 24 ($\pm$ 14 days). The proportion of subjects meeting this endpoint will be compared between CMX001 and placebo using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline CMV risk category (i.e., "higher" vs. "lower" risk of disease progression). Number of failures and failure rates will be presented for each treatment. CMH p-values, estimated common odds ratios, and corresponding approximate 95% confidence intervals (CIs) will be presented for each comparison. The Breslow-Day test will be used to test the homogeneity of the odds ratios. A Mantel-Haenszel test for risk difference will be conducted as a supportive analysis. The primary analysis will include subjects who receive anti-CMV PrT as failures (except those who receive anti-CMV PrT prematurely one time, as described previously), regardless of whether the PrT was initiated according to protocol-specified criteria. In the event that any subjects receive anti-CMV PrT outside of protocol-specified criteria, a sensitivity analysis will be conducted in which these subjects are excluded from the analysis set. In the event that any subjects do not initiate anti-CMV PrT when meeting protocol specific criteria, a sensitivity analysis will be conducted in which these subjects are counted as failures. Subjects for whom the primary endpoint is missing will be considered failures. Sensitivity analyses will be conducted to investigate the impact of this missing data imputation on the primary endpoint.

Secondary Efficacy Endpoints: Dichotomous secondary endpoints will be analyzed using the same method (i.e., CMH test) as used for the primary endpoint. Missing data will be imputed as failure. Time-to-event analyses will be performed using Kaplan-Meier methods/plots and log rank tests. P-values, hazard ratios, and 95% CIs will be presented for each treatment comparison. Missing data will be censored. Duration and number of courses of PrT will be summarized descriptively using

counts/percentages and/or summary statistics. In the event that the primary analysis is statistically significant, specific secondary endpoints will be tested sequentially as follows:

- The incidence of any non-CMV dsDNA virus end-organ disease (i.e., AdV, BKV, EBV, HSV-1/2, HHV-6, and VZV), through Week 24 will be tested at 5% alpha.
- In the event that the preceding test is statistically significant, the incidence of end organ disease due to each of the six individual viruses through Week 24 will be tested using the Hochberg method.

Further adjustments will not be made for multiple comparisons.

Safety Endpoints: Safety endpoints include the incidence and severity of all AEs and treatment-related AEs, incidence and severity of GVHD, withdrawal due to an AE, dose interruption or reduction due to AEs, clinically significant laboratory abnormalities, and change from baseline in laboratory values. Inferential analyses will not be performed for safety endpoints.

Pharmacokinetic Endpoints: CMX001 and CDV concentrations will be determined in plasma samples collected on the FDD and at each scheduled weekly assessment during the treatment phase while subjects remain on study drug.

Health Economic/Health-related Quality of Life Endpoints: Change from baseline HE/HRQL scores will be analyzed using an analysis of covariance (ANCOVA) model with factors of baseline score, treatment, and risk category. P-values and 95% CIs will be presented. Binary endpoints will be assessed via CMH test as used for the primary endpoint.

Other Analyses: Summaries of demographics, baseline characteristics, exposure/adherence, concomitant medications, data sets analyzed, and disposition will be presented.

Subgroup Analyses: The primary efficacy endpoint, incidence of TEAEs, and selected laboratory values (e.g., serum aminotransferases, albumin, and creatinine) will be summarized by age (tertiles), race/ethnicity (separate categories for racial/ethnic groups contributing at least 10% of study enrollment plus “other”), sex (male or female), weight (tertiles) and baseline CMV risk category (“higher” or ”lower” risk of disease progression).

This study will be conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the ICH Harmonized Tripartite Guidelines.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: List of Abbreviations and Specialist Terms

Abbreviation	Explanation
ACV	Acyclovir
ADL	Activities of Daily Living
AdV	Adenovirus(es)
AE	Adverse event
AEOSI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase (also alanine transaminase)
AME	Absorption, metabolism, and excretion
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ASBMT	American Society for Blood and Marrow Transplantation
AST	Aspartate aminotransferase (also aspartate transaminase)
ATG	Anti-thymocyte globulin
AUC	Area under the concentration versus time curve
AUCinf	Area under the plasma concentration versus time curve from time zero to infinity
AUClast	Area under the plasma concentration-time curve from time zero to time of last measurable plasma concentration
AUC0-24	Area under the plasma concentration-time curve from time zero to 24 hours
BCRP	Breast cancer resistance protein (also known as ATP-binding cassette sub-family G member 2 [ABCG2])
BIW	Twice-weekly, twice-a-week
BKV	BK virus
BLQ	Below the limit of quantitation
BMI	Body mass index
BTACT	Brief Test of Adult Cognition by Telephone
BUN	Blood urea nitrogen
°C	Degree(s) Celsius
CDV	Cidofovir (also Vistide® for injection)
CDV-PP	Cidofovir diphosphate

Abbreviation	Explanation
CE	Conformité Européene (Mark)
CFR	(US) Code of Federal Regulations

Table 2: List of Abbreviations and Specialist Terms (Continued)

Abbreviation	Explanation
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology equation
Cmax	Peak (maximum) plasma concentration of the drug
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus (also HHV type 5)
CMX001	Brincidofovir, hexadecyloxypropyl-cidofovir
CMX064	4-(3-propoxy)butanoic acid ester of CDV
CMX103	3-hydroxypropyl ester of CDV
CMX104	(3-propoxy)acetic acid ester of CDV
CNS	Central nervous system
CPT	Current Procedural Terminology (code)
(e)CRF	(Electronic) Case Report Form
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	(NIH/NCI) Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CYP3A4	Cytochrome P450, isoform 3A4
D-	Donor seronegative for CMV
D+	Donor seropositive for CMV
dGTP	Deoxyguanosine triphosphate
DiLI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded DNA
DSMB	Data and Safety Monitoring Board
EAC	Endpoint Adjudication Committee
EBV	Epstein-Barr virus (also HHV type 4)
(I)EC	(Independent) Ethics Committee

Abbreviation	Explanation
EC_{50}	Fifty percent (50%) of effective concentration
ECG	Electrocardiogram
EIA	Enzyme immunoassay
EIND	Emergency Investigational New Drug

Table 2: List of Abbreviations and Specialist Terms (Continued)

Abbreviation	Explanation
EORTC	European Organization for Research and Treatment of Cancer
EORTC-HDC29	EORTC treatment-specific module for high-dose chemotherapy
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30
EQ	EuroQol
EQ-5D(-5L)	EuroQol Health Utility Index 5D (5L version)
ESRD	End-stage renal disease
EudraCT	European Union Drug Regulating Authorities Clinical Trials
°F	Degree(s) Fahrenheit
FDA	(US) Food and Drug Administration
FDD	First dose day
Fg	Fraction of drug that escapes the gastrointestinal tract
Fh	Fraction of drug that escapes the liver
FOS	Foscarnet (also Foscavir®)
GAC	GVHD Adjudication Committee
GEE	Generalized estimating equation
GCP	Good Clinical Practice
GCV	Ganciclovir (also Cytovene®)
(e)GFR	(Estimated) Glomerular filtration rate
GI	Gastrointestinal
GI-GVHD	GVHD of the intestine
GLM	Geometric least-squares mean
(a)GVHD	(Acute) Graft versus host disease
HBV	Hepatitis B virus
HC	Hemorrhagic cystitis
(β-)hCG	(beta-)human chorionic gonadotropin

Abbreviation	Explanation
HCV	Hepatitis C virus
HE	Health economics
HHV(-5/6/8)	Human herpesvirus(es) (type 5, 6, or 8)
HIPAA	Health Insurance Portability and Accountability Act (in US)
HIV(-1/2)	Human immunodeficiency virus (type 1 or 2)
HRQL	Health-related quality-of-life

Table 2: List of Abbreviations and Specialist Terms (Continued)

Abbreviation	Explanation
HSCT	Hematopoietic stem cell transplantation
HSV(-1/2)	Herpes simplex virus (type 1 or 2)
ICF	Informed consent form
ICH	International Conference on Harmonization
ID	Identification
Ig	Immune globulin, immunoglobulin
IHC	Immunohistochemistry
IL-2/8	Interleukin 2 or 8
IND	Investigational New Drug Application (in US)
IRB	Institutional Review Board
ITT	Intent-to-Treat
IU	International Unit(s)
IV	Intravenous
IV/WRS	Integrated Voice/Web Response System
JCV	JC virus
KM	Kaplan-Meier
(L)LOD	(Lower) Limit of detection
(L)LOQ	(Lower) Limit of quantitation
MDRD4	Modification of Diet in Renal Disease equation 4
MDZ	Midazolam
MedDRA	Medical Dictionary for Regulatory Activities, MedDRA®
MI	Multiple imputation
mITT	Modified Intent-to-Treat

Abbreviation	Explanation
MMF	Mycophenolate mofetil
MMSE	Mini-mental state examination (also known as Folstein test)
MRD	Matched related donor
MUD	Matched unrelated donor
N, n	Sample size (typically refers to number of subjects)
NCI	(US) National Cancer Institute
NIH	(US) National Institutes of Health
No(s).	Number(s)

Table 2: List of Abbreviations and Specialist Terms (Continued)

Abbreviation	Explanation
NPO	Nil per os (nothing by mouth)
(h)OAT(1/3)	(Human) Organic anion transporter 1 or 3
OATP(1B1/1B3)	Organic anion transporting polypeptide 1B1 or 1B3 (also known as solute carrier organic anion transporter family member B1 or B3 [SLCOB1/B3], respectively)
OTMT-B	Oral Trail Making Test
PBMC	Peripheral blood mononuclear cell
(q)PCR	(Quantitative) Polymerase chain reaction
P-gp	P-glycoprotein (also known as multidrug resistance protein 1 [MDR1] or ATP-binding cassette sub-family B member 1 [ABCB1])
PK	Pharmacokinetic(s)
PO	Per os (by mouth)
PP	Per Protocol
PRN	Pro re nata (as circumstances require)
PrT	Preemptive therapy
PT-INR	Prothrombin time-international normalized ratio
PTLD	Posttransplant lymphoproliferative disorder
PVC	Polyvinylchloride
QoL	Quality-of-life
Q1	First quartile
Q3	Third quartile
QTcF	QT interval corrected according to Fridericia
QW	Once-weekly, once-a-week

Abbreviation	Explanation
R-	Recipient seronegative for CMV
R+	Recipient seropositive for CMV
REB	Research Ethics Board
RIC	Reduced intensity conditioning (regimen)
RNA	Ribonucleic acid
RRT	Renal replacement therapy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SMMP	Safety Monitoring and Management Plan
SoC	Standard of Care
SOP	Standard operating procedure

Table 2: List of Abbreviations and Specialist Terms (Continued)

Abbreviation	Explanation
SRM	Study Reference Manual
t1/2elim	Terminal-phase elimination half-life
TCD	T-cell depleted/depletion
TDD	Total daily dose
TEAE	Treatment-emergent adverse event
Theorem GSA	Theorem Global Safety Advantage, Theorem GSA^{SM}
Tmax	Time to peak (maximum) plasma concentration
TPN	Total parenteral nutrition
TQT	Thorough QT (study)
UL54	CMV polymerase
UL97	CMV phosphotransferase
ULN	Upper limit of normal reference range
US(A)	United States (of America)
vACV	Valacyclovir (also valaciclovir, Valtrex®)
vGCV	Valganciclovir (also Valcyte®)
vs.	Versus
VZV	Varicella-zoster virus (also HHV type 3)

Abbreviation	Explanation
WBC	White blood cell count
WHO	World Health Organization
Wk, wk	Week

5. GLOSSARY OF TERMS

The following terms will be used in this protocol when describing the study:

- **Clinically Significant Cytomegalovirus (CMV) Infection:** For the purposes of this study, "clinically significant CMV infection" is defined by either of the following outcomes: (1) the onset of CMV end-organ disease, or (2) the initiation of anti-CMV specific preemptive therapy (PrT) based on predefined risk factors, including baseline characteristics, emergent signs and symptoms, and documented CMV viremia as measured by the central virology laboratory; see also Section 6.3.5 and Figure 1. Subjects who meet either outcome during the treatment phase of the study must discontinue study treatment, but will continue to be followed in the study until Week 24.
- **CMV End-organ Disease:** Includes all of those events defined by Ljungman et al (Ljungman 2002) (i.e., pneumonia, gastrointestinal [GI] disease, hepatitis, central nervous system [CNS] disease, retinitis, nephritis, cystitis, myocarditis, pancreatitis) and must be confirmed by the presence of CMV in the infected tissue or body fluid as adjudicated by the Endpoint Adjudication Committee (EAC).
- **CMV Viremia:** Refers to the measurement of CMV deoxyribonucleic acid (DNA) in plasma (sometimes referred to as CMV DNAemia). For the purposes of this study, CMV viremia will be determined by the central virology laboratory using the Food and Drug Administration (FDA)-approved and CE (Conformité Européene)-marked Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test (see Section 12.1.1.1 for further details about the assay).
- **CMV Viremia Negative:** For the purposes of determining subject eligibility, CMV viremia negative refers to a CMV DNA concentration in plasma that is below the lower limit of detection (LLOD) for the polymerase chain reaction (PCR) assay (i.e., for the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test) used by the central virology laboratory, and reported as "Not Detected." This is to be distinguished from results that are detectable, but not quantifiable and reported as "Detected < 151 copies/mL," and which are exclusionary for the purposes of this protocol. In addition to being CMV viremia negative at screening based on the results of tests performed by the central virology laboratory, the results of any other CMV viremia testing (including CMV PCR, pp65 antigenemia, etc.) performed as part of local standard of care since the qualifying transplant must also be negative.
- **CMV Viremia Positive (also CMV Viremic):** For the purposes of determining subject eligibility, CMV viremia positive refers to a CMV DNA concentration in plasma that is detectable by the PCR assay (i.e., the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test) used by the central virology laboratory. This encompasses both quantifiable CMV DNA results (i.e., values at or above the LLOQ), reported as the actual numeric value in copies/mL, and CMV DNA results that are detectable, but not quantifiable and reported as "Detected < 151 copies/mL."

The reporting of CMV viremia results by the central virology laboratory is summarized as follows:

CMV Viremia	CMV Viral Load Reported as:	At Screening Assessment?	Initiation of Anti-CMV PrT under Aggressive CMV Viremia Management?	Initiation of Anti-CMV PrT under Standard CMV Viremia Management?
Negative	Not detected	Not exclusionary	No	No
Positive	Detected < 151 copies/mL[a]	Exclusionary	No	No
	Actual numeric value in copies/mL	Exclusionary	Yes	Only if ≥ 1,000 copies/mL

[a] Based on the manufacturer's conversion factor of 1.1, the LLOQ of 137 IU/mL for the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test equates to a LLOQ of 150.7 copies/mL, which is reported as 151 copies/mL, after rounding.

- **(Likelihood of) CMV Disease Progression:** Subjects who receive a matched, related, non-T-cell depleted graft (e.g., excluding cord blood), who do not have acute graft versus host disease (aGVHD), who have not received anti-thymocyte globulin (ATG) or alemtuzumab, and who are not receiving high-dose (≥ 1 mg/kg prednisone equivalent) systemic steroids are considered to have a "lower likelihood" for CMV disease progression for the purposes of this protocol. All other subjects are considered to have a "higher likelihood" of disease progression. The stratification of subjects between the "lower likelihood" and "higher likelihood" of disease progression at the time of randomization is different from the categorization to standard and aggressive CMV viremia management for the purposes of determining the appropriate threshold for discontinuation of study drug and initiation of anti-CMV PrT.
- **Dose Modification:** Refers to changing a subject's treatment regimen from the initial twice-weekly (BIW) regimen to a once-weekly (QW) regimen under blinded conditions. Dose Modification must be discussed with and approved by the Chimerix Medical Monitor (or designee) before implementation. Dose modification (unlike "dose reduction", see below) does not require a new study drug kit; instead, the subject takes both of the tablets on his or her existing card for that week at the same time. Dose modification must precede dose reduction.
- **Dose Reduction:** Refers to reducing the previously modified QW dose of study drug under blinded conditions. Dose reduction must be discussed with and approved by the Chimerix Medical Monitor (or designee) before implementation. Dose reduction (unlike "dose modification", see above) requires the investigator to request a new study drug kit for the subject through the integrated voice/web response system (IV/WRS).
- **Initiation of Anti-CMV Preemptive Therapy (Standard vs. Aggressive CMV Management):** To ensure a standardized approach between investigators at different institutions, the CMV viral threshold for initiating anti-CMV PrT is one CMV viremia result ≥ 1,000 copies/mL post-first dose day (FDD) based on PCR assays

performed by the central virology laboratory (as standard CMV management), unless the clinical condition of the subject meets the prespecified criteria based on the subject's baseline characteristics and/or emergent signs and symptoms for aggressive CMV viremia management (see Section 6.3.5 and Figure 1). If the subject meets the prespecified criteria for aggressive CMV viremia management, then the CMV viral threshold for initiating anti-CMV PrT is a confirmed CMV viremia level ≥ 150 copies/mL (i.e., ≥ LLOQ for the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test) post-FDD performed by the central virology laboratory. [Note: CMV viremia results < LLOQ will either be reported as "Not Detected" (if < LLOD) or "Detected < 151 copies/mL (if ≥ LLOD and < LLOQ). The latter result does not constitute a result meeting the threshold for initiation of PrT for the purposes of this protocol.] While two samples (initial and confirmatory) should be collected and sent to the central virology laboratory prior to initiation of PrT, the decision to await the second, confirmatory result will be left to the investigator's discretion, depending on the subject's clinical condition. Alternatively, in order to not delay the initiation of anti-CMV PrT, the confirmatory sample should still be drawn and submitted to the central virology laboratory prior to administration of the first dose of anti-CMV PrT and if the result is not confirmed, and no more than 48 hours of dosing with anti-CMV PrT has been completed, then the PrT may be discontinued and will be considered as having been initiated prematurely. In either case, a decision regarding the initiation of anti-CMV therapy should be made as soon as practicable in the circumstances, and preferably no more than 4 days after the initial CMV viremia result ≥ 150 copies/mL. **Only results from the central virology laboratory should be used for CMV viremia management.** If and when samples are collected for CMV viremia testing in the local virology laboratory, including any unscheduled CMV viremia assessments performed per local SoC, samples should be collected and sent to the central virology laboratory for analysis in parallel.

- **Posttreatment Phase:** The posttreatment phase encompasses Week 15 through Week 24.
- **Randomized Subject:** A subject who is randomized to a treatment group, regardless whether or not he/she takes a dose of study drug, is defined as "randomized".
- **Screened Subject:** Any subject who signs an informed consent form (ICF) will be considered to have been screened.
- **Screen Failure:** Any subject who signs an ICF but is not randomized will be considered a screen failure.
- **Treated Subject:** A subject is defined as "treated" when he/she takes at least one dose of study drug.
- **Treatment Phase:** The treatment phase encompasses the FDD through Week 14. Treatment may be initiated as soon as the subject completes the screening evaluation and is determined to be eligible to participate in the study, but no later than Day 28 posttransplant.

6. INTRODUCTION

6.1. Background

Cytomegalovirus (CMV), also known as human herpes virus type 5 (HHV-5), a member of the herpesviridae family, is a double-stranded deoxyribonucleic acid (dsDNA) virus, which causes persistent and latent infections in humans. While CMV normally remains latent in previously infected healthy individuals, impaired immune surveillance in immunocompromised individuals can result in reactivation of latent virus, leading to potentially life-threatening active infection. The most common manifestations of active CMV infection in immunocompromised individuals are pneumonia, gastrointestinal (GI) disease, hepatitis, and (to a lesser extent) retinitis (Ljungman 2010).

After allogeneic stem cell transplantation, the patients at greatest risk of CMV infection or disease are those individuals who have historical evidence of CMV prior to transplant. The risk of CMV reactivation in these patients is dictated by the period of immune system impairment resulting from the conditioning regimen, the administration of subsequent immunosuppressant therapy, and the timing of T-cell immune reconstitution postengraftment. CMV infections typically begin around the time of engraftment and continue to increase until Day 80 posttransplant (Nakamae 2009). The risk of CMV reactivation after Day 100 posttransplant is generally considered to be low. After this time frame, the immune system is typically able to prevent the new onset of CMV reactivation (Merindol 2011).

Three currently approved antiviral drugs are used for the prevention, preemptive treatment, or treatment of human CMV infections: ganciclovir (GCV; as Cytovene®) and its prodrug, valganciclovir (vGCV; as Valcyte®), intravenous (IV) cidofovir (CDV; as Vistide® for injection), and foscarnet (FOS; as Foscavir®). None of these drugs is approved for the prevention of CMV infection in at-risk hematopoietic stem cell transplant (HSCT) recipients due to limiting adverse events (AEs), including myelosuppression and renal dysfunction. Initiation of CMV-specific therapy after detection of CMV in the blood, preemptive therapy, is the current standard of care (SoC) post-HSCT.

Because of the importance of CMV as a pathogen in HSCT recipients, a number of clinical studies have been conducted to assess the effectiveness of antiviral agents administered as prevention, i.e., administration of antiviral therapy to all at risk subjects posttransplant, and/or as preemptive therapy (PrT), i.e., the initiation of antiviral therapy based on the detection of CMV replication during frequent monitoring post-HSCT. Randomized clinical trials examining the utility of GCV as a prevention demonstrated a significant reduction in early CMV disease, but no survival benefit due to the increased occurrence of invasive fungal and bacterial infections and late onset CMV disease (Goodrich 1993, Winston 1993). In a subsequent prospective study of 278 HSCT patients receiving GCV as CMV prevention, 57% of patients developed neutropenia (defined as absolute neutrophil counts [ANCs] of < 1,500 cells/μL); 41% of patients experienced a nadir of < 1,000 cells/μL; and 21% had a nadir of < 500 cells/μL for at least 2 consecutive days (Salzberger 1997). In this study, neutropenia was associated with an increase in infections and was a negative predictor of overall and event-free survival.

In contrast, the use of GCV as PrT in HSCT patients with detectable CMV viremia resulted in both a reduction in disease and a survival benefit; however, the clinical benefit was limited by

significant myelotoxicity in up to 40% of subjects and an increased risk of bacterial and fungal infections (Boeckh 1996, Ljungman 2010, Meijer 2003). Controlled studies of FOS for CMV prevention have not been conducted, but PrT studies have indicated that FOS is equivalent in efficacy to GCV (Reusser 2002); however, FOS treatment is associated with electrolyte abnormalities and the risk of nephrotoxicity. While IV CDV has been evaluated in small, retrospective studies, large randomized clinical trials of the antiviral activity of CDV against CMV infection in HSCT recipients have not been conducted. Clinical utility of CDV has been significantly limited by nephrotoxicity and neutropenia.

Based on current evidence, PrT in response to CMV viremia is the most commonly used strategy to prevent the development of CMV disease in HSCT recipients (reviewed in Meijer 2003). The potential benefit of GCV or vGCV is limited by high rates of neutropenia with associated increased risks of bacterial and fungal infections (Boeckh 1996), as well as anemia and thrombocytopenia requiring red blood cell and platelet transfusions (van der Heiden 2006). The second-line antiviral drugs, FOS and CDV, cause renal toxicity and other adverse side effects. In spite of the available antiviral therapies, R+ HSCT recipients continue to have a higher mortality than do CMV-seronegative recipients (R-) (Craddock 2001). Also, PrT, in contrast to prevention, has been associated with emergence of drug-resistant CMV isolates (Couzi 2012, Fishman 2012).

GCV, CDV, and FOS all ultimately target the CMV DNA polymerase encoded on the UL54 gene and resistance to these agents can be conferred by mutations in this gene (Gilbert 2005). Since GCV must be converted to the monophosphate by the CMV phosphotransferase UL97 before it can ultimately be converted to the triphosphate and act as an alternative competitive substrate of deoxyguanosine triphosphate (dGTP) for viral polymerase, mutations in this protein can also lead to resistance to GCV. UL97 mutations have been detected in the vast majority (90%) of GCV resistant clinical isolates (Gilbert 2005). However, UL97 mutations associated with GCV resistance do not appear to affect sensitivity to CDV as it is a nucleotide monophosphate analog and does not require phosphorylation by UL97. Mutations in UL54 can confer resistance to GCV, CDV, or FOS. Generally speaking, mutations associated with FOS do not overlap with those associated with GCV or CDV. In the case of GCV, the first mutations selected in the clinic are typically in UL97; mutations in UL54 may follow if treatment is continued, leading to higher level GCV resistance and CDV cross-resistance (Gilbert 2005, Smith 1997). Mutations selected by CDV in UL54 typically confer cross-resistance to GCV, but not FOS (Lurain 2010).

Although CMV is currently the single most clinically important viral pathogen in the transplant population, other dsDNA viruses cause significant disease syndromes following HSCT (Boeckh 2005, Marty 2006). These include other human herpes viruses, such as Epstein-Barr virus (EBV), varicella-zoster virus (VZV), and human herpes virus type 6 (HHV-6), as well as adenoviruses (AdV) and polyomaviruses, such as BK virus (BKV).

EBV has long been recognized as the most common causative agent of posttransplant lymphoproliferative disorder (PTLD), which is especially prevalent in the pediatric population. An increasing number of clinical syndromes, including neurological disease and pulmonary infections, have also been attributed to EBV infection. The potential increase in frequency of EBV infections in HSCT recipients has been linked to several risk factors, including use of cord blood and T-cell depleted (TCD) grafts (Bitan 2006, Meijer 2005).

VZV-associated disease, resulting from either reactivation of latent virus or primary infection, can cause serious morbidity and even mortality in HSCT recipients. Reactivation of VZV can present as localized herpes zoster (80% of cases) or disseminated disease (20% of cases) (Boeckh 2006).

HHV-6 is a lymphotropic herpesvirus that is often reactivated in immunocompromised patients. Although the overall clinical impact of HHV-6 infection is not completely understood, HHV-6 viremia has been associated with all-cause mortality, Stage 3 and 4 graft versus host disease (GVHD), and a lower probability of engraftment of monocytes and platelets. In addition, reports of encephalitis following transplant have demonstrated that HHV-6 can cause central nervous system (CNS) disease (Zerr 2006).

Primary infection with BKV normally occurs early in life, presenting as a mild disease with flu-like symptoms. Following primary infection, the virus establishes lifelong latency in urogenital epithelial cells, but rarely causes disease in healthy adults. Conversely, BKV causes significant disease in patients with prolonged immunosuppression, including hemorrhagic cystitis (HC) in HSCT recipients (Hirsch 2002, Hirsch 2005, Nickeleit 2006, Pavlakis 2006). BKV infection is associated with HC in approximately 30% (5 to 60%) of HSCT recipients, with the risk of HC increased after myeloablative conditioning regimens and after mismatched donor HSCT. Although rarely fatal, episodes of HC can vary in severity, can be very painful, can be associated with significant hematuria and clotting, may prolong hospitalization, and can result in impairment of kidney and/or bladder function (O'Donnell 2009, Pavlakis 2006).

Thus, the development of CMX001, also known as brincidofovir, an investigational antiviral agent with broad *in vitro* activity against dsDNA viruses and proven clinical activity in the prevention of CMV infection post-HSCT, with a safety and tolerability profile that may allow use as a prevention in recipients of allogeneic HSCT, has the potential to fulfill a significant unmet medical need.

6.2. CMX001

CMX001 (brincidofovir, hexadecyloxypropyl-cidofovir) is a novel, orally bioavailable, broad spectrum, lipid acyclic nucleoside phosphonate that is converted intracellularly into the active antiviral, cidofovir diphosphate (CDV-PP). CMX001 is designed to mimic a natural lipid, lysophosphatidylcholine, to utilize natural lipid uptake pathways to achieve high intracellular concentrations of CMX001. CMX001 is absorbed in the small intestine, processed through the liver, and delivered throughout the body, where it readily crosses target cell membranes (Aldern 2003). Inside the cell, CMX001 is cleaved to release CDV, which is then converted to CDV-PP by intracellular anabolic kinases. CDV-PP exerts its antiviral effects by acting as a potent alternate substrate inhibitor for viral DNA synthesis. Overall, lipid conjugation results in oral bioavailability, higher intracellular concentrations of CDV-PP, lower plasma concentrations of CDV (Cundy 1999), and increased antiviral potency across the dsDNA viruses. Significantly lower peak plasma concentrations of CDV and the inability of CMX001 to be a substrate for organic anion transporter 1 (OAT1) have effectively eliminated the risk of CDV-like nephrotoxicity.

The antiviral activity of CMX001 has been characterized *in vitro* in cell culture systems and *in vivo* in multiple animal models. In cell culture assays, CMX001 has demonstrated multiples of increased activity versus CDV against dsDNA viruses, including orthopoxviruses,

polyomaviruses, human herpesviruses, human papillomaviruses, and AdV. Against variola major, the causative agent of smallpox, CMX001 was approximately 250-fold more potent than CDV in inhibiting viral replication. Compared to CDV, CMX001 was 800-fold more active against BKV, more than 400-fold more active against CMV and 65-fold more active against AdV. *In vivo*, the antiviral activity of CMX001 has been characterized in animal models of orthopoxvirus, herpesvirus, and AdV infection. In each model, a dose of CMX001 was identified that provided protection against mortality from a lethal viral inoculum.

Compared to CDV, CMX001 has significantly increased antiviral activity against all dsDNA viruses of importance to the transplant community. In particular, CMX001 is highly active against CMV with an *in vitro* EC_{50} (50% of the effective concentration) of 0.0009 μM (Beadle 2002). For additional information, see the current edition of the CMX001 Investigator's Brochure.

Due to the broad spectrum antiviral activity of CMX001 and positive results from completed clinical studies, Chimerix is pursuing the development of CMX001 for the prevention and/or treatment of dsDNA virus infections in at-risk populations, including CMV prevention in the HSCT population.

6.2.1. Preclinical Pharmacokinetics and Metabolism of CMX001

The pharmacokinetics (PK) and metabolism of CMX001 were evaluated in single and multiple dose studies in mice, rats, rabbits, and monkeys. CMX001 was readily absorbed and widely distributed after oral administration, with lower systemic plasma concentrations of CMX001 in monkeys relative to those measured in rodents and rabbits. Following repeat daily dosing of CMX001, exposure to CMX001 remained consistent, while CDV concentrations were 2- to 3-fold higher at the end of the dosing period, relative to those observed on the first day of dosing, likely due to the long terminal phase elimination half-life (t1/2elim) observed for CDV after oral administration of CMX001, and the resulting additive effect of subsequent oral doses of CMX001.

The biotransformation of CMX001 was studied in *in vitro* hepatic systems and in animals. The qualitative *in vitro* metabolic profile was similar across species, and several metabolites were identified in plasma and excreta. CYP4F2 is the primary enzyme responsible for cytochrome P450 (CYP)-mediated metabolism of CMX001, with no significant contribution by other CYPs. Weak (CYP1A2, 2C9, 2C19, 2D6) to moderate (CYP3A4/5, 2B6, 2C8) inhibition of CYP enzymes by CMX001 was observed in human liver microsomes. No significant induction of CYP enzymes 1A2, 2C9, and 3A by CMX001 was observed after incubation with freshly isolated and cultured human hepatocytes.

Moderate inhibition of the drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3 by CMX001 was observed *in vitro*. CMX001 was not a substrate for P-gp or BCRP; however, CMX001 was a substrate for OATP1B1 or OATP1B3. CMX001 was not a substrate for the kidney transporters, organic anion transporter 1 (OAT1) or OAT3. CMX001 was a weak inhibitor of OAT1.

For additional information on the preclinical PK and metabolism of CMX001, see the current edition of the CMX001 Investigator's Brochure.

6.2.2. Summary of Toxicology Studies with CMX001

The toxicity profile of CMX001 has been defined in studies in rodents and non-rodents. Safety pharmacology studies revealed no important adverse pharmacological effects on the cardiovascular, respiratory, CNS, renal, or GI systems. CMX001 was negative for mutagenicity and clastogenicity in the Ames and *in vivo* mouse micronucleus assays, but was positive in the *in vitro* chromosome aberration assay. Dose-limiting GI events, specifically gastropathy and enteropathy/enteritis, were observed following daily oral dosing in rodents and non-rodents.

In a 13-week study in rats, irreversible decreases in testes and epididymides weights, as well as hypospermia, were observed at doses of CMX001 below those administered to humans. In addition, in the same 13-week study in rats, mammary gland adenocarcinomas and squamous cell carcinomas were noted around Week 9 of the posttreatment period, or approximately 22 weeks after the initiation of CMX001 dosing. The appearance of tumors after only 13 weeks of drug exposure is notable since rats, although prone to developing spontaneous mammary adenocarcinomas, typically do not do so until much later (around year 2) in life. Although an increased incidence of rodent carcinogenesis is common to other agents in the nucleoside/ nucleotide class of drugs, they have typically been observed only after much longer periods of treatment. Similar tumors (mammary gland and squamous cell/zymbal gland) were also observed in rats within approximately the same time frame (weeks 19 to 21) following IV administration of CDV, which shares the active moiety of CMX001, CDV-PP (see the Vistide® for injection package insert). The incidence of tumors was dose-related with the lowest doses of CMX001 associated with tumors producing exposures in rats that were lower than anticipated exposures in humans. Based on these findings, CMX001 should be considered a potential carcinogen.

In a 39-week study in monkeys with a 26-week recovery period, changes in menstrual cycle (extended cycles, decreased number of cycles) and decreased body weight were observed in females at the highest dose (25 mg/kg). Dose-related testicular, epididymal, and seminal vesicle/prostate changes, including decreased size, weight, and atrophy, resulting in decreased sperm count and motility, were observed in all treated males. Findings in both sexes included mild alanine aminotransferase (ALT) increases (2- to 4-fold from baseline, all dose levels) that reversed during the posttreatment recovery period with no histopathological correlate and minimal to mild karyomegaly of kidney tubular epithelial cells (at doses ≥ 15 mg/kg). No neoplastic or preneoplastic lesions were observed in the monkeys through the final sacrifice at the end of 26-week recovery period. Similarly, tumors were not observed in a 52-week study of CDV in monkeys (see Vistide® package insert).

Reproductive study findings included embryotoxicity and fetal morphological changes in rabbits, and decreased fertility, embryonal viability, and growth and development of pups with delayed sexual maturation in rats. Significant concentrations of CDV, but not CMX001, were present in rat maternal milk and fetal plasma but not in plasma obtained from nursing pups.

For additional information on the toxicology of CMX001, see the current edition of the CMX001 Investigator's Brochure.

6.2.3. Summary of Clinical Experience with CMX001

Completed studies with CMX001 in humans include six Phase 1 clinical studies in healthy subjects:

- a first-in-human, single- and multiple-dose, dose escalation study (Study CMX001-102);
- a single-dose, comparative bioavailability (tablet vs. solution) and food-effect study (Study CMX001-103);
- a Thorough QT (TQT) study evaluating the electrocardiogram (ECG) effects of CMX001 (Study CMX001-108);
- an absorption, metabolism, and elimination (AME) study in healthy male subjects (Study CMX001-112);
- a single dose, drug-drug interaction study with oral and intravenous (IV) midazolam (MDZ) (Study CMX001-113), and
- a study evaluating the effect of food as low- and moderate-fat content meals on CMX001 tablet bioavailability (Study CMX001-114).

Additional completed studies include:

- a Phase 1b, multiple-dose study in renal and stem cell transplant patients infected with BKV (Study CMX001-104);
- a Phase 1, single-dose study in subjects with moderate and severe hepatic impairment and in healthy control subjects with normal hepatic function (Study CMX001-106);
- a Phase 2 CMV prevention study in allogeneic CMV seropositive (R+) HSCT recipients (Study CMX001-201);
- a Phase 2 study evaluating CMX001 as a preemptive treatment for AdV disease following HSCT (Study CMX001-202), and
- an expanded access study of CMX001 for the treatment of serious or life-threatening infections caused by dsDNA viruses (Study CMX001-350).

CMX001 has also been administered to more than 200 patients with serious or life-threatening disease due to dsDNA virus infection under Emergency Investigational New Drug (EIND) regulations in the USA and under local equivalent regulations outside the USA.

To date, CMX001 has been given to more than 200 healthy or otherwise non-virally-infected subjects in clinical pharmacology (Phase 1) studies involving administration of single or limited (≤ 4) multiple doses. CMX001 has also been used as treatment, prevention, or preemption in more than 600 subjects infected with CMV and other dsDNA viruses in Phase 2 clinical studies and under expanded access regulations for periods of up to 6 months and longer in a few cases.

6.2.3.1. Summary of Clinical Pharmacology (Phase 1) Studies with CMX001

Study CMX001-102 was a single- and multiple-dose, first-time-in-human, dose-escalation study of the safety, tolerability, and PK of CMX001 in healthy subjects. A solution formulation of CMX001 was administered to subjects in a total of nine single ascending dose cohorts and five

multiple ascending dose cohorts. Each cohort (single- and multiple-dose) enrolled six subjects randomized 2:1 (active:placebo). Subjects in the single-dose cohorts received single doses of CMX001, ranging from 0.025 to 2 mg/kg, or placebo. Subjects in the multiple-dose cohorts received a total of three doses of CMX001, ranging from 0.1 to 1.0 mg/kg, or placebo at 6-day intervals (q6d). Peak plasma concentrations (Cmax) and systemic exposure (as measured by area under the plasma concentration-time curve [AUC]) for both CMX001 and CDV increased approximately in proportion to dose. The Cmax for CMX001 occurred about 2 to 3 hours after administration while that for CDV occurred about 9 to 15 hours after administration. At the 1 mg/kg dose level, t1/2elim for CMX001 was 27 hours and that for CDV was 65 hours. CDV was detectable in pre-dose plasma samples on Days 6 and 12 indicating a long half-life. CMX001 was not quantifiable in the urine.

Study CMX001-103 was an open-label, randomized, three-way crossover study to evaluate the comparative bioavailability of CMX001 tablet and solution formulations and the effect of food as a high-fat meal on the bioavailability of the CMX001 tablet formulation in healthy subjects. Each subject received three single 40 mg doses of CMX001 separated by a 14-day washout interval. Oral administration of CMX001 as a tablet resulted in systemic exposures that were about 13% lower than exposures following administration of the same dose as an oral solution. Mean Cmax was reduced by 48% and systemic exposure (as measured by mean area under the plasma concentration versus time curve from time zero to infinity [AUCinf]) was reduced 28% when CMX001 was given to subjects following a high fat meal as compared to fasted.

Study CMX001-106 was an open-label, single-dose study that evaluated the effect of moderate to severe hepatic impairment on the safety, tolerability, and PK of CMX001. Subjects with moderate hepatic impairment (corresponding to Child-Pugh-Turcotte Class B) and matched healthy control subjects with normal hepatic function were enrolled and dosed first, each receiving a single 200 mg dose of CMX001 under fasting conditions. The safety, tolerability and PK data from these subjects was reviewed prior to initiating dosing in subjects with severe hepatic impairment (corresponding to Child-Pugh-Turcotte Class C). The overall mean plasma concentration-time profiles for CMX001 and CDV were similar between all study groups. Mean CMX001 Cmax values in the severe hepatic impairment group (n=8 subjects) were lower when compared to both the healthy control subjects (n=8 subjects) and the moderate hepatic group (n=8 subjects), and the exposure (AUCinf) to CMX001 was greatest in the severe hepatic impairment group; however, these difference were not clinically meaningful. Peak concentrations (Cmax) and exposure (AUCinf) to CDV were similar between the healthy and hepatic impairment groups and the metabolite to parent AUCinf ratios of CDV to CMX001 were also consistent between study groups. Severe hepatic impairment resulted in longer time to peak plasma concentrations (Tmax) for CDV compared to healthy subjects, but not for CMX001. Hepatic impairment did not affect the percentage of CMX001 bound to plasma protein. Based on these PK data, no dose adjustment is recommended for subjects with hepatic impairment at doses up to 200 mg.

Study CMX001-108 was a Thorough QT (TQT) study designed to evaluate the ECG effects of single doses of CMX001 administered at clinical (200 mg) and supratherapeutic (350 mg) dose levels compared to single doses of placebo and moxifloxacin (positive control) in healthy subjects. This two-part study consisted of a lead-in cohort to evaluate the safety and tolerability of CMX001 when administered as the supratherapeutic dose, followed by a traditional TQT study in a second cohort of subjects. Consistent with ICH E14 guidance on the clinical

evaluation of QT/QTc interval prolongation, the primary study endpoint was the time-matched change from baseline in QT interval corrected for heart rate, placebo-adjusted, based on Fridericia's correction method (i.e., delta-delta QTcF). The therapeutic and supratherapeutic doses of CMX001 did not prolong the QTcF interval to a clinically relevant degree. The upper bound of the two-sided 90% confidence interval (CI) of the differences in change from baseline least-square means between the therapeutic dose of CMX001 and placebo and between the supratherapeutic dose of CMX001 and placebo were < 10 milliseconds (i.e., the accepted threshold of concern) at all postdose time points. The assay sensitivity was adequate to detect a clinically relevant prolongation in QTcF; thus, it was concluded that CMX001 had no effect on cardiodynamic/ECG parameters at either dose.

Study CMX001-112 was an AME study designed to evaluate the mass balance and metabolite profiles of CMX001 following administration of a single 200 mg dose of CMX001 containing ~ 100 μCi of ^{14}C-radiolabeled CMX001 to healthy male subjects. Good recovery of radioactivity was achieved in all subjects (≥ 90%), with approximately 50% of the radioactivity excreted in urine and 40% excreted in feces. The major CMX001-derived metabolites circulating in plasma were CMX103 [3-hydroxypropyl ester of CDV], CMX064 [4-(3-propoxy)butanoic acid ester of CDV], and CDV. Based on AUC using nanogram-equivalent concentrations of each metabolite, the AUC of CMX103 and CMX064 comprised approximately 32% and 23%, respectively, of total CMX001-derived radioactivity AUC through 24 hours postdose. Exposures to these metabolites have been previously characterized in animals, each having approximately equal or greater exposure in at least one of the primary toxicology species compared to that expected after administration of CMX001 at doses up to 200 mg. The major drug-derived metabolites found in urine in order of decreasing percent dose excreted were CMX103 (21%), CDV (10%), CMX064 (10%), and CMX104 [(3-propoxy)acetic acid ester of CDV] (3%). The major drug-derived metabolites found in feces in order of decreasing percent dose excreted were CDV (32%) and CMX103 (6%).

Study CMX001-113 was an open-label, randomized, two-period crossover study designed to evaluate the potential for and extent of any interaction that may be mediated through CMX001 inhibition of CYP3A activity. The effect of CMX001 coadministration on the PK of MDZ, which is a well-established CYP3A probe substrate, was evaluated following coadministration of CMX001 with both oral and IV single doses of MDZ. The overall mean concentration-time profiles of MDZ were similar when MDZ was administered alone and in combination with CMX001. Based on standard bioequivalence criteria (i.e., 90% CIs of geometric least-squares mean (GLM) ratios within 80% to 125%), CMX001 did not have a meaningful impact on the PK of IV or oral (PO) MDZ based on Cmax, area under the plasma concentration-time curve from time zero to time of last measurable plasma concentration (AUClast), area under the plasma concentration-time curve from time zero to 24 hours (AUC0-24), and AUCinf. Data obtained following administration of IV and PO MDZ allowed estimation of Fg (fraction of MDZ escaping gut metabolism) and Fh (fraction of MDZ escaping hepatic metabolism). Consistent with the primary analysis, mean estimates of Fg and Fh were comparable when MDZ was administered alone and in combination with CMX001. In addition, exposures of the primary metabolite of MDZ, 1-hydroxymidazolam, were comparable when MDZ was administered orally alone or in combination with CMX001. Consistent systemic exposures of CMX001 and CDV were observed when CMX001 was coadministered with IV or PO MDZ. Exposure concentrations of CMX001 and CDV were comparable to those achieved in prior studies in

healthy subjects, supporting the fact that anticipated levels of exposure were attained for the purpose of drug interaction assessment. Based on these results, no interaction would be expected between CMX001 and other drugs that are CYP3A substrates. Moreover, given that CMX001 was a comparable or weaker inhibitor of the other CYP isozymes evaluated *in vitro*, see Section 6.2.1, other drug-drug interactions mediated through CMX001 inhibition of CYP are also considered unlikely.

Study CMX001-114 was an open-label, randomized, single-dose, four-period, crossover study designed to evaluate the effect of food on the bioavailability of CMX001 following administration of single 200 mg doses using a tablet formulation with a low-fat meal (comprising approximately 6% of its total caloric value from fat) and with a moderate fat meal (comprising approximately 22% of its total caloric value from fat), as compared with administration under fasting conditions. The study also evaluated the relative bioavailability of CMX001 from the tablet formulation and a new oral suspension formulation under fasting conditions. Results from this study indicate that administration of CMX001 with a low-fat meal or a moderate-fat meal reduced both the overall systemic exposure (AUC) and the Cmax of plasma CMX001. The magnitude of exposure reduction associated with the moderate-fat meal was slightly greater than that observed with the low-fat meal. Compared with administration in the fasted stated, administration of CMX001 with the low-fat meal resulted in a 27% decrease in CMX001 exposure (as measured by AUCinf) and a 31% decrease in Cmax. Administration of CMX001 with a moderate fat meal resulted in a 33% decrease in CMX001 exposure (as measured by AUCinf) and a 50% decrease in Cmax. GLM ratios for AUC and Cmax were below the lower end of the standard bioequivalence bounds (i.e., below 80%) following administration with low- and moderate-fat meals. The preliminary results from this study are consistent with the results from Study CMX001-103, in which coadministration of CMX001 with a high-fat meal also significantly decreased mean Cmax and systemic exposure (AUCinf).

6.2.3.2. Study CMX001-201

Study CMX001-201 was a multicenter, randomized, double-blind, placebo-controlled, dose-escalation study of the safety, tolerability, and ability of CMX001 to prevent or control CMV infection in R+ HSCT recipients. Subjects were randomized 3:1 to receive either CMX001 or placebo in five successive cohorts as shown below:

- Cohort 1: CMX001 40 mg or matching placebo administered QW
- Cohort 2: CMX001 100 mg or matching placebo administered QW
- Cohort 3: CMX001 200 mg or matching placebo administered QW
- Cohort 4: CMX001 200 mg or matching placebo administered BIW initially, reduced to 200 mg QW for ongoing subjects following the recommendation of the Data and Safety Monitoring Board (DSMB) for CMX001-201
- Cohort 4A: 100 mg CMX001 or matching placebo administered BIW

All doses of study drug were to be administered in the fasted state, with subjects refraining from solid food or fat-containing beverages for a minimum of 4 hours prior to study drug administration.

Allogeneic stem cell transplant recipients ≥ 18 years of age who were CMV seropositive at the time of transplant were eligible for enrollment. After engraftment and randomization to CMX001 or placebo, the subjects received their first dose of study drug within 35 days posttransplant, inclusive. Subjects were stratified based on the presence or absence of CMV viremia at screening and the presence or absence of acute graft versus host disease (aGVHD) requiring treatment at baseline. Depending on the date treatment was initiated, subjects who completed the treatment phase of the study received from 9 to 11 doses (QW cohorts) or from 18 to 22 doses (BIW cohorts) of study drug.

Two-hundred and thirty-nine (239) subjects were enrolled into this study, of which 230 subjects were evaluable. Weekly monitoring for CMV viremia was performed using a central virology laboratory (Viracor-IBT Laboratories) and a plasma-based quantitative PCR assay (5500 Cytomegalovirus CMV Real-time qPCR Test, lower limit of detection [LLOD] = 100 copies/mL, lower limit of quantitation [LLOQ] = 200 copies/mL, all results reported as multiples of 100 copies/mL). PrT according to institutional guidelines was permitted for evidence of CMV viremia by PCR testing; when instituted GCV was the most frequent choice. If subjects initiated anti-CMV PrT, they were discontinued from study drug treatment and followed for an additional 4 weeks posttreatment. Subjects who completed the full treatment course were followed for an additional 8 weeks for CMV status and safety monitoring.

Safety assessments including clinical laboratory evaluations (biochemistry, hematology, and urinalysis), vital signs measurements, 12-lead ECGs, and physical examination were performed prior to initiating treatment to establish baseline and at periodic intervals (typically weekly) throughout the treatment phase and during the posttreatment follow-up period. AEs, serious adverse events (SAEs), and AEs of special interest (AEOSIs) (including nephrotoxicity, neutropenia, and ocular hypotony), the development or progression of GVHD, in particular, GVHD of the intestine (GI-GVHD), and concomitant medication use were recorded.

Due to an excess of SAEs associated with diarrhea during the dosing of Cohort 4, Chimerix subsequently convened an ad hoc meeting of the DSMB for the study and discontinued further enrollment in this cohort. After review of the data, the DSMB decided to dose reduce the subjects still on study drug from 200 mg BIW to 200 mg QW. Chimerix also implemented a Safety Monitoring and Management Plan (SMMP) across all CMX001 studies, including during the dosing of Cohort 4 and in Cohort 4A, which directed investigators to carefully monitor for GI and hepatic events, to thoroughly investigate these events, and to systematically interrupt study drug for subjects with ≥ Grade 3 GI AEs, as well as certain hepatic laboratory abnormalities.

6.2.3.2.1. Summary of Efficacy Results

The primary efficacy measure was treatment failure, defined as the diagnosis of CMV disease at any time during the treatment period or CMV viremia > 200 copies/mL at the end of treatment with study drug. Secondary efficacy endpoints included the following: occurrence and time to onset of CMV viremia, change from baseline in CMV viremia, peak CMV viremia, occurrence and time to onset of CMV disease, subject dropout rate and time to study discontinuation, and the development of AdV disease, BKV DNA (viruria and viremia), or EBV-associated syndromes.

All subjects who received at least one dose of drug/placebo and had at least one efficacy evaluation postbaseline were included in the primary analysis, regardless of their CMV viremia

status (negative or positive) at baseline (modified Intent-to-Treat [mITT] population). Results for the pooled CMX001 cohorts and for each cohort separately were analyzed versus that for pooled placebo.

The antiviral efficacy results from Study CMX001-201 are summarized in Table 3.

Significantly greater antiviral activity was observed in the ≥ 100-mg per week CMX001 treatment groups compared with the pooled-placebo group. In several analyses, the CMX001 100 mg BIW treatment group (Cohort 4A) showed statistically and clinically significant antiviral activity when compared with the pooled-placebo group. While the 200 mg QW and 100 mg BIW treatment groups (Cohorts 3 and 4A, respectively) had similar efficacy in many analyses, visual inspection of smooth-line scatter plots suggests that the BIW dose group may have been more effective in suppressing CMV viremia in subjects who were either CMV viremia negative or had low-level CMV viremia at the start of treatment.

In the largest CMX001 treatment group of the study (100 mg BIW, Cohort 4A), there was a statistically significant reduction versus the pooled-placebo group in the proportion of subjects who achieved the primary endpoint (incidence of CMV disease at any time during treatment or CMV viremia at the end of treatment) when analyzed for the mITT population (p-value = 0.002, Fisher exact test). This was also observed with the negative randomization strata of the sensitivity analyses (i.e., CMV status at baseline and the presence or absence of aGVHD requiring treatment).

Table 3: Study CMX001-201: Summary of Antiviral Efficacy Results

Protocol Specified Analyses Population	Results			
	Dose	% CMV Event Rate		*P* value
		CMX001	Placebo	
Primary Efficacy Analysis: CMV viremia > 200 copies/mL at end of treatment or diagnosis of CMV disease during treatment				
mITT *(P value derived from Cochran-Mantel-Haenszel test adjusted for CMV modified strata.)*	Pooled CMX001 (N=171)	43 (25.1%)	22 (37.3%)	0.041
	100 mg BIW (N=50)	5 (10.0%)		0.001
CMV modified strata: negative *(P value derived from Fisher exact test relative to pooled placebo group)*	All CMX001 (N=133)	21 (15.8%)	14 (29.8%)	0.052
	100 mg BIW (N=41)	2 (4.9%)		0.002
	Combined (100 mg QW, 200 mg BIW, 100 mg BIW) (N=86)	8 (9.3%)	10 (31.3%)	0.007
aGVHD modified strata: negative	All CMX001 (N=162)	41 (25.3%)	17 (32.1%)	NS[a]
	100 mg BIW (N=46)	4 (8.7%)		0.006
Other Efficacy Endpoints: Frequency of CMV disease, initiation of excluded CMV Medications, or CMV viremia ≥ 1,000 copies/mL at any time during treatment				
mITT (*P value derived using Fisher's exact test relative to pooled-placebo group)* CMV modified strata: negative	200 mg QW	4 (13.8%)	18 (38.3%)	0.036
	200 mg BIW	3 (13.6%)		0.050
	100 mg BIW	5 (12.2%)		0.007
Exploratory Endpoint: Frequency of CMV viremia ≥ 1,000 copies/mL at any time during treatment				
mITT (*P value derived using Fisher's exact test relative to pooled-placebo group)* CMV modified strata: negative	Pooled CMX001	8 (6.0%)	15 (31.9%)	<0.001
	100 mg QW	2 (8.7%)		0.040
	200 mg QW	2 (6.9%)		0.012
	200 mg BIW	0		0.002
	100 mg BIW	0		<0.001

[a] NS = not statistically significant at α <0.05.

With the exception of the 40 mg QW treatment group (Cohort 1), all other CMX001 treatment groups demonstrated antiviral activity as measured by a decreased incidence of CMV events. Depending upon the analysis, activity appeared to increase with dose and/or dose frequency.

Antiviral activity as measured by the most sensitive biomarker of infection (i.e., the incidence of CMV viremia by polymerase chain reaction (PCR) assay either at 100 copies/mL or at 1,000 copies/mL at any time during treatment) was observed in the ≥ 100-mg per week CMX001 treatment groups.

The higher CMX001 treatment groups (200 mg QW, 100 mg BIW, and 200 mg BIW) within the modified CMV viremia negative stratum were superior to the pooled-placebo group in reducing the proportion of subjects reaching a composite endpoint of the initiation of anti-CMV therapy or CMV disease or CMV viremia > 1,000 copies/mL. There was a trend in subjects who received CMX001 at doses ≥ 100 mg per week versus placebo in preventing CMV events, and the 40 mg QW dose was inactive, providing evidence for a dose response.

The results from the incidence and "time-to" analyses suggest that treatment with CMX001 at doses ≥ 100 mg per week were significantly superior to placebo in preventing the emergence of CMV viremia during both the treatment and posttreatment follow-up periods supporting the further evaluation of CMX001 treatment for the prevention of CMV infection. Furthermore, results from the frequency and time from first dose to onset of CMV viremia during the entire study period suggest that rebound viremia and/or disease following the end of treatment was not a significant issue in this study.

No UL97 or UL54 mutations proven to confer phenotypic drug resistance *in vitro* were detected in CMX001-treated subjects. The UL54 mutation R1052C appeared in association with viral emergence in 2 CMX001-treated subjects receiving QW dosing and was present at baseline for one subject who experienced virologic failure (3/171 subjects receiving CMX001 treatment). Recombinant phenotyping demonstrated that the sequence variant R1052C conferred no detectable resistance to CMX001, CDV, GCV, or FOS.

CMX001 treatment appeared to reduce the incidence of BKV events, despite a high incidence of BK viruria in subjects at the time of enrollment. Compared with placebo, this benefit was seen in a reduction of reported BKV-related bladder AEs (i.e., HC or hematuria) and a decrease in the overall incidence of confirmed, new onset microscopic hematuria noted during the treatment period in BK viruric subjects. In subjects with BK viruria randomized to CMX001, serum creatinine remained stable during the period of follow-up for the majority of subjects. BKV positive subjects randomized to placebo had twice the incidence of Grade 2 or greater increases in serum creatinine (34% vs. 14%).

Insufficient numbers of subjects who developed CMV disease, AdV disease, or EBV disease were observed to allow efficacy conclusions to be drawn.

6.2.3.2.2. Summary of Safety Results

There was a high frequency of AEs in the study population, consistent with the complexity of the underlying conditions of the subjects. None of the deaths that occurred during the study, which were distributed evenly across treatment groups, including placebo, were considered related to CMX001 by the investigators. Most of the deaths resulted from disease relapse or transplant-related complications.

Overall, more AEs were reported by subjects who received CMX001 BIW as compared to subjects who received CMX001 QW or placebo. CMX001 at doses of 40 and 100 mg QW had tolerability profiles broadly similar to that of placebo in terms of AEs and laboratory abnormalities. Of the most common AEs (i.e., those reported in ≥ 20% of subjects within ≥ 1 cohort), GI-associated events (including diarrhea, nausea, vomiting, and abdominal pain), increased ALT, and hyperglycemia generally increased in frequency with increasing dose of CMX001.

The most frequently reported SAEs were diarrhea and aGVHD, both of which were reported at a much higher frequency among CMX001 200 mg BIW-treated subjects compared with CMX001 QW-treated and placebo-treated subjects. While the rate of GI and GVHD AEs noted among CMX001 100 mg BIW recipients was higher than placebo recipients, most events were mild or moderate in intensity and typically responded to dose interruption. The rate of discontinuation for any AE was highest in the 40 mg QW and 200 mg BIW dose groups, and the rate of discontinuation for GI AEs overall was highest in the 200 mg BIW dose group. In the CMX001 100 mg BIW group, 10% of subjects discontinued CMX001 due to GI AEs.

The increase in AE reporting of GVHD for subjects who received CMX001 BIW was associated with an increased reporting of GI-GVHD, both in terms of frequency and severity, and was not associated with changes in the frequency and severity of GVHD of the skin or increases in bilirubin in subjects treated with CMX001 versus subjects treated with placebo. Analyses of these findings suggest that this increased reporting of GVHD was prompted by the occurrence of

GI symptoms commonly ascribed to a presumptive diagnosis of GVHD, but were in fact due to a CMX001-related diarrheal event. This increase in frequency and severity was not noted in the CMX001 QW cohorts, prior to the implementation of the SMMP during Cohort 4, which may have introduced a reporting bias. The increased frequency of clinical GVHD diagnoses led to more subjects being presumptively treated with corticosteroids, which, in turn, had an impact on the type of metabolic side effects (i.e., hyperglycemia) experienced by subjects receiving CMX001.

Few clinical hepatobiliary AEs were reported in association with CMX001 treatment, and most were mild or moderate in severity. No case of drug-induced liver injury (DiLI) clearly attributable to CMX001 was noted during the course of the study. One event of liver injury considered by the investigator to be possibly associated with the administration of CMX001 at 200 mg BIW was reported; this event resolved after discontinuation of CMX001.

A dose-related increase in ALT was noted in association with CMX001 therapy. The ALT increases were typically ≤ Grade 2 and 2- to 4-times baseline values, occurring between Weeks 2 and 4 of dosing, at CMX001 doses of ≥ 200 mg per week. These increases typically resolved after completion of CMX001 therapy and do not appear to be of toxicologic importance, based upon the preclinical and clinical safety profiles of the drug.

A small proportion of subjects receiving CMX001 demonstrated increases in serum bilirubin concentrations during the study, with no apparent dose response. Of note, more subjects (27%) in the 200 mg BIW group received total parenteral nutrition (TPN) during the course of the study than in the other treatment groups: 10% of subjects in the 200 mg QW and 100 mg BIW groups, and ≤ 5% of subjects in the 40 mg QW, 100 mg QW, and placebo groups. Administration of TPN may have contributed in some of the cases of bilirubin increases. Almost all incidences of bilirubin increases were not associated with concomitant ALT increases.

There was no indication of nephrotoxicity or myelotoxicity associated with CMX001, regardless of dose and dosing frequency.

6.2.3.3. Study CMX001-202

Study CMX001-202 was a Phase 2, multicenter, randomized, placebo-controlled PrT study in HSCT recipients with asymptomatic AdV viremia. Study participants were randomized to receive up to 12 weeks treatment with CMX001 or placebo under double-blind conditions, followed by a 4-week posttreatment follow-up period. Subjects assessed as treatment failures at any time during the randomized treatment phase of the study were offered open-label treatment with CMX001 for a period of up to 12 weeks, as an alternative to initiating SoC therapy. Subjects who developed AdV disease prior to initiating blinded study treatment were also offered open-label treatment with CMX001 under certain circumstances. Adult subjects were randomized to receive 100 mg BIW or 200 mg QW of CMX001 (not to exceed 4 mg/kg/week) or placebo for 6 to 12 weeks. Pediatric subjects (i.e., < 18 years old) were randomized to receive 2 mg/kg BIW or 4 mg/kg QW of CMX001 (not to exceed 200 mg/week) or placebo for 6 to 12 weeks. Assignment to dosing frequency (i.e., QW vs. BIW) was unblinded while treatment assignment (i.e., CMX001 vs. placebo) was double-blinded. Final safety and efficacy results for this study are summarized in the Investigator's Brochure for CMX001.

6.2.3.4. Study CMX001-350

Study CMX001-350 was a multi-center, open-label, expanded access study of the safety and antiviral activity of CMX001 in subjects with serious or life-threatening disease or condition caused by infection with a dsDNA virus. Adults and adolescent subjects received 100 mg BIW or 200 mg QW of CMX001 (not to exceed 4 mg/kg/week) for up to 6 months. Pediatric subjects (i.e., ≤ 12 years old) received 2 mg/kg BIW or 4 mg/kg QW of CMX001 (not to exceed 200 mg/week) for up to 6 months. The study has completed the clinic phase with a total of 210 subjects enrolled. Analysis of the study results is ongoing.

Subjects must have had a serious or life-threatening disease at entry and to have failed other available treatment options to qualify for enrollment in this study. Therefore, as might be expected, a large number of subjects in this severely compromised patient population have experienced at least one SAE and almost all SAEs include multiple terms. With the exception of diarrhea, with or without associated GI signs and symptoms, the vast majority of AEs were assessed as unrelated to CMX001. No new safety signals were identified in this study. Final safety and efficacy results for this study are summarized in the Investigator's Brochure for CMX001.

6.2.3.5. Additional Clinical Experience with CMX001 (EINDs)

CMX001 has been administered to more than 200 patients under EIND provisions in the USA and local equivalent regulations outside the USA. Most patients have been recipients of solid organ transplants or HSCT who had emergence of a serious viral infection caused by CMV, AdV, EBV, and/or BKV. Patients have been treated with doses of CMX001 ranging from approximately 1 mg/kg QW up to approximately 5 mg/kg or 350 mg BIW in an open-label clinical setting. Improvements in disease measurements in patients with CMV viremia, EBV disease, disseminated AdV infection, AdV pneumonia, BKV HC, and disseminated vaccinia virus infection have been observed or reported.

PK data are available from 111 EIND patients administered doses of up to 4 mg/kg CMX001 QW or BIW, as fixed or weight-adjusted doses. Approximately 40% of these EIND patients had moderate to severe renal impairment (Stage 3 to 5). There was no correlation between creatinine clearance and CMX001 clearance, indicating that renal impairment did not affect CMX001 exposure or elimination. As expected, higher CDV exposure (because of reduced clearance) was observed in the renal-impaired patients. Because the Cmax for CDV following administration of CMX001 remains more than 10-fold below that reported in the Prescribing Information for Vistide® for injection, the potential for CDV-like nephrotoxicity is considered to be low. Therefore, no dose adjustment is recommended for patients with renal impairment. However, because of the potential for CDV to accumulate during dosing with CMX001 in patients with end-stage renal disease (ESRD, creatinine clearance < 15 mL/min), dosing with CMX001 is not recommended in the ESRD population. Consequently, subjects with renal insufficiency, as evidenced by an eGFR < 15 mL/min or requiring renal dialysis, are excluded from participating in the current study.

For additional information on the clinical experience with CMX001, see the current edition of the CMX001 Investigator's Brochure.

6.3. Overview of CMX001-301 Study Design

Chimerix is developing CMX001 for the prevention of clinically significant CMV infection following HSCT. The results from Study CMX001-201 show that BIW dosing of CMX001 is the most active tested dose in preventing CMV reactivation, while both QW and BIW dosing regimens had activity in the prevention of CMV infection or disease. The safety profile of CMX001 at doses up to 200 mg per week is considered acceptable in the context of the benefit derived from the prevention of CMV reactivation, particularly as the identified side effects (namely GI symptoms and ALT increases) are easily managed through dose interruption/ reduction.

The current study is designed as a randomized, double-blind, placebo-controlled, parallel-group comparison of CMX001 (administered as 100 mg BIW) in CMV-seropositive adults following HSCT. The following sections outline key subject selection criteria, the rationale for selecting the CMX001 dose regimen to be evaluated, the primary and key secondary endpoints, key protocol design choices, and the safety data collection and monitoring plan.

6.3.1. Rationale for Subject Population

The current study will enroll recipients of allogeneic HSCT who have antibody evidence of prior CMV infection, and are thus at increased risk of CMV reactivation during the first 100 days following transplant.

Only subjects who are CMV viremia negative by PCR testing during screening will be selected for participation in the study, as subjects who are CMV viremia positive by PCR do not qualify for prevention. Subjects who were CMV viremia negative at screening, but who are subsequently found to have been CMV viremic on the FDD, will be continued in the study. Based on the subject population enrolled in Study CMX001-201, it is anticipated that subjects who are CMV viremia positive and enroll into the study will make up less than 5% of the total population enrolled.

Similar to the subject population in Study CMX001-201, subjects will be allowed to enroll in the current study regardless of the source or type of graft, and regardless of conditioning regimen. This population is purposely inclusive in order to reflect the actual make-up of at-risk patients post-HSCT and to allow for data-driven generalizability of the study results. During randomization, subjects will be stratified within an investigative center, based on their likelihood for progression to clinically significant CMV infection, i.e., a “lower likelihood” versus a “higher likelihood” of progression. Subjects who receive a matched, related, non-T-cell depleted graft (e.g., excluding cord blood), who do not have aGVHD, who have not received anti-thymocyte globulin (ATG) or alemtuzumab, and who are not receiving high-dose (≥ 1 mg/kg prednisone equivalent) systemic steroids will be stratified in the “lower likelihood” group. All other subjects will be stratified in the “higher likelihood” group.

6.3.2. Rationale for CMX001 Dose Regimen

As described previously, based on the results of Study CMX001-201, a range of CMX001 doses were characterized as having both antiviral activity and acceptable tolerability in adults following HSCT. This section will discuss the rationale for the selection of the CMX001 dose regimen (100 mg BIW) to be evaluated in the current study.

The lower range of CMX001 doses is bound by 40 mg QW, which is considered ineffective, given that the efficacy results in this cohort were not different from placebo, regardless of the endpoint considered. The highest evaluated CMX001 dose, 200 mg BIW was not sufficiently well tolerated for prevention purposes, due to the incidence of severe diarrhea and events reported as GVHD of the intestine. Other intermediate doses of CMX001 (100 mg QW, 200 mg QW, and 100 mg BIW) were generally well tolerated. Overall, weekly doses of CMX001 ranging from 100 to 200 mg showed antiviral activity and were generally tolerable, and BIW dosing appeared to provide antiviral activity advantage versus QW dosing.

Efficacy analyses suggest that a dose of 100 mg QW may be slightly less effective than higher doses, particularly when clinically relevant endpoints, including the need to initiate preemptive therapy, are considered. In addition, CMX001 will be administered with food in the current study, rather than the fasted state, which may decrease drug exposure (in Study CMX001-114, exposure to CMX001, as measured by AUCinf, was reduced by 27% when the drug was administered to healthy subjects with a low-fat meal and by 33% when administered with a moderate-fat meal; see Section 6.2.3.1). By contrast, a weekly 200 mg dose of CMX001 (either as 200 mg QW or 100 mg BIW) appeared to have antiviral activity as measured by virologic and clinical endpoints, but with evidence of greater activity for the BIW dose regimen in some analyses. Consequently, it was decided to evaluate a BIW dose regimen in the present study.

The 100 mg BIW dose was chosen based upon the overall efficacy and acceptable tolerability profile of this regimen in Study CMX001-201. In particular, the 100 mg BIW dose tended to show additional antiviral activity versus QW doses based upon the primary endpoint analysis. In addition, while the results of the 100 mg BIW group were similar to those of the 200 mg QW group across a range of endpoints, the 100 mg BIW dosing regimen had improved antiviral activity in subjects with detectable CMV viremia at baseline. Finally, regardless of CMV viremia status at baseline, when the activity data from individual subjects were examined, the 100 mg BIW dose appeared to achieve greater control of CMV reactivation and viremia, in comparison to the 200 mg QW dose. This greater viral suppression was in spite of an increased frequency of treatment with systemic steroids in the 100 mg BIW dose group, which, in theory, should have decreased the potential for CMX001 antiviral activity in that group, due to the immunosuppressive effect of systemic steroid therapies.

In order to potentially further improve tolerability and completion rates in the current study, CMX001 will be administered with food. Anecdotal reports from Study CMX001-202, as well as the expanded access protocol, Study CMX001-350, indicate that some GI symptoms may be mitigated by administering CMX001 with food. However, taking account of the results of CMX001-114 study, which showed CMX001 exposure (as measured by AUC) was reduced, when the drug was administered after the consumption of a low- or moderate-fat breakfast, it is recommended that each dose of study drug be taken with or within 30 minutes after finishing a low-fat meal containing no more than 20% of its total caloric value from fat. Examples of suitable low-fat meals will be provided in the study reference manual (SRM).

In addition, a dose interruption/dose reduction strategy is built into the design of the current study, based on refinements made to the original SMMP, which will be triggered in response to persistent diarrhea of Grade 2 severity, especially if accompanied by clinically significant decreases in serum albumin concentrations (to concentrations ≤ 30 g/L [≤ 3.0 g/dL] with a

decrease from baseline of ≥ 4 g/L [≥ 0.4 g/dL]), as described in Section 6.4. This strategy will prompt investigators to consider the following options:

- Dose interruption with resumption if clinically indicated or another cause for the diarrhea is found. Resumption would occur once the diarrhea has improved.
- Dose interruption followed by dose modification to 200 mg CMX001/placebo QW if Grade 2 diarrhea recurs or diarrhea progresses to Grade 3 upon resumption of BIW dosing. Resumption of dosing at 200 mg QW would occur if clinically indicated once the diarrhea has improved.
- Dose interruption followed by dose reduction to 100 mg CMX001/placebo QW if Grade 2 diarrhea recurs and is again associated with decreases in serum albumin to below the lower limit of normal or diarrhea progresses to Grade 3 after dose modification at 200 mg CMX001/placebo QW.

In all cases, study drug packaging and labeling will remain double-blinded, with appropriate use of exact match placebo tablet, as necessary. Further details of the dose interruption/dose reduction strategy are provided in Sections 8.4, 11.5, and 13.

6.3.3. Rationale for Placebo Comparator

Currently, there is an unmet medical need for a prevention for CMV infection in HSCT recipients. As no drug is approved or recommended by the American Society for Blood and Marrow Transplantation (ASBMT) guidelines (Tomblyn 2009) for this indication, placebo was selected as the control for the current study. This comparison (prevention of clinically significant CMV infection with CMX001 versus placebo) will represent the primary analysis in the study. Additional analyses will compare the safety and benefits of CMV prevention with CMX001 with those of preemptive therapy initiated based on protocol-defined criteria based on clinical condition and CMV DNA viremia. Previous studies with GCV for CMV prevention were unsuccessful because of an increase in secondary infections following GCV treatment and limited case studies with FOS were not expanded due to toxicity; for those reasons, preemptive therapy is the current practice. Therefore, a placebo-controlled study is considered acceptable since placebo recipients will receive SoC, i.e., PrT initiated on the basis of regular CMV viremia monitoring.

6.3.4. Rationale for Duration of Treatment Phase

Based on the available literature and current SoC, the risk for CMV reactivation post-HSCT is generally accepted to be highest between transplantation and Day 100 posttransplant. In addition, many patients are returned to the care of their primary oncologist (who may be in a location distant from the transplant center) by this time. In order to cover this period of greatest risk, dosing for all subjects will be initiated no later than Day 28 posttransplant, and will continue through Week 14 posttransplant, with subjects undergoing a first posttreatment assessment visit during Week 15 posttransplant. This should allow for all treatment visits and the first posttreatment assessment to occur at the study site before the subject is discharged back to the care of their "hometown" physician/oncologist. Depending on when CMX001 therapy is initiated relative to the date of transplant, the total duration of therapy will vary for individual subjects from a minimum of 10 weeks, up to a maximum of 14 weeks.

In Study CMX001-201, the total duration of treatment with CMX001 varied from 9 to 11 weeks depending on initiation of dosing as dictated by the time of engraftment. Analysis of the proportion of CMX001-201 subjects who met the proposed primary endpoint for the current study shows a trend for earlier initiation of treatment (i.e., closer to the day of transplant or Day 0) being associated with decreased risk of CMV infection (Table 4).

The initiation of CMV prevention at the time of engraftment is based on historical and practical factors more than a strong scientific rationale. Prior to availability of CMV PCR as a monitoring tool to initiate CMV preemption, the use of antigenemia precluded the detection of CMV infection prior to engraftment as the presence of peripheral blood mononuclear cells (PBMCs) is necessary to measure antigenemia. Therefore, the literature prior to the availability of CMV PCR does not document CMV events prior to engraftment. With the recent availability of "real-time" PCR methods, greater than 10% of patients were shown to have evidence of CMV viremia prior to engraftment and initiation of anti-CMV PrT (Marty 2011).

Table 4: Study CMX001-201: Incidence of Clinically Significant CMV Events by Week Elapsed Between Transplant and Initiation of Therapy

First Dose Posttransplant	100 mg BIW			Placebo		
	Fail	N	%	Fail	N	%
Week 3	1	8	13%	11	22	50%
Week 4	3	23	13%	7	13	54%
Week 5	6	14	43%	5	17	29%

As GCV, the first compound developed for CMV prevention post-HSCT, was known to have significant myelotoxicity, initiation of CMV prevention with this molecule was delayed until engraftment to avoid graft failure. No negative impact of CMX001 on circulating cells or on engraftment has been observed in subjects enrolled in Studies CMX001-201 (n=22), CMX001-202 (n=4), and CMX001-350 (n=9), as well as in EIND patients (n=4), who initiated therapy prior to Day 14 posttransplant or with neutropenia at baseline. While the dataset is small, based on these data, no adverse hematologic consequences are anticipated with the initiation of CMX001 therapy as soon after transplant as feasible (likely around Day 4) without regard to engraftment. Moreover, initiating CMX001 therapy as close to Day 0 as feasible could benefit the ~ 10 to 15% of patients who experience CMV reactivation prior to documented engraftment. Therefore, in the current study, investigators are encouraged to randomize and initiate therapy as soon as practical after a subject meets the inclusion/exclusion criteria for the study. However, since GI symptoms (related to myeloablative conditioning regimens in particular) remain the major limiting factor for the administration of oral medications, the initiation of dosing with randomized therapy is based on the ability of the individual subject to ingest and absorb oral medication.

After completing the treatment phase, subjects will be followed for an additional 10 weeks (i.e., from Weeks 15 to 24) in order to assess the risk of relapse after cessation of study drug. Results from Study CMX001-201 demonstrate that this duration of follow-up (through Week 24) is sufficient, since less than 10% of the subjects had emergence of CMV viremia between the end of study treatment and the end of the 8-week posttreatment follow-up (approximately Week 22) in that study.

Subjects who discontinue study treatment for any reason (except death, withdrawal of consent or loss to follow-up) will continue to follow the schedule of events through Week 24. Accordingly, investigators should make every effort to keep subjects in the study through its entirety.

6.3.5. Rationale for Primary Efficacy Endpoint

Because of the potential development of late CMV disease after stopping study drug, the primary efficacy endpoint will be the proportion of subjects who develop clinically significant CMV infection through Week 24. For the purposes of this study, "clinically significant CMV infection" is defined as the occurrence of either of the following outcomes:

- Onset of CMV end-organ disease, or
- Initiation of anti-CMV specific PrT based on documented CMV viremia (as measured by the central virology laboratory) and the clinical condition of the subject as described in Table 5.

During the treatment phase, subjects who meet either outcome must discontinue treatment with study drug, but will continue to be followed in the study until Week 24.

It is anticipated that, in comparison to placebo, CMX001 will reduce the percentage of patients developing clinically significant CMV infection, as defined, by at least 50% within the time period up to Week 24. The aim of this composite endpoint is to capture all clinical failures of the CMX001 treatment regimen, including the development of CMV disease, and the clinical decision to initiate PrT (and its associated toxicity), based on CMV viremia and clinical condition that predisposes subjects to the onset of CMV disease.

CMV end-organ disease is the most serious outcome of CMV infection and is characterized by significant morbidity and mortality. It was noted during the conduct of Study CMX001-201 that only two of the nine subjects who were recorded as having terminated the study due to the emergence of CMV disease had corroborative diagnostic data to confirm CMV disease. Therefore, for the present study, all incidences of CMV disease will be adjudicated by an independent Endpoint Adjudication Committee (EAC), which will examine all cases where CMV disease was diagnosed based on the criteria defined by Ljungman et al (Ljungman 2002). This paper provides definitions and guidelines for diagnosis of CMV pneumonia, GI disease, hepatitis, CNS disease, retinitis, nephritis, cystitis, myocarditis, pancreatitis, and CMV-associated graft failure. Further details for the EAC are provided in Section 6.5.2.

The initiation of anti-CMV PrT is also an important medical event, since the currently available anti-CMV therapies are all associated with significant toxicities (e.g., neutropenia, cytopenia, and nephrotoxicity). The decision to initiate anti-CMV PrT for any given HSCT recipient is based upon the assessment of the degree of the individual's risk of developing CMV disease. Numerous risk factors contribute to this decision including the level of CMV viremia, progressive CMV viremia, and factors promoting rapid progression to CMV disease (e.g., corticosteroid, ATG, or alemtuzumab therapy, cord blood or haploidentical transplantation, TCD, CD34+ selection, etc.), as well as current suspicion of symptomatic CMV infection (possible CMV disease, prior to confirmation of invasive disease; invasive bacterial or fungal infection; fever of unknown origin; graft failure, etc.)

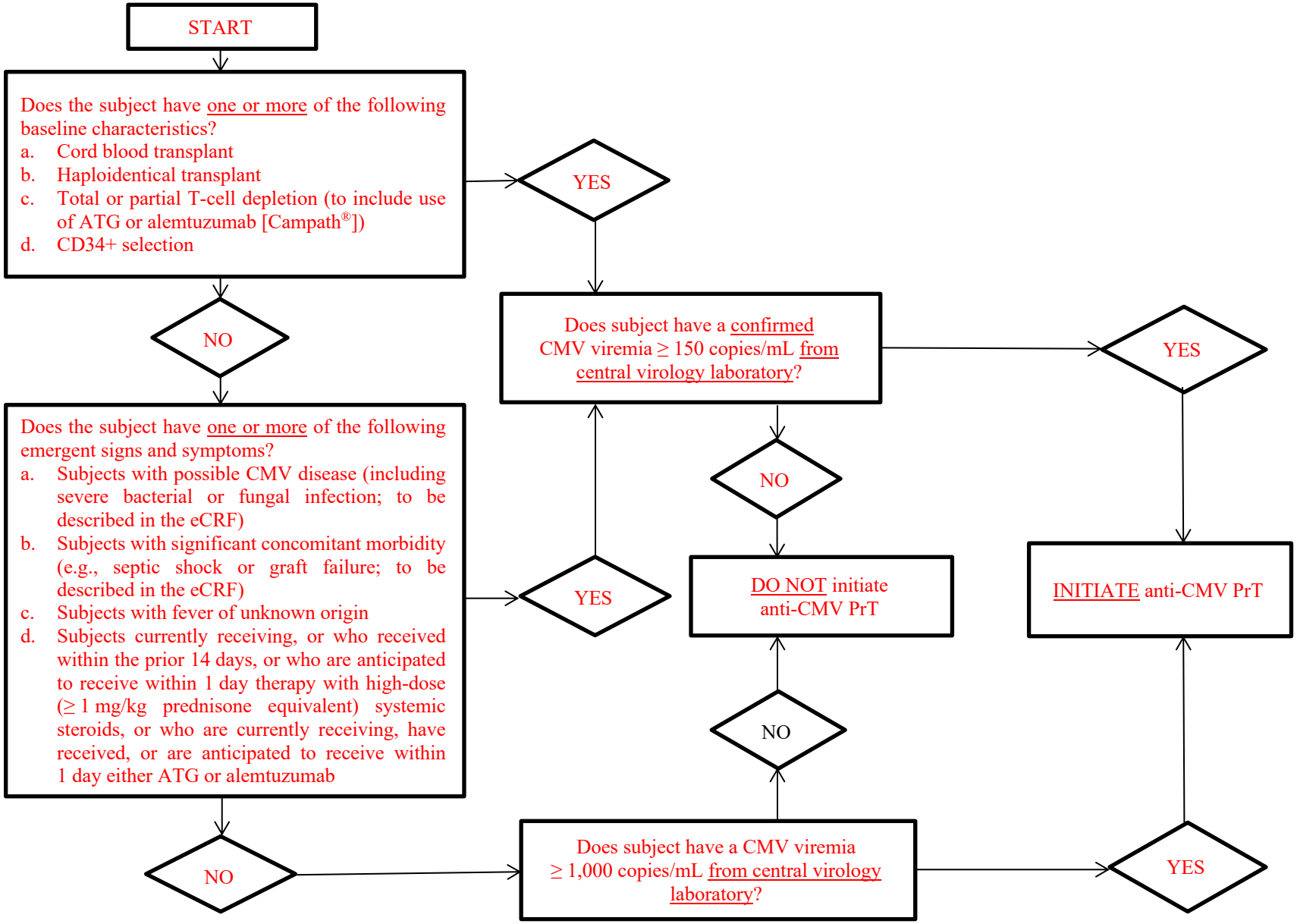
For the purposes of this study, to ensure a standardized approach between investigators at different institutions, the CMV viral threshold for stopping study drug treatment and the initiation of anti-CMV PrT is one CMV viremia result ≥ 1,000 copies/mL post-FDD (based on PCR assays performed only by the central virology laboratory), unless the clinical condition of the subject meets the prespecified criteria (based on baseline characteristics and emergent signs and symptoms, as described in Table 5) for aggressive CMV viremia management.

If the clinical condition of the subject meets the prespecified criteria for aggressive CMV viremia management, then the CMV viral threshold for initiating anti-CMV PrT is a confirmed CMV viremia level ≥ 150 copies/mL (i.e., ≥ LLOQ) post-FDD (based on PCR assays performed only by the central virology laboratory). This is represented graphically in Figure 1.

Table 5: Risk Factors Triggering Initiation of Anti-CMV Preemptive Therapy

Category	Risk Factor(s)	CMV Viremia Threshold for Initiation of Anti-CMV PrT
Aggressive CMV viremia management	Does subject have one or more of the following baseline characteristics?: 1. Cord blood transplant 2. Haploidentical transplant 3. Total or partial T-cell depletion (to include use of ATG or alemtuzumab [Campath®]) 4. CD34+ selection **- OR -** Does subject have one or more of the following clinical conditions?: 1. Possible CMV disease (including severe bacterial or fungal infection; to be described in the eCRF) 2. Significant concomitant morbidity (e.g., septic shock or graft failure; to be described in eCRF) 3. Fever of unknown origin 4. Currently receiving, have received within the prior 14 days, or are anticipated to receive within 1 day therapy with high-dose (≥ 1 mg/kg prednisone equivalent) systemic steroids, or are currently receiving, have received, or are anticipated to receive within 1 day either ATG or alemtuzumab	Confirmed CMV viremia level ≥ 150 copies/mL post-FDD as measured by the central virology laboratory (for both the initial and confirmatory sample)
Standard CMV viremia management	If subject has none of the baseline characteristics or clinical conditions described above	One CMV viremia result ≥ 1,000 copies/mL post-FDD as measured by the central virology laboratory

Figure 1: Flowchart for Initiating Anti-CMV Preemptive Therapy



For subjects in the aggressive CMV viremia management category who have an initial CMV viremia result of ≥ 150 copies/mL from the central virology laboratory, a confirmatory sample should be drawn and submitted to the central virology laboratory prior to administration of the first dose of anti-CMV PrT and, where clinically appropriate, the initiation of anti-CMV PrT should be postponed until after the confirmatory result is available. The decision to await the second, confirmatory result will be left to the investigator's discretion, depending on the subject's clinical condition. Alternatively, in order to not delay the initiation of anti-CMV PrT, the confirmatory sample should still be drawn and submitted to the central virology laboratory prior to administration of the first dose of anti-CMV PrT and if the result is not confirmed, and no more than 48 hours of dosing with anti-CMV PrT has been completed, then the PrT may be discontinued and will be considered as having been initiated prematurely. In either case, a decision regarding the initiation of anti-CMV therapy should be made as soon as practicable in the circumstances, and preferably no more than 4 days after the initial CMV viremia result ≥ 150 copies/mL.

The same criteria for initiating anti-CMV PrT will apply throughout the treatment and posttreatment phases of the study. If and when samples are collected for CMV viremia testing in the local virology laboratory, including any unscheduled CMV viremia assessments performed per local SoC, samples should be collected and sent to the central virology laboratory for analysis in parallel.

[Note: PrT therapy will <u>not</u> be supplied by Chimerix, Inc. and must be sourced by the investigator or treating physician in accordance with standard institutional practice.]

6.3.5.1. Secondary Endpoints

Anti-CMV Preemptive Therapy: The incidence and time to initiation of each anti-CMV PrT (including GCV, vGCV, FOS, or CDV) through Week 14 and through Week 24, and the number of courses of anti-CMV preemptive therapy per subject through Weeks 14 and 24 will be evaluated.

Emergence of CMV Viremia: In order to evaluate the activity of CMX001, the incidence of CMV viremia (defined as CMV viremia ≥ 150 copies/mL [≥ LLOQ]) through Week 14 and through Week 24 will be used as a measure of antiviral activity.

Incidence of Non-CMV dsDNA Viral Diseases: CMX001 is a broad-spectrum antiviral agent with demonstrated activity *in vitro* and in many animal models against a wide variety of dsDNA viruses. Many of these viruses cause significant morbidity (e.g., BKV, EBV, etc.) and, in some cases mortality (e.g., AdV), in HSCT recipients. Hence, another secondary endpoint will be a comparison of the emergence of clinical events associated with other dsDNA viral infections between CMX001- and placebo-treated subjects. Specifically, the emergence of confirmed disease(s) caused by dsDNA viruses, including AdV, BKV, EBV, HHV-6, HSV-1, HSV-2, or VZV, will be monitored. In addition, because CMX001 may also have provided additional benefit with respect to BKV-associated bladder and renal events in the CMX001-201 study, one secondary endpoint will be the incidence of BKV end-organ disease (through Week 14 and through Week 24), defined as symptoms associated with BKV-associated cystitis (e.g., increased frequency of urination, bladder pain, hematuria, clots, etc.) or a decrease in renal function (as measured by estimated glomerular filtration rate [eGFR] using the Chronic Kidney Disease

Epidemiology equation [CKD-EPI]) to a value < 60 mL/min/1.73 m^2 and a ≥ 30% decrease from baseline. The incidence of manifestations associated with HHV-6 (e.g., encephalitis, graft failure, and neurocognitive impairment) will also be evaluated.

All-cause Mortality, Non-relapse Mortality, Mortality Attributed to CMV, and Graft Failure: In order to characterize the outcome of therapy with CMX001 versus SoC, all-cause mortality, non-relapse mortality, mortality attributed to CMV, and graft failure will be compared between CMX001- and placebo-treated subjects.

Treatment-emergent Resistance: Generation of drug resistant virus may be a byproduct of the use of antiviral therapies and is a consideration whenever an antiviral drug is prescribed. Therefore, one secondary endpoint will be to compare the incidence of viral breakthrough and the emergence of antiviral-resistant CMV isolates, between CMX001- and placebo-treated subjects. Subjects experiencing virologic failure will be evaluated for genotypic changes in the CMV UL54 and UL97 genes; mutations identified will be characterized for phenotypic resistance, as appropriate.

Immune Reconstitution: The reconstitution of the anti-CMV immunological response will be evaluated by determining the number of CMV sensitive effector T cells among PBMCs isolated from blood samples collected during the treatment phase (Weeks 5 and 9), at the end of the treatment phase (Week 14), and at the end of the follow-up phase (Week 24) using the T-SPOT.® *CMV* Test available from Oxford Immunotec Limited (Abingdon, UK). These data will be used to evaluate the immune reconstitution between CMX001- and placebo-treated subjects, including the incidence of emergence of the anti-CMV immune response at specified time points (i.e., Weeks 5, 9, 14, and 24 posttransplant), and the impact of anti-CMV PrT on the observed anti CMV response, as well as possible identification of risk factors for CMV infection onset (after Day 100 posttransplant) and potential indication for longer prevention in CMX001-treated subjects.

Additional details on all study endpoints, including safety, PK, and health economic/ health-related quality of life (HE/HRQL) outcomes, are provided in Sections 7.3 and 14.

6.4. Potential Risks and Benefits

Because of the high rate of complications and intercurrent illnesses experienced by HSCT recipients, subjects in this study will require intensive clinical monitoring and safety assessments. It is expected that thorough clinical management of study participants, including targeted treatment of AEs, will be conducted throughout the entire study period, including the posttreatment phase, by clinical site personnel according to the site's standard practices.

In addition to surveillance for and reporting of all AEs, subjects enrolled in this study will be monitored specifically for GI signs and symptoms, reports of GVHD, especially GI-GVHD, and for serum aminotransferase elevations. Experience from Study CMX001-201 indicates that these events are likely associated with the administration of CMX001 and are, therefore, to be expected during the course of the present study. The continued use of a SMMP for CMX001, along with data-driven dose selection and the planned administration of CMX001 with food (as described in Section 6.3.2) are expected to minimize the rate of drug-related AEs in the present study. Nonetheless, an independent DSMB for this study will be convened to monitor subject safety on an ongoing basis, as described in Section 6.5.1 hereafter.

Diarrhea, often associated with other GI-associated AEs, was identified in Study CMX001-201 as dose-limiting at 200 mg BIW in the HSCT population. In contrast, QW CMX001 doses in the range studied (40 to 200 mg QW) were sufficiently well tolerated with respect to diarrhea. At 100 mg BIW, diarrheal events (often reported as GI-GVHD) were more frequent, as compared to placebo. However, while approximately one-third of the subjects in the 100 mg BIW cohort interrupted study drug treatment due to an AE, based on the guidance to investigators outlined in the SMMP, the majority of these subjects were able to successfully resume dosing. Therefore, diarrhea is considered to be a manageable AE in this patient population.

In this study, specific information on GI symptoms and GVHD will be captured in the eCRF. GI assessments will include the following: symptoms at each visit, measurements of stool volumes (if possible while subjects are inpatient) or number of stools, grading and staging of aGVHD, if present, assessed for each organ of involvement, the results of any local diagnostic investigations, including biopsies, centralized reading of biopsy slides (blinded to treatment assignment) for biopsies of gut and/or skin (at the request of the GVHD Adjudication Committee [GAC]), measurement of immunosuppressant blood concentrations, and the collection of treatment and response details. In addition, details of skin findings will be collected when skin GVHD is reported. Each case of possible GVHD reported during the study will be adjudicated based on these data by the GAC, which will be comprised of independent experts in the field of gastroenterology, pathology and HSCT transplantation, as described in Section 6.5.3. The GAC, which will be blinded to treatment assignment, will rate the likelihood of GVHD diagnosis for each case and provide their assessments to the DSMB for the study. The results from any analyses of the slides from GVHD biopsies will only be shared with the GAC and, if requested, the FDA. These results will not be provided to individual investigators.

In considering the design and conduct of the current study, Chimerix conducted additional analyses to refine the guidance to investigators set forth in the SMMP with a goal of further reducing the incidence of Grade 3 diarrhea, if possible. Based upon the safety and efficacy observations from the CMX001-201 study, two strategies are proposed to further mitigate the consequences of GI AEs during CMX001 dosing. First, the monitoring of serum albumin concentrations has been incorporated into the current SMMP. Second, dosing interruption has been suggested as the first dose adjustment, since it did not cause significant loss of antiviral activity when applied in the 100 mg BIW cohort in the CMX001-201 study and it allowed for the completion of the intended therapy duration. Under the current SMMP, the Diarrhea Events Algorithm suggests the interruption of study drug with the occurrence of Grade 2 diarrhea that persists for $\geq$ 3 days, especially if the diarrhea is associated with concomitant decreases in serum albumin ($\leq$ 30 g/L and $\geq$ 4 g/L lower than baseline values). If there is an occurrence of Grade 3 diarrhea, dose interruption is mandated. Further dose modification strategies have also been outlined, depending on the clinical course of GI symptoms and signs. More detailed information on the SMMP and the toxicity management strategy for this study is described in Section 13: Toxicity Monitoring and Management of this protocol.

The proposed primary endpoint for Study CMX001-301, as described in this protocol, was modeled based on the available data from Study CMX001-201, as presented in Table 6. Based on this analysis, it is expected that subjects randomized to CMX001 will derive benefit from participation in the study.

Table 6: Study CMX001-201: Rates of Failure due to CMV Disease OR CMV Preemption OR Risk-based Viremia Threshold Proposed for Study CMX001-301

	Pooled Placebo	Cohort 4A (100 mg CMX001 BIW)
Failure [n/N (%)][a]	24/52 (46.2%)	10/45 (22.2%)
Fisher p-value		0.019
Cochran-Mantel-Haenszel p-value[b]		0.006
Odds ratio (95% CI)[b]		3.70 (1.43, 9.61)

[a] One (1) placebo subject and 5 CMX001 subjects received anti-CMV PrT without achieving the proposed Study CMX001-301 viremia threshold at any time were counted as failures.
[b] Controlling for CMV risk category.

Although the risk of CMV disease is currently low after HSCT (Marty 2011, Marty 2013) and mortality due to CMV disease has been significantly reduced with frequent monitoring and current therapeutic approaches (Green 2012), the non-relapse mortality of CMV-seropositive subjects remains 33% higher than the non-relapse mortality of CMV-seronegative subjects (Green 2012). This excess in non-relapse mortality is likely the result of multiple factors, including the indirect effects of CMV reactivation, such as altered host immune responses; graft failure/dysfunction; opportunistic infections, such as bacterial, fungal, protozoal, and viral superinfections, and decreased graft and patient survival, each of which could be addressed with an effective CMV prevention regimen that can be given prophylactically to recipients of allogeneic HSCT without significant myelotoxicity.

In addition to the potential benefit of preventing the direct and indirect effects of CMV reactivation, CMX001 offers potential benefit in the prevention of other dsDNA viral infections, including:

- AdV infections which are much less common than CMV but are often fatal and have no currently approved therapy;
- BKV infections which are common and lead to significant morbidity (renal impairment and hemorrhagic cystitis);
- EBV which is associated with PTLD, a condition which is rare in adults, but which has a high mortality (Bitan 2006, Meijer 2005); and
- HHV-6 infections for which little epidemiologic data exist, but which can lead to graft failure, encephalitis with long term sequelae (Zerr 2012), or pneumonitis.

As an orally administered drug, CMX001 also avoids the need for hospitalization and the placement of central lines for IV infusion, which are associated with risks of nosocomial infections.

As described in Section 6.2.2, based on the findings from a 13-week toxicology study in rats, in which specific tumors (mainly adenocarcinomas) were observed much earlier than would be expected over the course of a normal lifespan in animals dosed with CMX001, CMX001 is considered a potential human carcinogen. CMX001 shares a common active metabolite

(CDV-PP) with CDV, which has the same potential human carcinogenic risk as CMX001. The early onset of tumors was observed in rats administered CDV, but like CMX001, tumors were not observed in monkeys administered CDV in chronic toxicology studies. Due to the difficulty in extrapolating rodent carcinogenesis data to humans, Gilead Sciences, Inc., the manufacturer of Vistide, committed to a Phase 4 malignancy assessment program as a condition of FDA approval. While originally approved in the USA for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS), CDV has also received extensive off-label use for the treatment of CMV and other dsDNA virus infections more generally for many years, and examination of clinical follow-up data in patients provides the best opportunity for examining the actual carcinogenic potential of CDV in humans. Patients receiving CDV were found to have a low incidence of malignancy while on therapy or after extended follow-up with no reports of enhanced carcinogenic potential or unusual tumors. In the years immediately following CDV approval, the tumors observed in AIDS patients receiving CDV were generally either Kaposi's sarcoma or AIDS-related lymphomas, which are malignancies characteristic of this patient population. The observed incidence of these tumors was comparable to or less than the reported incidence associated with nucleoside/nucleotide analogs administered for antiretroviral therapy in this patient population.

In the current study, the maximum 14-week treatment period was selected to provide CMV prevention therapy for HSCT recipients during the first 100 days posttransplant when the risk for CMV reactivation is generally accepted to be highest. Thus, any carcinogenic risk associated with administration of CMX001 in this patient population is believed to be outweighed by the potential benefit of preventing both the direct and indirect negative health effects of CMV reactivation, as well as other dsDNA virus infections, and the associated morbidity/mortality. Nonetheless, all study participants will be advised of the potential carcinogenic risk from CMX001 prior to study enrollment and they will be encouraged to additionally enroll in the "Chimerix Registry for CMX001" (Study CMX001-333: A Prospective Observational Study for the Long-term Follow-up of Subjects Previously Enrolled in Selected Clinical Studies of CMX001) to assess the long-term impact of exposure to CMX001, including on carcinogenicity to better understand the relevance to humans of this preclinical signal in rats.

6.5. Independent Safety Oversight

6.5.1. Data and Safety Monitoring Board (DSMB)

A DSMB will be convened according to FDA and European Medicines Agency (EMA) guidelines on clinical trial data monitoring committees and will monitor safety for this study, reviewing unblinded safety data on an ongoing basis on a schedule determined by the DSMB and detailed in the DSMB charter with the following caveats:

1. Once the first subject has been dosed, the DSMB must meet at least once every three months.
2. The DSMB meetings must be more frequent if unexpected safety issues arise (e.g., unexpectedly high rate of ≥ Grade 3 events and/or SAEs).
3. The DSMB Chair will be allowed to convene ad-hoc meetings, as necessary.

The DSMB will define specific safety information to be provided for review at each meeting, but the DSMB review package will minimally include:

- All SAEs;
- Grade 3 or higher AEs;
- AEs leading to study drug discontinuation;
- Laboratory parameters predictive of liver abnormalities (e.g., ALT, AST, alkaline phosphatase, prothrombin time-international normalized ratio [PT-INR], and total and direct bilirubin) and hematologic cell counts predictive of graft function;
- Incidence and frequency of study drug dose reductions and/or discontinuations for GI and hepatobiliary events, and
- Incidence and severity of aGVHD events, as adjudicated by the GAC, including organ system involvement.

The DSMB may elect to consult with other independent experts to adjudicate specific adverse drug reactions. The DSMB Chair will receive copies of all IND safety reports ("expedited safety reports") issued for CMX001 at the same time these reports are submitted to investigators, will have access to the unblinding codes, and may decide to convene ad hoc DSMB meetings based on these expedited reports. If the DSMB recommends changes to the study design, including changes to the protocol dosing regimens because of safety issues, the FDA and other regulatory authorities will be consulted, as appropriate, prior to implementation.

6.5.2. Endpoint Adjudication Committee (EAC)

The EAC will comprise at least two members who are experts in the field of CMV infection and/or HSCT and not otherwise involved in the study. Their role will be to provide an independent assessment of whether the definition of CMV disease has been met based on the criteria defined by Ljungman et al (Ljungman 2002) and whether deaths in the study are considered relapse related.

6.5.3. GVHD Adjudication Committee (GAC)

The GAC will comprise at least two members who are experts in pathology, gastroenterology and/or HSCT transplantation, and not otherwise involved in the study. Their role will be to provide an independent assessment of whether each GVHD diagnosis is likely, presumptive, or unlikely. The GAC blinded assessment of GVHD cases will be provided to the DSMB only during the course of the study. Assessment of the probability of GVHD will be based on risk factors, current immunosuppression, clinical characteristics, biopsy results (as available), laboratory assessments and response to treatment, at a minimum. For presumptive or likely cases of GVHD identified by the GAC, the committee will provide an independent assessment of stage and grade based on available information.

7. TRIAL OBJECTIVES AND PURPOSE

7.1. Primary Objective

- To compare the efficacy of CMX001 to placebo for the prevention of clinically significant CMV infection in R+ allogeneic HSCT recipients
- To compare the safety and tolerability of CMX001 to placebo for the prevention of clinically significant CMV infection in R+ allogeneic HSCT recipients

7.2. Secondary Objectives

- To describe the effect of CMX001 versus placebo on all-cause mortality, non-relapse mortality, mortality attributed to CMV, and graft failure
- To evaluate the virologic response for subjects treated with CMX001 who are CMV viremic on the FDD and the emergence of resistance for subjects treated with CMX001 compared to placebo
- To characterize the effect of CMX001 in preventing clinical manifestations associated with non-CMV dsDNA viruses, including: manifestations associated with BKV infections (e.g., bladder and kidney infections, and renal insufficiency); manifestations associated with HHV-6 infections (e.g., encephalitis, graft failure, and neurocognitive impairment), and manifestations associated with infections with HSV-1/2, VZV, AdV, and EBV, separately and in aggregate
- To describe plasma concentrations of CMX001 and CDV in R+ allogeneic HSCT recipients
- To compare HE/HRQL outcome parameters between CMX001- and placebo-treated subjects
- To compare reconstitution of the anti-CMV immunological response between CMX001- and placebo-treated subjects and the impact of anti-CMV PrT on the observed responses

7.3. Outcome Measures

7.3.1. Primary Efficacy Endpoint:

The primary efficacy endpoint of this study will be the incidence of clinically significant CMV infection through Week 24. For the purposes of this study, “clinically significant CMV infection” is defined as the occurrence of either of the following outcomes:

- Onset of CMV end-organ disease, or
- Initiation of anti-CMV specific PrT based on documented CMV viremia (as measured by the central virology laboratory) and the clinical condition of the subject as described in Section 6.3.5.

During the treatment phase, subjects who meet either outcome must discontinue treatment with study drug, but will continue to be followed in the study until Week 24.

7.3.2. Secondary Efficacy Endpoints:

- Incidence of and time to all-cause mortality through Week 14 and through Week 24
- Incidence of and time to non-relapse mortality (i.e., mortality not associated with the relapse of the underlying malignancy) through Week 14 and through Week 24
- Incidence of and time to mortality attributed to CMV through Week 14 and through Week 24
- Incidence of and time to graft failure through Week 14 and through Week 24
- Incidence of clinically significant CMV infection through Week 14
- Time to clinically significant CMV infection through Week 14 and through Week 24
- Incidence of clinically significant CMV infection during the posttreatment phase (i.e., from Week 15 through Week 24). The analysis will adjust for subject characteristics existing at Week 15 [e.g., the presence of GVHD of Grades II to IV severity, use of high-dose (≥ 1 mg/kg prednisone equivalent) steroids, persistent lymphopenia, the presence or absence of CMV-specific cellular immunity, etc.]
- Incidence, time to initiation and number of anti-CMV PrT courses (e.g., GCV, vGCV, FOS, or CDV) through Week 14 and through Week 24
- Incidence of and time to CMV end-organ disease, as adjudicated by the blinded EAC according to the definitions/procedures described by Ljungman et al (Ljungman 2002), through Week 14 and through Week 24
- Incidence of BKV end-organ disease during study drug administration (through last dose of study drug +7 days, through Week 14, and through Week 24), defined as symptoms associated with BKV-associated cystitis (e.g., increased frequency of urination, bladder pain, hematuria, clots, etc.) or a decrease in renal function (as measured by eGFR using CKD-EPI; Levey 2009) to a value < 60 mL/min/1.73 m^2 and a ≥ 30% decrease from baseline
- Incidence of and time to CMV viremia ≥ 150 copies/mL (≥ LLOQ) through Week 14 and through Week 24
- Incidence of and time to virologic breakthrough and emergence of CMV mutations associated with phenotypic resistance to CMX001
- Incidence of and time to emergence of clinical and laboratory events associated with other dsDNA viruses, including AdV, BKV, EBV, HSV-1/2, HHV-6, and VZV, through Week 14 and through Week 24
- Incidence of emergence of anti-CMV immune response (as measured by the T-SPOT.® *CMV* Test) through Weeks 5, 9, 14, and 24

7.3.3. Safety Endpoints:

- Incidence of and time to discontinuation from study drug due to AEs

- Incidence of treatment-emergent AEs (TEAEs), in particular TEAEs of ≥ Grade 3 severity, as defined by the National Institutes of Health/National Cancer Institute (NIH/NCI) Common Terminology Criteria for Adverse Events (CTCAE)
- Incidence and severity of treatment-related TEAEs
- Incidence, severity, and worsening of GI-related events, in particular diarrhea
- Incidence, severity, and worsening of aGVHD, in particular GI-GVHD, as adjudicated by the blinded GAC
- Incidence, severity, and worsening of hepatobiliary events, in particular liver-related laboratory abnormalities
- Incidence of TEAEs leading to dose interruption, dose reduction, or dose discontinuation

Pharmacokinetic Endpoints:

- Plasma concentrations of CMX001 and CDV

Other Clinical Endpoints:

- Total number and duration of hospitalizations and the use of transfusions, hematopoietic growth factors, and anti-infective medications through Week 14 and through Week 24
- Incidence and severity of non-CMV infections (i.e., bacterial, protozoal, fungal, or viral) through Week 14 and through Week 24
- Incidence and severity of new onset (i.e., post-FDD) renal dysfunction through Week 14 and through Week 24
- Frequency of diagnostic or therapeutic procedures not related to the primary HSCT (e.g., endoscopies, imaging, biopsies and related procedures) through Week 24

Health-related Quality of Life Endpoints:

- Subject responses to EuroQol Health Utility Index 5D, version 5L (EQ-5D-5L) and European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30 with (EORTC-QLQ-C30/HDC29) questionnaires

8. INVESTIGATIONAL PLAN

8.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel group, multicenter study of CMX001 in CMV-seropositive subjects who have undergone allogeneic HSCT. The study will comprise a screening evaluation, a treatment phase of 10 to 14 weeks' duration (through Week 14), followed by a 10-week posttreatment phase (to Week 24), which are described as follows:

Screening: Potential subjects may be consented for participation in the study before or after transplant. Subjects providing written informed consent will be screened following transplant as soon as the subject can ingest tablets. As part of the screening procedures, CMV viremia (i.e., the measurement of CMV DNA in plasma by PCR assay) must be assessed by the designated central virology laboratory within 5 days prior to randomization and only those subjects who are determined to be CMV viremia negative at screening (i.e., CMV DNA in plasma is "Not Detected" for the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test used by the central virology laboratory) will be eligible for randomization. In addition, the results of any CMV viremia testing (including CMV PCR, pp65 antigenemia, etc.) performed as part of local SoC since the qualifying transplant must also be negative. Subjects who were CMV viremia negative at screening, but who are subsequently found to have been CMV viremic at baseline (i.e., at the predose assessment on the FDD) will be continued in the study.

Randomization: Subjects who meet all applicable eligibility criteria will be randomized to one of the following two treatment arms in a 2:1 ratio using an automated integrated voice/web response system (IV/WRS):

- Treatment 1: 100 mg CMX001 BIW
- Treatment 2: placebo BIW

Both treatments will be administered under double-blind conditions (i.e., neither the subject nor the investigator and clinic staff will be aware of the individual subject treatment assignment). During randomization, subjects will be stratified within an investigative center, based on their likelihood for progression to clinically significant CMV infection, defined as a "lower likelihood" versus a "higher likelihood" of progression. Subjects who receive a matched, related, non-T-cell depleted graft (e.g., excluding cord blood), who do not have aGVHD, who have not received ATG or alemtuzumab, and who are not receiving high-dose (≥ 1 mg/kg prednisone equivalent) systemic steroids will be stratified in the "lower likelihood" group. All other subjects will be stratified in the "higher likelihood" group. Following randomization, subjects must begin study drug (CMX001 or placebo) within 1 business day.

Treatment Phase (FDD to Week 14): Dosing for all subjects will be initiated after transplant as soon as subjects can ingest tablets, but no later than Day 28 posttransplant, and will continue through Week 14. The first dose of blinded study drug (CMX001 or placebo) will be administered after completion of all predose (baseline) clinic and laboratory assessments on the FDD, with subsequent doses administered at alternating 3- and 4-day intervals through Week 14. Following randomization, all subjects will undergo weekly assessments through Week 14, before transitioning to the posttreatment phase. Thus, the planned duration of the treatment phase will

vary for individual subjects from a minimum of 10 weeks, up to a maximum of 14 weeks, depending on when treatment is initiated relative to the date of transplant. Subjects who initiate treatment during the first week after transplant will complete the longest period of treatment at 14 weeks, while subjects who initiate treatment in the fourth week after transplant will complete the shortest period of treatment at 10 weeks.

Subjects who develop CMV disease or initiate anti-CMV specific PrT during the treatment phase must discontinue study drug, but will continue to be followed in the study until Week 24. In circumstances where PrT is initiated prematurely (as described in Section 6.3.5 or based on local virology laboratory results that have not been confirmed by the central virology laboratory), subjects will be authorized to resume study drug if the duration of the PrT was ≤ 48 hours. Such allowance can only be for a single episode during each subject's study participation. If the duration of the PrT is > 48 hours, then the subject may not resume study drug. If PrT is initiated for a second time, the subject must permanently discontinue study drug.

Posttreatment Phase (Week 15 to Week 24): All randomized subjects will follow the same schedule of assessments through Week 24. Subjects will undergo a first follow-up assessment during Week 15, with additional follow-up assessments at Weeks 18, 21, and 24.

During the posttreatment phase (Week 15 to Week 24), any supplemental CMV viremia assessments (i.e., in addition to the scheduled assessments by the central virology laboratory at Weeks 15, 18, 21, and 24) may be guided by local SoC, but should be conducted at the central virology laboratory. If this is not medically feasible, any positive CMV PCR result performed at the local virology laboratory should have a confirmatory PCR test performed in parallel at the central virology laboratory.

Early Study Drug Discontinuation: If study drug is discontinued for safety, tolerability, or due to efficacy failure, subjects must remain on the schedule of assessments and complete all protocol-scheduled assessments at each visit through Week 24 except those related to study drug dosing, study drug accountability, or the collection of blood samples for PK analysis.

It is expected that all subjects should complete all study assessments, up to and including Week 15, at their designated study center. For those subjects who are unable to return to the transplant center after being discharged from the clinic, site personnel should make other arrangements for subjects to complete all assessments through Week 24.

For subjects who do not return to their transplant centers during the posttreatment phase the following assessments must be completed at a minimum:

- CMV viremia as assessed by the central virology laboratory;
- urine and plasma for storage at the central virology laboratory, and
- safety laboratory assessments as performed by the central safety laboratory.

Additionally, a telephone contact (supported by copies of local medical records) between study personnel and the local physician will be performed to assess:

- emergence of CMV infection or disease requiring PrT,
- cause of death, where applicable; and

- the follow-up of any ongoing AEs (including SAEs) and the reporting of new (S)AEs.

Long-term Follow-up for Carcinogenicity/Late-CMV-associated Events/Survival: Each subject enrolled into the study will be asked to additionally participate in the 'Chimerix Registry for Former CMX001 Study Participants' (Protocol No. CMX001-333) to assess the long-term impact of CMX001 administration on carcinogenicity, late CMV-associated events, and survival. While participation in the Registry is to be encouraged, a subject will not be required to participate in the Registry in order to participate in this study. Participation in the Registry will be documented in a separate consent form (to be administered at any time prior to study completion, but preferably prior to the subject leaving the transplant center and returning to the care of his or her local oncologist). A subject may choose to participate in or withdraw from the Registry at any time.

8.1.1. Study Visit Schedule

A detailed schedule of the study procedures/assessments to be completed during the screening, treatment and posttreatment phases of the study is provided in Table 9 hereafter.

All subjects will complete the following assessments:

- Screening evaluation
- From 11 to 14 treatment phase assessments, including the FDD, followed by weekly assessments, approximately every 7 days, through Week 14, inclusive. The duration of the treatment phase and, therefore, the number of assessments completed will depend on when treatment is initiated relative to the date of transplant. Table 7 summarizes which assessments must be completed and which should be omitted, based on the FDD date, to ensure that each subject completes the protocol-specified duration of study treatment, i.e., approximately 100 days posttransplant, with the last dose administered within a nominal window of Day 95 to Day 101 posttransplant. [Note: For this purpose, the day of transplant is assumed to be Day 0, NOT Day 1. This nomenclature may or may not be in accordance with individual institutional practice.] Subjects who discontinue study drug prior to Week 14 will remain on the same schedule of assessments through Week 24. All procedures will be required at those visits except those related to study drug dosing, study drug accountability, and the collection of blood samples for PK analysis.
- Four posttreatment assessments (Weeks 15, 18, 21, and 24) over a follow-up period of 10 weeks.

Site personnel should make arrangements for all subjects to complete all assessments up to and inclusive of the Week 24 assessment, including those subjects who are unable to return to the transplant center after being discharged from the clinic. Every effort should be made to ensure all subjects who leave the geographic area of the transplant center have the opportunity to remain in the study and complete all assessments.

In order to maximize the opportunity for data collection and minimize the loss to follow-up of study participants after discharge from the care of the transplant center, especially during the posttreatment follow-up phase of the study, with the prior approval of Chimerix, some or all of the scheduled study assessments (including the collection of blood and other samples, as

appropriate) may be performed by a third party providing remote (home) visits by suitably-qualified personnel. Investigators must contact the Chimerix Medical Monitor to request prior approval to use such a service and agree on an action plan detailing which of the scheduled study assessments can be reasonably completed in this manner. Section 8.1 describes the minimum assessments that should be completed for subjects who do not return to their transplant centers during the posttreatment phase, but efforts should be made to complete as many assessments and collect as much data as is reasonable in the circumstances for individual subjects. If a subject has been discharged from the care of the original investigator, permission will be sought from the subject and/or his or her new healthcare provider(s), as appropriate, to request copies of medical records related to events of interest.

Table 7: Determination of Treatment Phase Assessments Based on Date of First Dose Day

If first dose day (FDD) occurs on posttransplant day # (where Day 0 = transplant day)	Visits/assessments that must be completed after the FDD	Visits/assessments that should NOT be completed after the FDD
FDD = Day 1 through Day 7 posttransplant	Wk 2, Wk 3, Wk 4, Wk 5, Wk 6, etc. through Wk 24	N/A
FDD = Day 8 through Day 14 posttransplant	Wk 3, Wk 4, Wk 5, Wk 6, etc. through Wk 24	Wk 2
FDD = Day 15 through Day 21 posttransplant	Wk 4, Wk5, Wk 6, etc. through Wk 24	Wk 2, Wk 3
FDD = Day 22 through Day 28 posttransplant	Wk5, Wk 6, etc. through Wk 24	Wk 2, Wk 3, Wk 4

8.1.2. Study Windows

The time schedule described in the protocol for each scheduled activity should be followed as closely as possible. The time windows detailed in Table 8 are allowed without incurring a protocol deviation.

Table 8: Allowable Time Windows

Protocol Specified Timeframe	Allowable Window
First dose day (FDD)	No later than Day 28 posttransplant
Treatment Phase (Weeks 2 to 14)	Within the relevant week posttransplant
Posttreatment Phase (Weeks 15, 18, 21, and 24)	Within the relevant week posttransplant

8.2. Number of Subjects

Approximately 450 eligible subjects will be randomized between the two treatment arms in a 2:1 ratio, i.e., approximately 300 subjects will be randomized to CMX001 (Treatment 1) and approximately 150 subjects will be randomized to placebo (Treatment 2).

8.3. Treatment Assignment

Subjects who meet all applicable eligibility criteria will be randomized to one of the following two treatment arms in a 2:1 ratio using an automated IV/WRS system:

- Treatment 1: 100 mg CMX001 BIW
- Treatment 2: placebo BIW

Both treatments will be administered under double-blind conditions, i.e., neither the subject nor the investigator and clinic staff will be aware of the individual subject treatment assignment.

Table 9: Schedule of Study Assessments/Procedures

Procedure	Screening[a]	Treatment Phase (weeks posttransplant)[b]														Posttreatment Phase[c] (weeks posttransplant)			
		FDD (Baseline)[d]		2	3	4	5	6	7	8	9	10	11	12	13	14	15	18	21	24
Written informed consent[e]	X																			
Review inclusion/exclusion criteria	X	X																		
Medical/medication history, including transplant history[f]	X	X																		
Physical examination[g]	X	X					X				X						X			X
Vital signs measurement[h]	X	X					X				X						X			X
Height/Body weight[i]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory evaluations[j]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[k]	X	X					X				X						X			X
HIV serology/HBV and HCV viral load[l]	X																			
Blood (plasma) for virologic analyses[m]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for analysis of anti-CMV response[n]							X				X					X				X
Lymphocyte subset (CD4+ and CD8+)		X				X		X				X					X			X
Urine for virologic analyses[o]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other samples for virologic analyses (as needed)[p]	<---------- X ---------->																			
Record immunosuppressant(s) concentration[q]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomize subject[r]		X																		
Dispense study drug		X							X[s]											
Study drug dosing[t]		X		X	X	X	X	X	X	X	X	X	X	X	X	X				
Drug accountability				X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Procedure	Screening[a]	Treatment Phase (weeks posttransplant)[b]															Posttreatment Phase[c] (weeks posttransplant)			
		FDD (Baseline)[d]		2	3	4	5	6	7	8	9	10	11	12	13	14	15	18	21	24
Blood (plasma) samples for PK analysis[u]		X		X	X	X	X	X	X	X	X	X	X	X	X	X				
HE/HRQL questionnaires[v]	<---------- X ---------->							X									X			X
Neurocognitive assessments[w]		X						X				X					X			X
Assess CMV/Other dsDNA virus signs and symptoms[x,y]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide/review of study diary card[z]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diarrhea and GVHD assessments[y,aa]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X[bb]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] All screening procedures do not need to be completed on the same day, but all screening procedures must be completed and the results reviewed prior to initiating treatment on the FDD.

[b] The duration of the treatment phase will vary for individual subjects from 10 to 14 weeks, depending on when treatment is initiated relative to the date of transplant. During the treatment phase, subjects will be assessed weekly. Table 7 summarizes which of the Week 2-4 assessments must be completed and which should be omitted based on the FDD to ensure that each subject completes the protocol-specified duration of study treatment, i.e., approximately 100 days posttransplant. If a subject should discontinue study drug (for whatever reason) prior to Week 14, which will be the last week of study drug for all subjects, the subject should continue to be assessed on a weekly basis and complete all study procedures and assessments, with the exception of study drug dosing, the collection of blood samples for PK assessments, and study drug accountability, through Week 14.

[c] The posttreatment phase (Weeks 15 to 24) is scheduled relative to the transplant date and is fixed for all subjects, regardless of whether they complete the study drug.

[d] Dosing with study drug (CMX001 or placebo) will be initiated after transplant as soon as the subject is able to ingest tablet, but no later than Day 28 posttransplant. Other than study drug dosing and the collection of the 3 (± 1) hour postdose PK blood sample, all study procedures should be performed prior to dosing (to serve as baseline measures).

[e] Potential subjects may be consented for participation in the study before or after transplant. However, subjects may only be screened following transplant.

[f] If preferred, medical history may be obtained before transplant (and after written informed consent has been obtained) but must be updated following transplant and prior to dosing.

[g] A complete physical examination (PE) will be performed at screening and at Week 24; abbreviated PEs, targeted to new signs and symptoms, will be performed at all other assessments.

[h] Blood pressure and pulse rate, after the subject has rested quietly for ≥ 5 minutes, and temperature (any measurement site).

[i] Height will be captured at screening only.

[j] Blood and urine will be collected for testing by the designated central safety laboratory using standard hematology (including PT-INR), serum chemistry, and urinalysis panels. To monitor renal function, eGFR will be calculated by the central safety laboratory using MDRD4 (Levey 2006). See Table 12 for a list of test parameters.

[k] Urine beta-human chorionic gonadotropin (β-hCG) for women of childbearing potential, reflex to serum β-hCG if positive.

[l] Pretransplant results may be used to satisfy the protocol entry criteria, if collected within 6 months prior to the qualifying transplant.

[m] Blood (plasma) samples will be collected at screening, on the FDD, and weekly throughout the treatment phase and at each posttreatment assessment. Each sample will be divided into aliquots for (1) “real-time” assay of CMV viremia in plasma using the FDA-approved and CE-marked Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test;

(2) possible "real-time" testing for other dsDNA viruses (e.g., AdV, BKV, EBV, HHV-6, etc.) in the presence of suggestive clinical symptoms, and (3) one or more storage samples for resistance testing (genotypic and/or phenotypic); additional CMV viremia assessments, based on newly available assays; for retrospective analyses for other dsDNA viruses; and/or for possible testing for biomarkers of GVHD or CMV-specific immunity. [Note: Plasma CMV viremia must be assessed by the designated central virology laboratory within 5 days prior to randomization; only subjects who are determined to be CMV viremia negative on screening assessment (i.e., CMV DNA in plasma is "Not Detected" for the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test used by the central virology laboratory) will be eligible for randomization. In addition, the results of any CMV viremia testing (including CMV PCR, pp65 antigenemia, etc.) performed as part of local SoC since the qualifying transplant must also be negative.]

[n] A blood sample to evaluate the potential for reconstitution of the anti-CMV immune response using the T-SPOT.® *CMV* Test (Oxford Immunotec Limited, Abingdon, UK) will be collected at Weeks 5, 9, 14, and 24. These samples will be collected from individual study participants where the investigator believes the additional blood loss resulting from the collection of the samples is medically acceptable. For those individuals where the investigator feels that the additional blood loss is not medically acceptable, then some or all of these samples may be omitted, as necessary. A collection window of up to +2 weeks from the scheduled collection date is provided to allow for additional flexibility in the collection of these samples.

[o] Urine collected at screening, on the FDD, and weekly throughout the treatment phase and at each posttreatment assessment will be divided into one or more aliquots and stored for possible future analysis, including retrospective analyses of CMV and/or other dsDNA viruses, resistance testing, etc. In consultation with the Chimerix Medical Monitor (or designee), investigators may request real time analysis of the urine samples for subjects with known or suspected BK viruria or subjects exhibiting signs/symptoms consistent with BKV or AdV infection, such as cystitis or renal impairment.

[p] When a dsDNA viral syndrome or disease is suspected, other relevant biological samples (e.g., stool, cerebrospinal fluid [CSF], sputum, bronchoalveolar lavage, skin or nasopharyngeal swab, tissue biopsy, etc., as appropriate) should be sent to the designated central virology laboratory for "real time" analysis and/or storage for possible future analysis. Prior approval is required from the Chimerix Medical Monitor (or designee) for the analysis of any samples other than blood (plasma) for CMV viremia.

[q] The following information will be captured for each immunosuppressant: dose, concentration value (most recent value since last study visit if multiple values are available), concentration units, matrix (whole blood, plasma, or serum), date and time of sample collection, and date and time of last dose of immunosuppressant medication prior to sample collection.

[r] Subjects will be randomized within 1 business day of their scheduled FDD, taking into account normal site logistics, using the IV/WRS. During randomization, subjects will be stratified within an investigative center, based on their likelihood for progression to clinically significant CMV infection, i.e., a "lower likelihood" versus a "higher likelihood" of progression. Subjects who receive a matched, related, non-T-cell depleted graft (e.g., excluding cord blood), who do not have aGVHD, who have not received ATG or alemtuzumab, and who are not receiving high-dose (≥ 1 mg/kg prednisone equivalent) systemic steroids will be stratified in the "lower likelihood" group. All other subjects will be stratified in the "higher likelihood" group.

Error! Reference source not found. The second card of study drug in each study drug kit should be dispensed to subject at an appropriate time, taking into account the actual duration of the individual subject's treatment, any dose interruptions due to AEs, other missed doses, logistical issues (e.g., public holidays, vacation), etc. If a subject dose reduces in response to a treatment-emergent toxicity, then the dispensing of the new study drug kit can occur at any time during the treatment phase.

[t] Subjects will be randomized in a 2:1 ratio under double-blind conditions to either 100 mg CMX001 BIW or placebo BIW. Study drug will be dosed orally, using CMX001 tablets or matching placebo, and taken with food (as a low-fat meal comprising no more than 20% of its total caloric value from fat) where subjects are able to tolerate oral intake. Where possible, at least one of the two weekly doses of study drug will be administered by the investigator or designee; otherwise, study drug will be self-administered by the subject on the protocol-specified day or as close as possible thereto. Doses should be administered at alternating 3- and 4-day intervals (e.g., each Monday and Thursday, each Tuesday and Friday, each Wednesday and Saturday, etc.)

[u] A single timed blood sample for analysis of plasma concentrations of CMX001 and CDV (and possibly other metabolites) will be collected on the FDD at 3 (± 1) hours postdose. In addition, a single PK blood sample for analysis of plasma concentrations of CMX001 and CDV (and possibly other metabolites) will be collected during each scheduled weekly assessment for as long as the subjects remain on blinded study treatment. If the timed blood sample cannot be collected on the FDD, e.g., due to scheduling or resource issues, it may be collected within the same time window, i.e., at 3 (± 1) hours postdose, following administration of the second dose of study drug.

[v] Each subject will complete the EQ-5D-5L and EORTC-QLQ-C30/HDC29 questionnaires during the screening evaluation or prior to study drug administration on the FDD (to establish baseline), then at Week 6, Week 15, and Week 24.

[w] A mini-mental state examination (MMSE) will be performed in all subjects on the FDD prior to study drug administration (to establish baseline), with subsequent assessments performed at Week 6, Week 10, Week 15, and Week 24. At selected sites, subjects may be asked to undergo a more detailed assessment of their neurocognitive function using the validated Brief Test of Adult Cognition by Telephone (BTACT) and Oral Trail Making Test (OTMT-B) instruments. This optional assessment will be performed one time at Week 24. The test will be administered over the telephone and the subject's responses will be recorded, for scoring purposes, using audio recording software. Subjects who agree to undergo the more detailed neurocognitive assessment do not have to complete the MMSEs scheduled for Weeks 6, 10, 15, and 24. Additional MMSEs may be

performed in individual subjects (whether participating in the optional Week 24 assessment or not), when deemed clinically appropriate to do so by the investigator, e.g., based on responses to screening questions on the study diary card.

[x] For assessment of the onset of CMV disease and other dsDNA viral syndrome or disease (e.g., assessments for BK urinary symptoms, initiated in subjects with increased urine frequency during the day, increased nocturia, or bladder pain or MMSE testing in subjects suspected of HHV-6 CNS impairment). [Note: Common disease manifestations of dsDNA virus infections are listed in Appendix 2]

[y] Slides from any biopsy performed for the diagnosis of GVHD (regardless of the organ involved), and all GI biopsies or biopsies from any organ conducted to diagnose CMV disease (or other dsDNA viral syndrome or disease), should be sent to the designated central laboratory. Specific guidance with respect to biopsy sampling and handling will be provided in the SRM and/or applicable central laboratory manual.

[z] The study diary card will contain dosing information (date and time of dosing, whether the dose was taken with or within 30 minutes after finishing a meal), number of liquid stools per day, urine frequency if > 4-times per day or nocturia, bladder pain and delirium screening questions, contact information for the site when specific criteria are met.

[aa] Diarrhea and/or GVHD will be assessed weekly and during any unscheduled assessments where symptoms have changed since the previous assessment.

[bb] AEs will be recorded from the time of administration of the first dose of study drug until the subject has completed the study, i.e., following completion of the Week 24 assessment or premature discontinuation from the study, whichever occurs first. In addition, any study procedure-related AE that occurs after study participants have signed the informed consent from (ICF) and prior to administration of the first dose of study drug will be recorded as an AE.

8.4. Dose Adjustment Criteria

8.4.1. Dose Interruption or Discontinuation

For subjects who experience TEAEs during the study, the investigator will have the option of interrupting dosing (for up to 4 doses or 18 consecutive days) and resuming dosing once the AE has improved as described in the toxicity management section of the protocol (Section 13).

Study drug may be interrupted for:

- Persistent diarrhea, defined as Grade 2 diarrhea for more than 3 consecutive days, if no other etiology has been identified, particularly if the symptoms are noted 2 to 8 weeks after the initiation of blinded study drug and when a decrease in serum albumin from baseline of ≥ 4 g/L reaching to serum albumin concentrations of ≤ 30 g/L is noted in the absence of other etiology for hypoalbuminemia

Study drug will be interrupted for:

- Grade 3 or higher diarrhea;
- Confirmed increase in serum aminotransferases (ALT or AST) that is 1) > 8x ULN and 2x baseline; 2) > 5x ULN for at least 2 weeks and 2x baseline; 3) > 3x ULN (and 2x baseline) and with a total bilirubin > 2x ULN or PT-INR > 1.5x ULN, or 4) > 3x ULN (and 2x baseline) with the appearance of clinically relevant signs/symptoms of liver injury, including fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia (> 5% of total white blood cell [WBC] count), or
- Stage 3 or higher GI-GVHD that is unresponsive to SoC therapy.

If the subject is unable to take his/her study drug on the protocol-specified day due to AEs, then the subject should be treated for the event, as appropriate, and returned to the clinic to be dosed as soon as possible. Please refer to Section 11.5 for additional guidance on resuming dosing in subjects who interrupt dosing (up to the maximum permitted interruption of 4 doses or 18 days).

8.4.2. Dose Modification or Dose Reduction

In certain circumstances, a change in dose frequency ("dose modification") may be an appropriate course of action in response to a TEAE, followed by a reduction in dose ("dose reduction"), as necessary, if the TEAE persists or the subject experiences a new TEAE of concern. When a dose modification, or subsequent dose reduction, is being considered, the investigator must first contact the Chimerix Medical Monitor (or designee) to discuss the proposed change before initiating the dose modification or reduction.

For the purposes of this protocol, "dose modification" describes administering the same total weekly dose, but changing the dose frequency from BIW to QW, i.e., from 100 mg CMX001 BIW to 200 mg CMX001 QW for subjects randomized to Treatment 1. "Dose reduction" describes reducing the previously modified dose while keeping the QW administration, i.e., from 200 mg CMX001 QW to 100 mg CMX001 QW for subjects randomized to Treatment 1. Similar changes will be made for subjects randomized to Treatment 2 (i.e., changing from placebo BIW to placebo QW for requests to both dose modify and dose reduce), thereby allowing for changes

to be made to both treatment regimens in response to potential treatment-related toxicities, while maintaining the overall study blind.

9. SELECTION AND WITHDRAWAL OF SUBJECTS

9.1. Screening Procedures

The following procedures will be performed for all potential subjects during the screening evaluation. All screening procedures do not need to be completed on the same day, but all screening procedures must be completed and the results reviewed prior to initiating treatment on the FDD.

- Obtain written informed consent
- Obtain medical and medication history, including transplant history, current immunosuppressive regimen, etc.
- Complete physical examination
- Height
- Body weight
- Vital signs measurements (blood pressure and pulse rate, after the subject has rested quietly for ≥ 5 minutes, and temperature [any measurement site])
- CMV and other dsDNA virus signs and symptoms assessment
- Diarrhea and GVHD assessment
- Complete EQ-5D-5L and EORTC-QLQ-C30/HDC29 questionnaires
- Clinical laboratory evaluations: hematology, including coagulation panel; serum biochemistry, including eGFR; urinalysis; serology for HIV and viral load for HBV and HCV (unless performed within 6 months prior to the qualifying transplant); and pregnancy test (women of childbearing potential only) (see Table 12 for a list of individual test parameters)
- Blood (plasma) for virologic analyses (see Section 12.1.1)
- Urine for virologic analyses (see Section 12.1.1)
- Other samples for virologic analysis, as applicable (see Section 12.1.1)
- Review protocol entry criteria and other protocol restrictions

Potential subjects may be consented for participation in the study before or after transplant. Subjects providing written informed consent will be screened following transplant as soon as the subject can ingest tablets, but no later than Day 28 posttransplant. If preferred, medical history may be obtained before transplant (and after written informed consent has been obtained) but must be updated following transplant and prior to dosing. CMV viremia must be assessed by the central virology laboratory within 5 days prior to randomization and only those subjects who are determined to be CMV viremia negative at screening (i.e., CMV DNA in plasma is "Not Detected" for the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test used by the central virology laboratory), and at all prior assessments (including CMV PCR and pp65 antigenemia test results) performed under local SoC since the qualifying transplant, will be eligible for randomization.

9.2. First Dose Day (FDD)

The following procedures will be performed on the FDD. Unless specifically noted otherwise, all procedures should be performed prior to administration of the first dose of study drug to establish baseline measures.

- Update medical and medication history, including current immunosuppressive regimen, since the screening evaluation
- Abbreviated physical examination, targeted to new signs/symptoms
- Body weight
- Vital signs measurements (blood pressure and pulse rate, after the subject has rested quietly for ≥ 5 minutes, and temperature [any measurement site])
- CMV signs and symptoms assessment
- Diarrhea and GVHD assessment
- Clinical laboratory evaluations: hematology; lymphocyte subset (CD4+ and CD8+); coagulation panel; serum biochemistry, including eGFR; urinalysis; pregnancy test (women of childbearing potential only) (see Table 12 for a list of individual test parameters), results of urine pregnancy test must be obtained and confirmed as negative prior to dosing
- Blood (plasma) for virologic analyses
- Urine for virologic analyses
- Other samples for virologic analysis, as applicable
- Complete EQ-5D-5L and EORTC-QLQ-C30/HDC29 questionnaires (if not completed at screening)
- Complete neurocognitive questionnaire (e.g., MMSE)
- Review protocol entry criteria and other protocol restrictions
- Review/record AEs, as applicable
- Randomize subject in the IV/WRS
- Dispense and administer first dose of study drug
- Provide study diary card/aide mémoire
- Blood for analysis of plasma concentrations of CMX001 and CDV: 3 (± 1) hours postdose (i.e., between 2 and 4 hours postdose). If the blood sample cannot be collected on the FDD, e.g., due to scheduling or resource issues, it may be collected within the same time window, i.e., at 3 (± 1) hours postdose, following administration of the second dose of study drug.

9.3. Subject Inclusion Criteria

Subjects must meet all of the following criteria, as applicable, to be eligible to participate in this study:

1. Allogeneic HSCT recipient who has prior evidence of CMV exposure before transplantation and who is CMV viremia negative at screening and at any other assessments performed prior to the FDD.

   [Note: CMV viremia must be reported as negative by the central virology laboratory (i.e., CMV DNA in plasma is "Not Detected" for the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test used by the central virology laboratory) no more than 5 days prior to randomization. In addition, all CMV viremia test results (including CMV PCR, pp65 antigenemia, etc.) performed as part of local SoC since the qualifying transplant must also be negative.]

2. Aged ≥ 18 years.

   [Note: The minimum acceptable age may be higher depending on local regulations.]

3. If male, willing to use an acceptable contraceptive method(s) throughout the duration of his participation in the study, i.e., through Week 24, when engaging in sexual intercourse with a female subject of childbearing potential.

4. If a female of childbearing potential, i.e., not postmenopausal or surgically sterile, willing to use two acceptable contraceptive methods, one of which must be a barrier method, throughout the duration of her participation in the study, i.e., through Week 24, when engaging in sexual intercourse with a non-sterile male partner.

   [Note: For assessing inclusion criterion 3 or 4, a promise to abstain from sexual intercourse is not an acceptable method of preventing pregnancy for the purposes of this protocol. However, subjects who are currently sexually abstinent and who indicate a willingness to use an acceptable contraceptive method(s), as described above, should they begin or resume sexual activity may be enrolled into the study. As applicable, female subjects of childbearing potential who discontinue the study prior to Week 24 (e.g., who withdraw consent) should be advised to continue their contraceptive methods with a non-sterile male partner for at least 90 days after the last study drug administration. Male subjects who discontinue the study prior to Week 24 should be advised to continue their contraceptive method(s) with a female partner of childbearing potential for at least 90 days after their last study drug administration).]

5. Able to begin study drug dosing within 28 days following HSCT.

6. Able to comfortably ingest and absorb oral medication (in the judgment of the investigator and based on lack of significant GI events/medical history).

   [Note: The use of TPN or NPO (nil per os) is not in and of itself exclusionary as long as the reason would not disqualify the subject based on this criterion.]

7. Willing and able to understand and provide written informed consent.

8. Willing and able to participate in all required study activities for the entire duration of the study (i.e., through Week 24).

9.4. Subject Exclusion Criteria

Subjects who meet *any* of the following criteria are not eligible to participate in this study:

1. If female, the subject is pregnant or planning to become pregnant during the anticipated duration of her participation in the study (i.e., through Week 24), or nursing a child.
2. Subjects who have a positive CMV viremia test (through central or local virology laboratory) at any time between transplant and the FDD.
3. Subjects who weigh ≥ 120 kg (~ 265 lbs.)
4. Subjects with hypersensitivity (not renal dysfunction or eye disorder) to CDV or to CMX001 or its excipients.
5. Subjects who have received (or who are anticipated to need treatment with) any of the following:
   - GCV, vGCV, FOS, IV CDV, or any other anti-CMV therapy (including CMV immune globulin [CMV Ig], cell-based therapies, and investigational anti-CMV drugs, e.g., leflunomide, letermovir [previously AIC246], or maribavir) at any time posttransplant;
   - any anti-CMV vaccine at any time;
   - any other investigational drug within 14 days prior to the FDD (unless prior approval has been received from the Chimerix Medical Monitor or designee), or
   - prior treatment with CMX001 at any time.

   [Note: An "investigational drug" is defined as any drug that is not approved for any indication by the FDA (or appropriate regulatory authority).]
6. Subjects receiving acyclovir (ACV) orally at > 2,000 mg total daily dose (TDD) or intravenously at > 15 mg/kg TDD, valacyclovir (vACV) at > 3,000 mg TDD or leflunomide at any dose on the FDD or who are anticipated to receive any of these drugs at the doses described after the FDD.
7. Subjects who are receiving digoxin or ketoconazole (other than topical formulations) at the FDD or are anticipated to need treatment with digoxin or ketoconazole during the treatment phase (through Week 14).
8. Subjects with possible, probable or definitive CMV disease diagnosed within 6 months prior to the FDD.
9. Subjects who are HIV-infected (based on serology), or who have an active HCV or HBV infection as evidenced by detectable plasma HCV ribonucleic acid (RNA) or HBV DNA, respectively.

   [Note: Documented results from tests performed up to 6 months prior to the qualifying transplant may be used to satisfy this criterion. Negative results for HBV and HCV PCR tests are required to confirm the absence of active infection(s). If necessary, investigators should contact the Chimerix Medical Monitor for prior approval to randomize a subject who meets all other entry criteria based on the results of negative PCR testing performed at a local laboratory in lieu of pending results from the relevant central laboratory.]

10. Subjects who have received another allogeneic HSCT (i.e., other than the qualifying HSCT) within 2 years prior to the FDD.

    [Note: Subjects who have received one or more autologous transplants, in addition to the qualifying allogeneic HSCT, are not excluded from participation in the study.]

11. Subjects with renal insufficiency, as evidenced by an eGFR < 15 mL/min or requiring renal dialysis.

    [Note: Each subject's eGFR will be calculated by the central safety laboratory using MDRD4 (Levey 2006).]

12. Subjects with hepatic abnormalities as evidenced by a screening ALT or AST > 5x ULN as reported by the central safety laboratory.

13. Subjects with a screening total bilirubin > 2x ULN and direct bilirubin > 1.5x ULN as reported by the central safety laboratory.

    [Note: In consultation with the Chimerix Medical Monitor (or designee), subjects with laboratory values that meet a disqualifying threshold in either exclusion criterion 12 or 13 may be enrolled based on acceptable repeat test results performed within 28 days posttransplant. One repeat test will be allowed per subject. At the discretion of the Chimerix Medical Monitor (or designee), local laboratory tests results may be assessed in lieu of pending tests results from the central safety laboratory (e.g., where logistical issues would preclude waiting for the central safety laboratory tests results). Blood and urine samples for assessment by the central safety laboratory should be drawn in parallel to the blood and urine samples sent to the local laboratory. For subjects for whom serum aminotransferase and/or total or direct bilirubin concentrations drawn prior to the FDD, are subsequently found to be disqualifying, as per exclusion criterion 12 or 13, at the time of FDD, the investigator should immediately contact the Chimerix Medical Monitor (or designee) to discuss continuation of the subject in the study. Subjects who meet any of the dose interruption criteria described in Section 13.1.3 must have study drug interrupted.]

14. Subjects with active solid tumor malignancies with the exception of basal cell carcinoma or the underlying condition necessitating the stem cell transplant (e.g., lymphomas).

15. Subjects with Stage 2 or higher GI-GVHD or any other GI disease that would, in the judgment of the investigator, preclude the subject from taking or absorbing oral medication (e.g., clinically active Crohn's disease, ischemic colitis, moderate or severe ulcerative colitis, small bowel resection, ileus, or any condition expected to require abdominal surgery during the course of study participation).

16. Any other condition, including abnormal laboratory values, that would, in the judgment of the investigator, put the subject at increased risk by participating in the study, or would interfere with the conduct or planned analyses of the study.

9.5. Subject Withdrawal and Replacement

Subjects who experience any of the following criteria after initiating study drug will be required to discontinue study drug:

- Treatment with, or requirement for treatment with, an excluded medication (see Section 10.2.1). This criterion includes subjects who meet the primary endpoint and require anti-CMV PrT during the treatment phase as described in Section 8.1.
- Persistent neutropenia without an alternative explanation. "Persistent" is defined by the investigator using standard site definitions, as applicable. In the absence of a definitive alternative explanation, subjects with persistent neutropenia will be discontinued from study drug.
- Decrease in eGFR to < 15 mL/min or a new or persistent requirement for renal dialysis, if the eGFR change or the requirement for dialysis is considered to be study drug-related. If there is an alternative explanation for the decrease in eGFR or the requirement for dialysis, the investigator should contact the Chimerix Medical Monitor (or designee) to discuss the subject's condition and most appropriate course of action. For subjects with an on-treatment decrease in eGFR to < 15 mL/min that is not related to study drug, then study drug treatment may be continued if dialysis or other renal replacement therapy (RRT) is initiated. RRT must be continued for as long as the subject's eGFR remains < 15 mL/min and the subject remains on study drug.
- Female subjects who become pregnant will be immediately discontinued from study drug, but will continue to be followed in the study.

  If a subject suspects that she is pregnant, a urine test will be performed at the site. If the urine test is positive, study drug administration will be interrupted pending the results of a confirmatory blood/serum test. If the pregnancy is confirmed with a positive blood/serum test, then the subject will be permanently discontinued from study drug, but should remain in the study, where possible.

  If the female partner of a male subject becomes pregnant, the investigator will contact the Chimerix medical monitor (or designee) to discuss the most appropriate course of action, up to and including withdrawal of study drug. [Note: Pregnancy is not in and of itself considered an AE or SAE for the purposes of this protocol; however, the pregnancy (in a female subject or the female partner of a male subject) must be followed through termination or delivery, as applicable, provided the appropriate consent is obtained from the female partner.]

In addition, if any of the following criteria are met, study drug may be discontinued at the discretion of the investigator, in consultation with the Chimerix Medical Monitor (or designee):

- Development of an exclusionary condition other than CMV infection/disease
- Unacceptable toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest (see also Section 13)
- Request of the primary care provider if (s)/he believes that the study is no longer in the best interest of the subject
- Subject request to discontinue for any reason
- Subject is not compliant with the protocol (i.e., significant protocol deviation)

- Discontinuation of the study at the request of Chimerix, Inc., a regulatory agency, or the governing institutional review board (IRB)/research ethics board (REB) in USA/Canada or an independent ethics committee (IEC) outside USA/Canada

Subjects who discontinue study drug (for whatever reason) prior to Week 14 and subjects who are randomized but not dosed will remain in the study through Week 24. The subjects will be managed at the discretion of the responsible investigator according to local SoC, but will continue to be monitored in accordance with the Schedule of Study Assessments/Procedures (see Table 9).

Subjects who are randomized, but not dosed will not be counted as part of the targeted 450 subject sample size (and will not be considered in the ITT analysis). Subjects who are randomized and dosed, but who do not complete the study will not be replaced.

9.5.1. End-of-Study Scenarios

The following end-of-study scenarios will be followed, as appropriate:

- If the subject does not have any ongoing GI or hepatic AEs or any ongoing SAEs, then the subject will be discontinued from the study following completion of the Week 24 assessment.
- If the subject has an ongoing Grade 3 or higher GI or hepatic AE (not isolated laboratory abnormalities) with no identified explanation or has an ongoing SAE, then (s)he will be followed until the event resolves or returns to baseline, stabilizes, or until the subject is considered lost to follow-up.

10. TREATMENT OF SUBJECTS

10.1. Description of Study Drug

Subjects randomized to the CMX001 treatment arm will receive the following:

- Treatment 1: 100 mg CMX001, administered orally as one 100 mg CMX001 tablet, BIW

Subjects randomized to the placebo treatment arm will receive the following:

- Treatment 2: placebo, administered orally as one matched tablet, BIW

All doses should be given with or within 30 minutes after finishing a low-fat meal. The study drug doses should be administered at alternating 3- and 4-day intervals (e.g., each Monday and Thursday, each Tuesday and Friday, each Wednesday and Saturday, etc.)

The overall duration of study drug will depend on when the subject initiates blinded treatment relative to the date of transplant. Treatment will begin no later than Day 28 posttransplant, and will continue through Week 14. Subjects completing the entire treatment phase of the study will receive from 10 to 14 weeks of study drug. All randomized subjects will be followed until Week 24, regardless of whether the subject completes the treatment phase. Thus, each subject's participation in the study will range from approximately 20 to 24 weeks.

10.2. Concomitant Medications

Medications that may not be used throughout the conduct of this study are described in Section 10.2.1.

To date, there is no evidence of any significant drug:drug interactions occurring between CMX001 and immunosuppressant or other medications commonly used in this population. However, until definitive data are available, investigators should remain cautious regarding the potential for drug:drug interactions and conduct therapeutic drug monitoring of concomitant immunosuppressive therapies according to site standard practices. Concentration results of plasma or blood samples collected to assess exposure to immunosuppressant drugs as part of the local SoC should be reported on the eCRF and include for each immunosuppressant: the immunosuppressant dose, concentration value, concentration units, matrix (whole blood, plasma, or serum), date and time of sample collection, and date and time of last dose of immunosuppressant medication prior to sample collection. This information will be compiled together with CMX001 *in vitro* drug interaction data in order to inform the need for formal drug:drug interaction studies with individual immunosuppressant drugs.

Prior and concomitant medications should be recorded as follows:

1. Prior medications to be recorded are those taken within the 30-day period prior to the FDD, and are limited to anti-infectives, immunosuppressants, GI medications, steroids, and the subject's conditioning regimen.
2. Concomitant medications to be recorded are all medications (both over-the-counter and prescription drugs) taken during the course of the study, i.e., from the FDD through study completion. However, IV fluids, vitamins, and nutritional or electrolyte supplements

(other than oral magnesium) do not need to be entered in the eCRF. Herbal supplements are considered medications for the purpose of this study.

3. Non-steroid medications, including medications that qualify a subject for "high likelihood of CMV infection" stratification or "aggressive CMV management", i.e., ATG or alemtuzumab, and all anti-CMV PrT medications, should be recorded on the Prior and Concomitant Medications eCRF.
4. Steroid medications (both topical and systemic), including any steroids that qualify a subject for "high likelihood of CMV infection" stratification or "aggressive CMV management", should be recorded on the Prior and Concomitant Steroid Medications eCRF, not on the Prior and Concomitant Medications eCRF.
5. For each recorded medication, the indication should be the condition necessitating the use of the medication and not the therapeutic class of the drug. For indications of acute or chronic GVHD, the indication must indicate whether the treatment is for prophylaxis, presumptive treatment, or treatment of GVHD. For anti-CMV PrT medications, the recorded indication should be "Preemptive therapy CMV".

See the SRM for additional guidance on the recording of prior and concomitant medications.

10.2.1. Prohibited Medications

Antiviral Medications:

The following is a list of antiviral medications that are prohibited either prior to or starting on the FDD (as specified below):

Prohibited at any time (prior to and during the study):

- anti-CMV vaccines
- prior treatment with CMX001

Prohibited from transplant through Week 24:

- leflunomide
- letermovir
- maribavir
- other investigational anti-CMV drugs
- cell-based anti-CMV therapies

Prohibited from transplant through Week 24 unless initiated post-FDD as anti-CMV PrT per protocol:

- vGCV
- IV and PO GCV
- FOS
- IV CDV

- CMV Ig (such as Cytogam®)

Prohibited from FDD through the end of treatment (i.e., last dose of study drug + 7 days):

- high-dose ACV (i.e., > 2,000 mg PO TDD or > 15 mg/kg IV TDD)
- high-dose vACV (i.e., > 3,000 mg TDD)

  [Note: These ACV and vACV doses are for subjects with normal renal function. Subjects who are taking high doses of ACV or vACV prior to the FDD are allowed to reduce their dose of these medications on the FDD]

Antiviral agents that are administered systemically to treat other dsDNA viruses, or signs and symptoms associated with such viruses, may only be used if the agent does not have known anti-CMV activity. For example, the use of fluoroquinolones, ribavirin, and rituximab would be permitted, while the use of FOS to treat ACV-resistant HSV would not be permitted and its use would necessitate the immediate discontinuation of study treatment. The topical use of other antiviral agents (e.g., intravesical CDV for HC) is permitted.

Other Medications:

The following medications are prohibited:

Prohibited from FDD through the end of treatment (last dose of study drug + 7 days):

- Digoxin
- ketoconazole (non-topical formulations)

In vitro data suggest that CMX001 may inhibit the P-gp (P-glycoprotein) efflux transporter, an important membrane transporter involved in the uptake of digoxin, a P-gp substrate with a narrow therapeutic range, from the gut; therefore, the concurrent use of digoxin is prohibited throughout the treatment phase of the study (i.e., from the FDD until last dose of study drug + 7 days). Caution should be exercised when coadministering other drugs with a narrow therapeutic index for which P-gp plays a significant role in the uptake or elimination of those drugs (see also Section 6.2.1).

In vitro data suggest that CYP-mediated metabolism of CMX001 is primarily mediated by CYP4F2, and therefore the potential for a drug-drug interaction mediated by modulators of CYP4F2 activity is theoretically possible. For example, coadministration of the CYP4F2 inhibitor, ketoconazole, with CMX001 may result in an increase in exposure to CMX001, based on literature precedent with other drugs eliminated primarily by CYP4F2; therefore, the concurrent use of ketoconazole (other than in topical formulations) is prohibited throughout the treatment phase of the study (i.e., from the FDD until last dose of study drug + 7 days). No interaction is expected with other azole antifungal agents, including voriconazole, fluconazole or posaconazole, based on *in vitro* data demonstrating that these drugs do not inhibit CYP4F2 at relevant physiological concentrations.

Coenrollment in Other Studies:

Coenrollment of subjects in other interventional clinical studies involving the administration of an investigational drug(s) (i.e., a drug or drugs not approved by FDA [or appropriate regulatory authority] for any indication) is not permitted while the participants are enrolled in the current study (including the 10-week posttreatment phase).

Coenrollment into other interventional studies involving the administration of non-investigational drugs, which includes the administration of FDA (or other regulatory authority)-approved drugs being evaluated for non-approved indications, is permitted with the prior approval of the Chimerix Medical Monitor (or designee).

Coenrollment in interventional studies prior to the FDD will be evaluated on a case by case basis after consultation with the Chimerix Medical Monitor (or designee).

Generally, coenrollment in studies involving conditioning regimens or graft manipulation will be allowed as long as the study intervention and endpoint exclude impact on CMV infection.

10.3. Treatment Compliance

While subjects are inpatient, the twice-weekly doses of study drug should be administered under the supervision of site personnel. If the subjects are outpatient, at least one of the two weekly doses of study drug should be administered in the clinic under supervision. The second weekly dose may also be administered in the clinic, if preferred, or it may be self-administered by the subject away from the clinic on the specified day. Subjects will be required to document on a diary card the actual date and time that they take each self-administered dose of study drug, and whether the dose was taken with or within 30 minutes after a meal (see Section 10.3.1 for more information about the diary card). Subjects will be required to bring the study drug card (even if empty) and the diary card back to the clinic at each weekly visit, so site personnel can complete study drug accountability. Each site will be encouraged to put in place a documented procedure to remind the subject to take any self-administered doses on schedule (e.g., by sending the subject a reminder email/text message and/or placing a reminder telephone call to the subject).

10.3.1. Study Diary Card/Aide-mémoire

Each subject will be provided with a diary card on which (s)he can record the actual date and time that each self-administered dose of study drug is taken, and whether the dose was taken with or within 30 minutes after finishing a meal. The diary card will also be used as a prompt for or means to record information related to signs and symptoms of interest, such as GI-related symptoms (e.g., number of liquid stools per day), urinary or bladder-related symptoms (e.g., urine frequency if > 4 times per day or increased nocturia, bladder pain, cystitis, dysuria, etc.) and screening questions for delirium. The main purpose of the diary card is to serve as an aide mémoire for subjects to complete and for the sites to use in discussing signs and symptoms with outpatient subjects during their study visits. As such, not all information collected on the diary card will be entered in the eCRF. The diary card will also contain contact information that the subject can use to contact the site when these specific criteria are met. A sample diary card is provided in the SRM.

10.4. Randomization and Blinding

All treatments will be administered under double-blind conditions, i.e., neither the subject nor the investigator and clinic staff will be aware of the individual subject treatment assignment.

Subjects who meet all applicable eligibility criteria will be randomized to one of two treatment arms in a 2:1 ratio using an automated IV/WRS system. During randomization, subjects will be stratified within an investigative center, based on their likelihood for progression to clinically

significant CMV infection, i.e., a "lower likelihood" versus a "higher likelihood" of progression. Subjects who receive a matched, related, non-T-cell depleted graft (e.g., excluding cord blood), who do not have aGVHD, who have not received ATG or alemtuzumab, and who are not receiving high-dose (≥ 1 mg/kg prednisone equivalent) systemic steroids will be stratified in the "lower likelihood" group. All other subjects will be stratified in the "higher likelihood" group.

10.4.1. Breaking the Blind

Throughout the conduct of the study, breaking the blind by the investigator should only be considered as a last resort when subject safety is clearly at risk and the knowledge of treatment assignment is necessary to make medical decisions. If an investigator is considering breaking the blind, he/she should first contact the Chimerix Medical Monitor (or designee) to discuss the need for unblinding. When a study subject experiences an AE or SAE that, in the opinion of the investigator, requires breaking of the blind in order to effectively treat the subject, then the investigator should use the IV/WRS to break the blind and notify the Chimerix Medical Monitor (or designee) of the breaking of the blind, but should not reveal the treatment assignment. Reasons for breaking the blind should be documented in the subject's source documentation and his/her electronic case report form (eCRF). If the blind is broken for any given subject, the subject should be discontinued from study treatment, but will continue to be followed in the study. Even if the investigator is unblinded, other study personnel and the subject should remain blinded to the extent possible.

In addition to the investigator, the DSMB Chairperson and/or DSMB may unblind a subject or treatment groups according to the procedures detailed in the DSMB Charter. For safety reporting purposes the treatment blind may be broken by specified and documented personnel in the Chimerix regulatory affairs group (or designee), as required by local regulations. Such information will not be communicated to non-specified individuals, other departments within Chimerix or to the investigative site. One or more individuals independent of the study team at the clinical research services vendor will be responsible for preparing and providing unblinded data packages to the DSMB.

The independent statistician responsible for generating the randomization schedule for the study will be unblinded, as will relevant personnel at the independent drug packaging facility. The unblinded statistician will be independent of all study design, conduct, and analysis activities. He or she will not be an employee of Chimerix and will not be a part of the study team at the clinical research services vendor. He or she will solely be responsible for generating the unblinded subject randomization schedule, ensuring its alignment with the study protocol, and transmitting the schedule in a secure manner to the drug packaging vendor.

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Study Drug

CMX001 will be administered orally as dry-blend, direct-compressed tablets of 100 mg strength. In addition to the active ingredient, CMX001 tablets contain microcrystalline cellulose, mannitol, crospovidone, and magnesium stearate. Placebo will be administered orally using matched tablets. Additional information on the CMX001 and placebo tablets is provided in Table 10.

Table 10: Summary of Investigational Product

Product Name:	CMX001 Tablets, 100 mg, debossed "CMX"	Placebo to match CMX001 Tablets, 100 mg, debossed "CMX"
Dosage Form:	Tablet	
Unit Dose:	100 mg	0 mg
Route of Administration:	Per os (oral)	
Physical Description:	White to off-white, round biconvex tablets debossed with "CMX" on one side	
Manufacturer:	UPM Pharmaceuticals, Inc. 6200 Seaforth Street Baltimore, MD 21224, USA	

Study drug will be administered as shown in Table 11.

Table 11: Summary of Study Drug Administration

Treatment Group	**Original BIW Treatment Assignment** [a]		**Dose Modification Treatment (*if needed*)**	**Dose Reduction Treatment (*if needed*)**
	First dose	**Second dose**		
1	One 100 mg CMX001 tablet	One 100 mg CMX001 tablet	Two 100 mg CMX001 tablets (200 mg) QW	One 100 mg CMX001 tablet and one placebo tablet (100 mg) QW
2	One placebo tablet	One placebo tablet	Two placebo tablets QW	Two placebo tablets QW

[a] During the initial treatment assignment, the twice-weekly doses of study drug should be administered at alternating 3- and 4-day intervals. Where possible, all doses of study drug should be taken on the same two days each week (e.g., each Monday and Thursday, each Tuesday and Friday, each Wednesday and Saturday, etc.) Regardless, there must be a washout interval of at least 2 days between two consecutive doses of study drug.

11.2. Study Drug Packaging and Labeling

The CMX001 and placebo tablets are blister packaged into strips (7 tablets per strip) using an Aclar® fluropolymer film on polyvinylchloride (PVC) with an aluminum foil 20 μm (micron) "push-through" blister lid.

Once blister packaged, the tablets will be assembled into a blinded study kit that contains two child-resistant, Key-Pac™ fold-over style cards of study drug (CMX001 and/or placebo).

Each card contains sufficient study drug for 7 weeks treatment (i.e., 2 strips or 14 tablets/card), so each kit contains enough study drug (28 tablets/kit) for the maximum possible duration of study treatment (i.e., 14 weeks or 28 doses) for one subject. At the start of treatment, each subject will be dispensed one card from the kit according to the randomization number assigned to that subject by the IV/WRS. When the first card is completed, the subject will receive the remaining card from the same study kit.

Each card will be labeled in accordance with applicable regulatory requirements. Cards supplied in the USA will include, at a minimum, the following information:

- Chimerix protocol number (CMX001-301)
- Product description ("CMX001 Tablet, 100 mg and/or Placebo to Match CMX001 Tablet, 100 mg")
- Contents (14 tablets per card)
- Kit identification (ID) number
- Space to record the assigned subject number
- Federal caution statement: "Caution: New Drug - Limited by Federal (or United States) Law to investigational use"
- Storage conditions (15°C to 25°C [59°F to 77°F]; excursions permitted to 15°C to 30°C [59°F to 86°F])
- Dosing instructions
- Sponsor name and address

In the USA, the expiration date is documented separately in a 'retest date memorandum', which is available on request.

In Canada, the Federal caution statement is replaced with "The drug is an investigational drug to be used only by a qualified investigator" and the expiration (repass) date is included on an auxiliary label. In Europe, the Federal caution statement is replaced with "For clinical trial use only" and the expiration (repass) date is included on the card label.

Label information will be provided in duplicate in both English (US spelling) and French (French-Canadian spelling). Other languages may be used, as appropriate, as additional countries are added.

All drug packaging and labeling activities will be completed by Xerimis, Inc., Moorestown, NJ, USA. North American distribution activities will be completed by Xerimis, Inc.; in Europe, distribution activities will be completed by Biotec Services International (Bridgend, UK), including Qualified Person (QP) batch release.

In addition to the study drug kits corresponding to the initial treatment assignment, i.e., 100 mg CMX001 BIW or placebo BIW, separate study kits will be provided to each study site to allow investigators to dose reduce the study treatment in response to a potential treatment-emergent toxicity while maintaining the study blind, as described in Section 8.4.2 and Section 11.5.

11.3. Study Drug Storage

Once received at the study center, the study drug kits should be stored in a securely locked area, accessible only to authorized site personnel.

The study drug kits should be stored at controlled room temperature, i.e., 15 to 25°C (59 to 77°F), with excursions permitted to 30°C (86°F), and protected from freezing.

11.4. Assigning Subjects to Study Treatment

All drug packaging, labeling and distribution activities will be completed by Xerimis, Inc., Moorestown, NJ, USA. An unblinded, independent statistician will generate a randomization schedule and send it to Xerimis, Inc. Xerimis, Inc. will use the randomization schedule to assemble blinded study drug kits for the study. Each study drug kit will comprise sufficient study drug (either CMX001 or placebo) for one subject to complete the entire treatment phase (up to 14 weeks) and will be identified by a unique kit identification (ID) number.

A quantity of study drug kits will be sent to each study site following approval of that site by Chimerix Inc. (or designee) to receive study drug and begin screening prospective subjects. Once a subject has been screened and confirmed as eligible for the study, i.e., meeting all relevant entry criteria, then study site personnel will use the IV/WRS to randomize the subject and determine which kit should be allocated to that subject by selecting the kit bearing the relevant ID number. The time between subject randomization and the initiation of study drug dosing should be kept to a minimum to minimize the chances that subjects are randomized, but not dosed. Subjects should be randomized on the day that they are anticipated to begin study treatment and no more than 1 business day before the planned FDD.

In the event that a decision is made to dose reduce in response to a treatment-emergent toxicity, as described in Sections 8.4.2 and 11.5, site personnel will use the IV/WRS to determine which kit should be selected for the reduced treatment. Kits will be resupplied to the study site automatically.

11.5. Study Drug Administration

Inpatient vs. Outpatient Dosing: With study drug treatment initiated as early as the first week posttransplant up to a maximum of 4 weeks (Day 28) posttransplant, it is anticipated that all randomized subjects will begin treatment while they are still inpatient following transplant. Similarly, it is anticipated that most, if not all, subjects who complete the entire treatment phase, i.e., through Week 14, without significant illness or transplant-related complications will have transitioned to outpatient status at some point during the treatment period. While subjects are inpatient, the twice-weekly doses of study drug should be administered in the clinic under the supervision of site personnel. During this time, it is preferred that site personnel dispense the study drug from the relevant card in the study drug kit assigned to the subject. However, to accommodate normal site pharmacy practices, it is permissible for the relevant dose(s) of study drug to be removed from the card ahead of time and dispensed into a separate dose container. Once subjects are outpatient, at least one of the two weekly doses should be administered in the clinic under supervision. The other weekly dose may also be administered in the clinic under supervision, if preferred, or it may be self-administered by the subject away from the clinic. If

self-administered, a dose diary card will be provided to the subject so (s)he can document the actual date and time of dosing and whether the dose was taken with food.

Once subjects are scheduled to be discharged from the hospital, the subjects must receive careful instructions on dosing prior to discharge. Subjects should make every reasonable effort to adhere to the dosing instructions upon discharge and should alert site personnel as soon as practicable if a dose is missed or if dosing days need to be changed.

Twice-weekly Dosing: During the initial treatment assignment, the twice-weekly doses of study drug should be administered at an interval of 3 days followed by an interval of 4 days, as shown below:

First Dose	Second Dose
Monday	Thursday
or	
Tuesday	Friday
or	
Wednesday	Saturday
or	
Thursday	Sunday
or	
Friday	Monday
or	
Saturday	Tuesday

Where possible, subjects should take all doses of study drug on the same two days each week throughout the treatment phase maintaining a minimum 2-day interval between consecutive doses of study drug. However, the first dose of study drug need not be withheld to accommodate the above schedule. It is acceptable to start the first dose on a different day from those anticipated to be the regular dosing days, for example, to start dosing on a Friday for a subject who anticipates a regular Monday/Thursday dose schedule on subsequent weeks, providing there is a minimum interval of 2 days between administration of the first and second doses of study drug.

Each dose of study drug should be administered at a time that best suits the individual subject, e.g., if a subject is better able to tolerate oral intake in the afternoon or evening, then the study drug dose should be given in the afternoon or evening once (s)he has eaten. Study drug may also be administered in the evenings prior to retiring for the night if that improves tolerability.

Where the agreed dose schedule cannot be adhered to, subjects who do not or who are unable to take a given dose on the scheduled day may take a missed dose:

- up to 1 day after the original dose time if the next dose is scheduled for 3 days later,

  - or -

- up to 2 days after the original dose time if the next dose is scheduled for 4 days later.

By way of example, a subject who normally takes his/her study drug on Mondays and Thursdays may take a missed Monday dose on Tuesday and a missed Thursday dose as late as Saturday, as long as the minimum 2-day interval is maintained between doses. If the subject cannot take the study drug within these timeframes, the late dose should be omitted and the subject should wait until the next regularly scheduled dosing day to take the next dose. Once established, the dosing schedule should not be adjusted based on doses taken outside the normal dosing window, e.g., if the same Monday/Thursday subject cannot be dosed on a Thursday, but is dosed on Saturday, then the next dose of study drug should still be administered the following Monday, since the minimum 2-day interval between doses is maintained, and not moved to Wednesday, unless done in response to a dose interruption due to a treatment-emergent toxicity as described in Section 13. If a subject cannot be dosed more than 2 days prior to the next scheduled dose, then the "late" dose should be omitted and the normal schedule followed for the next and subsequent doses. If a subject should need to switch dosing days, e.g., from Monday/Thursday to Tuesday/Friday, consideration should be given as to whether the subject will be switched back to the original schedule or remain on the new schedule throughout the remainder of the study.

Any changes to a subject's dosing regimen should be noted on the study drug dosing eCRF.

In the event that a subject should need additional study drug to complete his or her study treatment, e.g., because a subject needs to replace a lost study drug card or in the event that a subject should need to repeat one or more doses, e.g., because of emesis, as described below, please consult the SRM for guidance.

Dose Interruption, Modification or Reduction: For subjects who experience TEAEs during the study, as described in Section 13, the investigator will have the option of:

1. Interrupting dosing (for up to 18 consecutive days, i.e., for up to 4 consecutive scheduled doses plus the 4-day interval from the scheduled 4th dose),
2. Reducing the dosing frequency to once-weekly (i.e., 200 mg/placebo QW) under double blind conditions, referred to as "dose modification" (or "dose consolidation"), followed by reducing the total weekly dose (i.e., to 100 mg/placebo QW) under double blind conditions, referred to as "dose reduction" if the AE persists or the subject experiences a new TEAE.

Subjects who are dose interrupted due to a treatment-emergent toxicity should resume dosing as soon as permitted, based on the guidance provided in Section 13. Subjects do not need to wait until a previously established dosing day to resume dosing.

Dose modification and dose reduction both require the subject to switch to a new QW regimen. As described previously, the investigator must contact the Chimerix Medical Monitor (or designee) to discuss any proposed dose modification or dose reduction before implementing the change. A new study drug assignment does not need to be requested for a dose modification. Instead, the subject will continue with his existing study drug kit but take both tablets for that week on his/her new once-weekly dose day. In the event that a TEAE does not resolve following dose modification, or if a subject should experience a new TEAE of concern following dose modification, then dose reduction may be requested for the subject. Once a dose reduction has been agreed upon, a new study drug assignment will need to be requested by site personnel

through the IV/WRS and a new study drug kit provided to the subject. Once a subject has been switched to a QW regimen and has been assigned a new study drug kit, (s)he may not be switched back to a BIW regimen, even if the toxicity which prompted the change resolves or is determined to be unrelated to the study drug. Note, however, that this restriction does not apply to subjects on a de facto QW regimen because of missed doses (for whatever reason) or doses being held by the investigator in response to a treatment-emergent toxicity.

Where possible, subjects switching to a QW regimen should take all subsequent doses of study drug on the same day each week for the remainder of the treatment phase. The dose day for the new QW regimen does not need to be on one of the two dose days from the original BIW regimen. However, there must be a minimum interval of 5 days from the last study drug administration under the prior BIW regimen before administration of the first dose under the new QW regimen. Subjects should receive careful instruction from site personnel about their new regimen to avoid dose errors due to misunderstanding. Subjects should clearly understand that they are to take both tablets on the dose day under the QW regimen following dose modification/reduction and not one tablet as happened under the BIW dose regimen.

Subjects on a QW regimen who miss a dose for any reason, should be dosed as soon as possible thereafter. As per the BIW dose regimens, successive doses of study drug must be separated by a minimum of 2 days. Therefore, if a subject cannot be dosed within 5 days of the missed dose, then that dose should be omitted and the normal schedule followed for the next and subsequent weeks. If the subject is dosed within 5 days of the missed dose, then the subject should return to the normal schedule for the next and subsequent weeks.

Missed Doses: If any subject misses 2 consecutive weeks of study drug (i.e., the subject does not take the study drug for more than 18 days; which is 4 doses plus the 4-day interval that would have followed that last missed dose), then the subject will, ordinarily, be discontinued from study treatment. In addition, any subject who misses a cumulative total of 4 weeks of study drug (i.e., 8 doses of a BIW regimen or 4 doses of a QW regimen following dose modification/reduction) will be discontinued from study treatment.

In the event that a subject does interrupt dosing with study drug (for whatever reason), the subject should continue with the study schedule, completing all planned assessments (including PK sample collection) except for study drug administration.

Subjects Who Vomit After Dosing: If a subject vomits within 30 minutes of receiving a dose of study drug, the subject may be redosed as described in the SRM. This may require requesting an additional study drug card for the subject to ensure that s/he has sufficient drug to complete the treatment phase. If vomiting occurs more than 30 minutes after dosing, it should be assumed that there was significant absorption of study drug, in which case, subjects should not be redosed unless the intact study drug tablet(s) are present in the vomitus. If the intact study drug tablet(s) are observed in the vomitus, then the subject may be redosed, preferably the next day (i.e., after the underlying symptoms for the vomiting have improved/resolved).

Dosing with Food: In Study CMX001-114, administration of CMX001 with a low-fat meal or a moderate-fat meal (compared to the fasted state) reduced both the overall systemic exposure (AUC) and the Cmax of plasma CMX001. The magnitude of exposure reduction associated with the moderate-fat meal was slightly greater than that observed with the low-fat meal. The clinical significance of these findings is currently unknown. However, as anecdotal reports from Study

CMX001-202, as well as the expanded access protocol, Study CMX001-350, indicate that some GI symptoms during CMX001 therapy may be mitigated by administering CMX001 with food, it is currently recommended that the study drug doses be administered with a meal. For the purposes of this study, "with a meal" means taking the study drug dose either with or within 30 minutes after finishing a low-fat meal comprising no more than 20% of its total caloric value from fat. Examples of suitable low-fat meals are provided in the SRM. For subjects who are unable to tolerate oral intake on a short-term basis or who are otherwise unable or unwilling to take the study drug doses with a low-fat meal, it is acceptable to take the study drug doses without regard to food.

11.6. Study Drug Accountability

The investigator (or qualified designee) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of the shipment(s) of study drug kits (date, quantity and condition), subject dispensing records and returned or destroyed study drug kits/study drug. Dispensing records will document the dispensing of the kits to individual subjects, including kit number, date dispensed, and subject identifier number, and the initials of the person(s) dispensing the study drugs, and the return and/or disposal of those kits, including any unused study drug returned by subjects. Subjects will be required to bring their current study drug card (even if empty) and diary card to each study visit, so site personnel can conduct drug accountability. Subjects will be instructed not to dispose of the study drug card once empty. All study drug records must be maintained at the site and copies must be submitted to Chimerix, Inc. at the end of the study.

11.7. Study Drug Handling and Disposal

After verification of the study drug records by the study monitor, all remaining study drug supplies should be destroyed according to directions provided in the CMX001-301 Pharmacy Manual and/or any applicable site-specific standard operating procedures (SOPs). If necessary, unused study drug supplies may also be returned to Xerimis, Inc. (for sites in North America) or to Biotec Services International (for sites in Europe) with prior approval from Chimerix, Inc. (or designee). If unused study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and person who disposed of the drug.

12. STUDY ASSESSMENTS

12.1. Efficacy Assessments

12.1.1. Virologic Evaluations

Blood (plasma) and urine for virologic evaluations will be collected at screening, predose on the FDD, and throughout the treatment and posttreatment phases of the study, as outlined in the schedule of study procedures/assessments, and sent to the designated central virology laboratory(ies) for analysis.

Blood (plasma) samples will be divided into aliquots for:

- "real-time" assay of CMV viremia in plasma using the FDA-approved and CE-marked Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test;
- possible "real-time" testing for other dsDNA viruses (e.g., AdV, BKV, EBV, HHV-6, etc.) in the presence of suggestive clinical symptoms, and
- one or more storage samples for resistance testing (genotypic and/or phenotypic); additional CMV viremia assessments, based on newly available assays; for retrospective analyses for other dsDNA viruses; and/or for testing for possible biomarkers of GVHD or CMV-specific immunity.

Urine will be divided into one or more aliquots and stored for possible future analysis, including retrospective analyses of CMV and/or other dsDNA viruses, resistance testing, etc. In consultation with the Chimerix Medical Monitor (or designee), investigators may request real-time analysis of the urine samples for subjects with known or suspected BK viruria or subjects exhibiting signs/symptoms consistent with BKV or AdV infection, such as cystitis or renal impairment.

In addition, when a dsDNA viral syndrome or disease is suspected, other relevant biological samples (e.g., stool, CSF, sputum, bronchoalveolar lavage, skin or nasopharyngeal swab, tissue biopsy etc., as appropriate) should be collected and sent to the central virology laboratory for "real-time" analysis and/or storage for possible future analysis.

Investigators may request real-time analysis of plasma, urine, and "other" samples as clinically indicated for subjects exhibiting signs/symptoms compatible with infection with other dsDNA viruses. If any of these samples test positive for other dsDNA viruses, then the same samples collected at each subsequent visit may be analyzed for that/those virus(es) without obtaining prior approval.

Prior approval is required from the Chimerix Medical Monitor (or designee) for the analysis of any samples other than blood (plasma) for CMV viremia.

Slides from GI biopsies or biopsies from any organ conducted to diagnose CMV disease (or other dsDNA viral syndrome or disease) should be sent to the designated central laboratory. Suspected CMV end-organ disease will be adjudicated by the EAC according to the definitions/procedures described by Ljungman et al (Ljungman 2002).

All samples (including slides from any biopsies performed for the diagnosis of CMV/other dsDNA virus disease or GVHD) will be stored for a period of up to 15 years after study

completion. Stored samples will not be used for any other purposes than virology/immunology testing for the viruses of interest (i.e., dsDNA viruses), testing of GVHD biomarkers, and/or additional testing to measure concentrations of CMX001 and its metabolites, as described in this protocol. No stored samples will be used for human genomic analyses. Potential additional use of the samples for research purposes, not inclusive of human genomics, will be subject to approval by a central IRB-REB or IEC, as applicable.

Detailed instructions for the collection, processing, storage, and shipping of the blood (plasma) and urine samples for virologic analysis to the central virology laboratory are provided in the SRM.

12.1.1.1. CMV Viremia in Plasma

CMV plasma viremia will be determined by the central virology laboratory using the FDA-approved and CE-marked Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test. This test is standardized to the First World Health Organization (WHO) International Standard for Human Cytomegalovirus (NIBSC 09/162), and results are reported in international units per milliliter (IU/mL). Assay measurements will be converted to copies/mL using the manufacturer's conversion factor of 1.1 copies per IU. The stated range of quantitation in human plasma is 137 to 9.1 x 10^6 IU/mL (150.7 to 1.0 x 10^7 copies/mL) and the lower limit of detection (LLOD) is 91 IU/mL (100 copies/mL).

If and when samples are collected for CMV viremia testing in the local virology laboratory, including any unscheduled CMV viremia assessments performed per local SoC, samples should be collected and sent to the central virology laboratory for analysis in parallel.

12.1.1.2. Virologic Data obtained from Local Virology Laboratories

The results of any CMV viral load tests (i.e., qualitative or quantitative CMV PCR assay or pp65 antigenemia) performed by the investigator using his or her local virology laboratory will be documented in the eCRF. The information to be captured will include the assay used, the date of sample collection, and the result, including units. These results are captured for information purposes only and should not be used to make treatment decisions with the exception of a positive CMV PCR result obtained during the screening period, and prior to the FDD, which would exclude a potential subject from the study. Concordance between the results from the local virology laboratory and the central virology laboratory will be assessed. FDA will be notified if > 10% of the viral load results from local virology laboratories show detectable CMV viremia when the corresponding result from the central virology laboratory is negative.

12.1.2. CMX001-related Resistance Tests

Stored samples may be evaluated for viral resistance, as applicable.

Genotypic assays to assess the presence of mutations associated with viral resistance will be performed by Viracor-IBT Laboratories (5600 Cytomegalovirus CMV Antiviral Resistance Assay) using conventional PCR followed by DNA sequencing of the UL54 and UL97 genes. Sequencing will span the regions that are known to contain the site of resistance mutations. The standard Viracor-IBT Laboratories UL97 target is between codons 438 and 658 on the UL97 gene, and the UL54 target is between codons 252 and 1138 on the UL54 gene. The standard UL54 assay will be expanded to include the entire UL54 gene for this study. Additional

sequencing will be performed on a case-by-case basis, but will include the complete UL54 gene in cases of clear virologic failure on CMX001 (i.e., sustained viremia > 150 copies/mL on therapy). It is anticipated that samples with < 500 CMV DNA copies/mL are unlikely to yield genotypic results, but that most samples > 500 CMV DNA copies/mL should yield a genotype. As outlined in the Virology Plan for Monitoring the Selection of Resistant Viruses in Clinical Studies of CMV with CMX001, all samples with a confirmed CMV viremia result of ≥ 150 copies/mL at the central virology laboratory will be submitted for genotyping.

Phenotypic analysis of samples may be performed in cases of virologic failure where mutations in UL54 known to be associated with resistance are not detected, but other mutations in UL54 are identified. It is expected that phenotyping from frozen, stored samples will not reliably provide data. However, phenotyping of site-directed mutants containing mutations that appear to be associated with virologic failure may provide useful insights into the development of resistance to CMX001.

Analysis of viral samples from baseline and emergent viremia during study conduct will be conducted retrospectively and will not be communicated to the sites.

12.1.3. Emergent CMV and Other dsDNA Viral Infections

Subjects will be monitored for CMV viremia and CMV disease and for reactivation or infection with other dsDNA viruses (e.g., AdV, BKV, EBV, HHV-6, etc.) throughout the study. Common disease manifestations of dsDNA virus infections are listed in Appendix 2. Each sign/symptom/condition should be graded subjectively (present, improved, stable, worsened) as well as objectively using the CTCAE scale where appropriate.

CMV and other dsDNA virus signs and symptoms (e.g., BKV-associated urinary symptoms, HHV-6-associated CNS symptoms) will be assessed at the screening evaluation, prior to dosing on the FDD, at each weekly assessment throughout the treatment phase of the study, and during the posttreatment phase at the visits performed during Weeks 15, 18, 21, and 24.

Subjects requiring treatment with prohibited concomitant medications listed in Section 10.2.1 should be discontinued from study treatment, as described in Section 8.1.

12.1.3.1. BKV-associated Urinary Symptoms

Subjects should be assessed for BKV-associated urinary symptoms, such as increased urine frequency during the day, increased nocturia, bladder pain, cystitis, and dysuria, at each visit. The study diary card may be used to capture information on these symptoms, see Section 10.3.1. Subjects reporting viral-related cystitis symptoms will be further evaluated according to a cystitis scale presented in Appendix 3 to this protocol and provided in the SRM. Cystitis and other urinary symptoms not associated with viral infection should be assessed using the appropriate CTCAE scale. With prior approval from the Chimerix Medical Monitor (or designee), investigators may request real time analysis of the urine samples described in Section 12.1.1 for subjects with known or suspected BK viruria or subjects exhibiting signs/symptoms consistent with BKV or AdV infection, such as cystitis or renal impairment.

12.1.3.2. HHV-6-associated Symptoms

Subjects should be assessed for manifestations associated with HHV-6 infection, such as encephalitis, neurocognitive impairment, and graft failure. The study diary card will include screening questions for delirium with a more detailed neurocognitive assessment performed by study personnel based on the responses to those questions. A neurocognitive assessment, such as the MMSE (Folstein test), may be implemented for subjects with known or suspected HHV-6 infection with CNS involvement (see Section 12.4.5).

12.1.4. Use of Anti-CMV Therapy

Information on the use of GCV, vGCV, FOS, IV CDV, or any other anti-CMV specific treatment (including dose and duration of treatment) will be captured through Week 24. The drug selection, dose and duration of treatment should follow local SoC; however, for IV GCV every effort should be made to follow the FDA-approved dosing recommendation contained in the current Cytovene package insert (Genentech 2010). A copy of the current Cytovene package insert is provided in the SRM.

12.2. Pharmacokinetic Assessments

A single blood sample will be collected from all subjects on the FDD at 3 (± 1) hours postdose (i.e., around the estimated Tmax for CMX001) for analysis of plasma concentrations of CMX001 and CDV (and possibly other metabolites of interest). Additional single blood samples for analysis of plasma concentrations of CMX001 and CDV (and possibly other metabolites of interest) will be collected from all subjects at each scheduled clinic visit during the treatment phase of the study for as long as the subject remains on blinded study treatment. Once a subject has discontinued blinded study treatment, further blood sample collection may be omitted. Unlike the timed blood sample collected on the FDD, these samples do not need to be collected at a specific time point with respect to study drug administration during the study visit.

The actual date and time of the last study drug administration prior to each blood sample collection (including the timed sample collected on the FDD) should be documented. In the event that the study drug dose is administered in the clinic prior to collection of the blood sample, the date/time of the clinic administered dose should be recorded. In the event that the dose of study drug is self-administered by the subject prior to arriving at the clinic, the blood sample should still be collected and the date/time of the self-administered dose recorded.

If a timed blood sample cannot be obtained on the FDD, e.g., due to scheduling or resource issues, then it may be collected within the same time window, i.e., at 3 (± 1) hours postdose, following administration of the second dose of study drug (which may require an unscheduled visit for subjects who are already outpatient).

Detailed instructions for the collection and processing of the PK blood samples are provided in the SRM.

12.3. Health Economics/Health-related Quality of Life Assessments

The health economic impact of treatment with CMX001, as compared to treatment with placebo, will be assessed by collecting the following information through Week 24:

- AEs/SAEs;
- number and duration of hospitalizations (i.e., initial and subsequent hospitalizations), including admission and discharge dates, hospitalization setting (e.g., transplant center, ICU, etc.), and discharge status (e.g., home, transferred to skilled nursing facilities, death, etc.);
- receipt of and duration of relevant concomitant therapies (e.g., transfusions, receipt of hematopoietic growth factors, anti-infective medications, calcineurin inhibitors and other immunosuppressive agents of interest), including indication, medication name, generic/brand status, start and stop dates, dose and dose frequency, and route of administration;
- type and number of diagnostic or therapeutic procedures not related to the primary HSCT (e.g., invasive GI procedures, such as endoscopies, biopsies, renal dialysis, bladder irrigations, etc.), including date of procedure and CPT (Current Procedural Terminology) code; and
- subject responses to the EQ-5D-5L.

The EQ-5D™ health questionnaire is a standardized instrument for use as a measure of health outcome and provides a simple descriptive profile and a single index value for health status. The EQ-5D is maintained by the EuroQol Group (http://www.euroqol.org) and contains one item for each of five dimensions: mobility, self-care, performing usual activities, pain/discomfort, and anxiety/depression. A newer version of the EQ-5D, the EQ-5D-5L, which includes five levels of health per item, will be used in this study. A second section of the EQ-5D presents a single visual analogue scale for overall health, in which the subject rates his/her present health state from 0, "worst imaginable," to 100, "best imaginable."

HRQL will be assessed based on subject responses to the EORTC-QLQ-C30 questionnaire (European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30) with treatment-specific HDC29 module (for use in high-dose chemotherapy). The EORTC-QLQ system is a validated cancer QOL measurement system, comprising a core module addressing general "quality-of-life" (QoL) in cancer supplemented by tumor-, treatment-, and symptom-specific modules. Originally developed in 1988 (Aaronson 1988), the current version of the EORTC-QLQ-C30 is version 3.0, which has been validated in twelve countries (Bjordal 2000). The EORTC-QLQ system is administered by the European Organization for Research and Treatment of Cancer (http://groups.eortc.be) and is a validated self-report questionnaire based on a 4- or 7-point Likert scale that includes 5 functioning scales: Physical Functioning (5 items), Role Functioning (2 items), Emotional Functioning (4 items), Social Functioning (2 items), and Cognitive Functioning (2 items); 9 symptom scales: Fatigue (3 items), Pain (2 items), Nausea and vomiting (2 items), Dyspnea (1 item), Insomnia (1 item), Appetite loss (1 item), Constipation (1 item), Diarrhea (1 item), Financial impact (1 item), and 1 overall QoL scale (2 items).

The HDC29 module was developed to assess treatment-specific side-effects/comorbidity and additional QOL dimensions for patients with malignancies treated with high-dose myeloablative treatment with HSCT, including allogeneic/autologous bone marrow transplantation or peripheral stem cell transplantation (Velikova 2007). The HDC29 module contains multi-item scales for: GI side effects (4), Worry/Anxiety (5), Impact on family (4), Body image (2),

Sexuality (2), and In-patient issues (3), and single item scales for symptom items: Taking regular drugs, Finishing things, Ability to have children, and Distinguishing what is important in life.

Each subject will complete the EQ-5D-5L and EORTC-QLQ-C30/HDC29 questionnaires during the screening evaluation or prior to study drug administration on the FDD (to establish baseline), then at Week 6, Week 15, and Week 24.

Further details on the use of the EQ-5D-5L and EORTC-QLQ-C30/HDC29 questionnaires are provided in the SRM.

12.4. Safety Assessments

Safety monitoring procedures, including physical examination, vital signs measurement, the collection of blood and urine for clinical laboratory testing, and the recording of AEs, concomitant medication intake and intervention with non-drug therapies or procedures, will be performed prior to study drug administration (to establish baseline) and at periodic intervals throughout the treatment and posttreatment phases of the study.

12.4.1. Demographic/Baseline Characteristics/Medical History

Subject demographics and other baseline characteristics, including birth date, gender, race, ethnicity, and medical/medication history (medications taken within 30 days prior to the FDD, but limited to anti-infectives, immunosuppressant drugs, and GI medications), including transplantation history (inclusive of conditioning regimen), and immunosuppressive regimen, will be obtained from each subject as part of the screening evaluation.

Medical history will be obtained from available medical records and by consulting with the subject. If there is a question concerning items in the subject's medical history, then medical records may be requested from the subject's primary care physician, if appropriate. Any items in the subject's medical history that are still ongoing should be noted. If preferred, medical history may be obtained before transplant (and after written informed consent has been obtained) but must be updated following transplant and prior to dosing.

Transplantation history will include transplant date, underlying condition responsible for qualifying transplant, donor CMV serostatus, the type of graft received, including graft manipulation (e.g., cord blood, MRD, MUD, etc.), and pretransplant conditioning regimen, where applicable (i.e., myeloablative, reduced intensity conditioning (RIC), TCD, etc., with the relevant drugs/interventions specified).

Methods of contraception, as applicable, should be documented in the source documentation.

12.4.2. Vital Signs

Vital signs measurements (including blood pressure and pulse rate, after the subject has rested quietly for ≥ 5 minutes, and temperature [any measurement site]) will be performed at the screening evaluation, on the FDD (prior to study drug dosing, to establish baseline), and during the assessments performed at Week 5, Week 9, Week 15, and Week 24 (see Table 9).

12.4.3. Weight and Body Height

Height should be recorded once as part of the screening evaluation. Body weight should be recorded as part of the screening evaluation, on the FDD, and at each assessment during the treatment and posttreatment phases to facilitate calculation of eGFR (see Section 12.4.6.1).

12.4.4. Physical Examination

A complete physical examination will be performed as part of the screening evaluation and at Week 24. An abbreviated physical examination, targeted to new signs and symptoms, will be performed on the FDD prior to study drug dosing to establish baseline, then during the assessments at Week 5, Week 9, and Week 15 (see Table 9). The complete physical examination will, ordinarily, include examination of all body organ systems (though a full pelvic examination for women may be omitted unless medically indicated), whereas the abbreviated physical examination will assess for any changes from previous status and review of those organ systems as deemed appropriate for that subject by the responsible clinician. Clinically significant abnormalities or findings that meet the definition of an AE (see Section 12.5.1.1) should be recorded on the Adverse Event eCRF, and abnormalities present at screening or prior to dosing on the FDD should be recorded as part of the medical history eCRF.

12.4.5. Neurocognitive Assessments

A MMSE will be performed in all subjects on the FDD prior to study drug administration to establish baseline, with subsequent assessments performed at Week 6, Week 10, Week 15, and Week 24 posttransplant (see Table 9). At selected sites, subjects may be asked to undergo a more detailed assessment of their neurocognitive function using the validated BTACT and OTMT-B instruments. This optional assessment will be performed one time at Week 24. The assessment will be administered over the telephone by trained research staff from Seattle Children's Research Institute and the subject's responses will be recorded, for scoring purposes, using audio recording software. The assessment should take approximately 30 minutes to complete. Subjects who agree to undergo the more detailed neurocognitive assessment do not have to complete the MMSEs scheduled for Weeks 6, 10, 15, and 24. Additional MMSEs may be performed on individual subjects (whether participating in the optional Week 24 assessment or not), when deemed clinically appropriate to do so by the investigator, e.g., based on responses to screening questions on the study diary card.

12.4.6. Laboratory Assessments

12.4.6.1. Hematology and Serum Biochemistry

Blood for hematology, coagulation panel testing, and serum biochemistry testing will be collected as part of the screening evaluation, prior to dosing on the FDD (to establish baseline) and then weekly throughout the treatment phase, and during the posttreatment phase at Weeks 15, 18, 21, and 24 (see Table 9). The minimum parameters to be evaluated are presented in Table 12. Lymphocyte subset (percent and total [absolute] CD4+ and CD8+ counts) will be performed on the FDD, at Week 4, Week 6, Week 10, Week 15, and Week 24 only. Estimated GFR will be calculated by the central safety laboratory using MDRD4 (Levey 2006).

12.4.6.2. Anti-CMV Immune Response

A blood sample to evaluate the potential for reconstitution of the anti-CMV immune response using the T-SPOT.® *CMV* Test (Oxford Immunotec Limited, Abingdon, UK) will be collected at Weeks 5, 9, 14, and 24. These samples will be collected from individual study participants where the investigator believes the additional blood loss resulting from the collection of the samples is medically acceptable. For those individuals where the investigator feels that the additional blood loss is not medically acceptable, e.g., because the subject is markedly anemic, then some or all of these samples may be omitted, as necessary. A collection window of up to +2 weeks from the scheduled collection date is provided to allow for additional flexibility in the collection of these samples.

12.4.6.3. Urinalysis

A urinalysis will be performed as part of the screening evaluation, prior to dosing on the FDD to establish baseline and then weekly throughout the treatment phase, and during the posttreatment phase at Weeks 15, 18, 21, and 24 (see Table 9). The minimum parameters to be evaluated are presented in Table 12.

12.4.6.4. Non-dsDNA Viruses

Serological testing for evidence of HIV infection and measurement of HBV DNA and HCV RNA viral loads in plasma or serum will be performed by the central safety laboratory or the central virology laboratory at the screening evaluation to determine possible HIV-infection and/or active HBV or HCV infection, unless these tests were performed within 6 months prior to the qualifying transplant. Negative results for HBV and HCV PCR tests are required to confirm the absence of active infection(s). If necessary, investigators should contact the Chimerix Medical Monitor for prior approval to randomize a subject who meets all other entry criteria based on the results of negative PCR testing performed at a local laboratory in lieu of pending results from the relevant central laboratory.

Table 12: Clinical and Virologic Laboratory Evaluations

BIOCHEMISTRY PANEL	HEMATOLOGY PANEL
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Amylase Aspartate aminotransferase (AST) Bilirubin (total and direct) Blood urea nitrogen (BUN) Calcium (ionized) Creatine kinase (CK) Creatinine Electrolyte Panel (Na^+, K^+, Cl^-, HCO_3 [or CO_2]) Gamma-glutamyltransferase (GGT) Globulin, total	Absolute neutrophil count (total) Hematocrit Hemoglobin Mean cell hemoglobin (MCH) Mean cell hemoglobin concentration (MCHC) Mean cell volume (MCV) Platelet count (PLT) Red blood count (RBC) RBC morphology (reticulocytes, schistocytes, etc.) White blood count (WBC) with differential (percent and absolute) Lymphocyte subset (percent and total [absolute] CD4+ and CD8+) on the FDD, at Week 4, Week 6, Week 10, Week 15, and Week 24 only

Glucose Haptoglobin Lactate dehydrogenase (LDH) Lipase Phosphate Protein (total) Uric acid	**URINALYSIS PANEL** Albumin (microalbumin) Blood Glucose Leukocytes (leukocyte esterase) Microscopic analysis, if blood or leukocytes present Protein
MISCELLANEOUS TESTS	**VIROLOGIC EVALUATIONS (dsDNA VIRUSES)**
Coagulation Panel: Prothrombin time-international normalized ratio (PT-INR) **Estimated GFR** (using MDRD4) **Pregnancy Test:** β-human chorionic gonadotropin (β-hCG) in urine **Non-dsDNA Viral Serology/Viral Load:** HBV DNA, HCV RNA, and HIV Ab, as needed[a] **Immune Reconstitution:** Anti-CMV response (using the T-SPOT.® *CMV* Test) at Weeks 5, 9, 14, and Week 24	**Viral Detection:** Routine: CMV in blood (plasma) at all visits Testing for other dsDNA viruses in blood (plasma), urine and/or other biological samples (e.g., stool, CSF, sputum, bronchoalveolar lavage, skin or nasopharyngeal swab, tissue biopsy, etc., as appropriate) at some or all visits (based on signs/symptoms compatible with CMV and/or other dsDNA viral syndrome or disease and with prior approval of the Chimerix Medical Monitor [or designee]) **For storage:** Blood (plasma) and urine (and, where applicable, other biological samples) at all visits for resistance testing and possible future virologic analyses (as well as possible testing for biomarkers of GVHD or CMV-specific immunity); see Section 12.1.1 for additional information

[a] If documented results from viral serology/infection tests performed within 6 months prior to the qualifying transplant are not available.

12.4.6.5. Pregnancy Screen

Urine screens for pregnancy will be performed at the screening evaluation, on the FDD (prior to study drug dosing), and at Week 5, Week 9, Week 15, and Week 24 in women of childbearing potential (see Table 9). The central safety laboratory will provide urine pregnancy test kits for use at each site, although, if preferred, the site may use its own tests as specified by standard site practice.

12.4.6.6. Immunosuppressant Monitoring

Where available, the results of any therapeutic drug monitoring of the blood/plasma/serum concentrations of immunosuppressive therapy (e.g., tacrolimus, sirolimus, everolimus, and/or cyclosporine A) performed according to site SoC will be documented in the eCRF at each visit. This will include dose, concentration value (most recent value since last study visit if multiple values are available), concentration units, matrix (whole blood, plasma, or serum), date and time of sample collection, and date and time of last dose of immunosuppressant medication prior to sample collection.

12.5. Adverse and Serious Adverse Events

12.5.1. Definition of Adverse Events

12.5.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated), temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For all study participants, AEs will be recorded from the time of administration of the first dose of study drug until the subject has completed the study, i.e., following completion of the Week 24 assessment or premature discontinuation from the study, whichever occurs first. In addition, any study procedure-related AE that occurs after study participants have signed the ICF and prior to administration of the first dose of study drug will be recorded as an AE for the purposes of this protocol.

Disease-specific signs and symptoms (including clinical laboratory abnormalities) that were ongoing before administration of the first dose of study drug should not be considered AEs unless they worsen (i.e., increase in frequency or severity by at least one grade) post-study drug administration. In addition, unless fatal, AEs related to CMV infection (including viremia) do not need to be reported as AEs or SAEs for the purposes of this protocol; these events will be captured as part of the endpoints for this study.

In addition, the following will NOT be considered AEs for the purposes of this protocol:

- Medical or surgical procedures (e.g., surgery, endoscopy, transfusion, etc.); the condition that requires the procedure is the AE
- Situations where an untoward medical occurrence had not occurred (e.g., hospitalization for elective surgery or social and/or convenience admissions)
- Overdose of study drug or concomitant medication without any signs or symptoms, unless the subject was hospitalized for observation
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason

Subjects experiencing clinically significant AEs must be monitored periodically until symptoms subside or until there is a satisfactory explanation for the AE. Additionally, clinically significant abnormal laboratory values should be monitored periodically until the abnormality resolves, returns to baseline levels, or is otherwise explained.

12.5.1.2. Serious Adverse Event (SAE)

An SAE is any AE occurring at any study drug dose that results in any of the following outcomes:

- Death;
- Life-threatening (subject at immediate risk of death);
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant disability or incapacity.

Important medical events that may not result in death, be life-threatening, or require/prolong hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.5.1.3. Adverse Events of Special Interest (AEOSIs)

The following AEOSIs will be reported by investigators within the same timelines as SAEs as described in Section 12.5.3:

- Any AE term of diarrhea, abdominal pain, ileus, nausea, vomiting, jaundice, elevation in ALT or AST, increased total serum bilirubin, or new onset of or exacerbation of acute GI-GVHD or acute GVHD of the liver that meets at least one of the following criteria:
  - The event is Grade 3 or Grade 4 in intensity (CTCAE scale), or clinical organ Stage 3 or 4 (NIH scale) for acute GI-GVHD or acute GVHD of the liver
  - The event led to permanent discontinuation of study drug
- Graft failure

[Note: Only AE terms which meet the prespecified criteria are to be reported as AEOSIs and not every reported diagnoses that may include one or more of these events as individual signs/ symptoms, e.g., Grade 3 diarrhea would be reported as an AEOSI under this protocol, whereas, Grade 3 diarrhea that was secondary to *C. difficile* colitis would be reported as a diagnosis of "*C. difficile* colitis", rather than diarrhea, and would, therefore, not be considered an AEOSI for the purposes of this protocol.]

12.5.1.3.1. Diarrhea and GVHD

Events of diarrhea and GVHD will be captured on the AE eCRF page and assessed in more detail on separate eCRF modules designed to capture individual events.

For diarrhea, the frequency, estimated volume (where available from subjects who are inpatient), diagnostic procedures performed, and the CTCAE grade will be recorded at each visit, in addition to specific dates of worsening and/or improvement.

For aGVHD, the organ stage and overall grade, and diagnostic procedures performed will be recorded at each visit and more frequently if aGVHD events persist or require additional, unscheduled visits. These data are considered to be more objective and standardized than the reporting of aGVHD as an AE. The stage and grade of aGVHD will be evaluated, per the NIH consensus guidelines (Przepiorka 1995), which focus on the severity of symptoms or laboratory abnormalities associated with aGVHD (e.g., the staging of aGVHD of the intestine is based on

the volume of diarrhea). Appendix 1 provides a table for grading the aGVHD stage according to the modified Glucksberg system (Przepiorka 1995). Events of chronic GVHD should be captured as an AE with intensity noted; in addition, the nature of the symptoms (e.g., dry eye, diarrhea, etc.) should be captured as symptoms related to chronic GVHD, with each symptom graded for intensity separately.

The results of any diagnostic procedures performed for diarrhea and aGVHD events meeting the criteria for reporting as an SAE or AEOSI may be requested for possible adjudication by the GAC.

Medications administered for GVHD will be specifically recorded, including indication (prophylaxis, presumptive use, or treatment), dose, duration of therapy, and dose adjustments, as applicable.

Study drug treatment interruptions and dose frequency changes or dose reductions (as described in Section 11.5 and Section 13) for diarrhea and/or GVHD will be recorded. Correlation of diarrhea to GI-GVHD will be assessed by the responsible investigator and a blinded GAC. Slides from any biopsy performed for the diagnosis of GVHD (regardless of the organ involved) should be sent to the designated central safety laboratory. Specific guidance with respect to biopsy sampling and handling is provided in the SRM and/or applicable central lab manual.

Blood (plasma) samples collected for storage purposes (Section 12.1.1) may be assessed retrospectively for biomarkers of GVHD, possibly including one or more of the following, interleukin 2 (IL-2) receptor-α, tumor necrosis factor receptor-1, hepatocyte growth factor, interleukin 8 (IL-8), elafin, which is a skin-specific marker, or regenerating islet-derived 3-α, which is a GI-specific marker.

12.5.2. Recording Adverse Events

AEs spontaneously reported by the subject, in response to an open question from study personnel and/or revealed by observation will be recorded during the study. For each AE, the investigator will evaluate and report the onset date, resolution date, intensity (severity), causality (relatedness to study drug), action taken (with the study drug as well as other action taken), seriousness, outcome (if applicable), and whether or not it caused the subject to discontinue study drug.

All AEs and SAEs should be recorded on the appropriate AE module of the eCRF. The intensity (severity) of all AEs will be graded according to the NIH/NCI CTCAE as follows:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADLs; see below)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

A copy of the full NIH/NCI CTCAE grading tables is provided in the SRM.

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities independent of the underlying medical condition that require medical or surgical intervention or lead to study drug interruption or discontinuation should be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., ECG, x-rays, or vital signs measurements) that are associated with signs and/or symptoms may be recorded as an AE or SAE if they meet the definitions described in Sections 12.5.1.1 and 12.5.1.2, respectively. The S/AE term should be reported in standard medical terminology whenever possible. If a laboratory abnormality is part of a syndrome, the syndrome or diagnosis should be recorded as the S/AE, not the laboratory result (e.g., record anemia, not decreased hemoglobin as the S/AE). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying condition; this may or may not be in agreement with the grading of the laboratory abnormality, e.g., anemia may be assessed as Grade 1 (mild) though the recorded hemoglobin falls within the range for a Grade 2 (moderate) value.

The investigator is also obligated to assess the causality of each S/AE, i.e., the relationship between the study drug and the occurrence of each event. The relationship to the study drug should be assessed using clinical judgment and the following definitions:

"Related": A temporal relationship exists between the AE onset and administration of the study drug that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the study drug. In case of cessation or reduction of the dose, the AE may abate or resolve and reappear upon rechallenge.

"Not Related": Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

Should a pregnancy occur, including in the female partner of a male subject, it must be reported and recorded on a pregnancy report form. However, pregnancy is not regarded as an AE for the purposes of this protocol, unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (i.e., spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are to be considered SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications will not be regarded as AEs.

12.5.3. Reporting Serious Adverse Events/Adverse Events of Special Interest

All SAEs must be recorded from the time of administration of the first dose of study drug until the subject has completed the study, i.e., following completion of the Week 24 assessment. However, any SAE that is considered to be related to the study drug and discovered by the investigator at any time after the subject has completed the study should also be reported. In addition, any study procedure-related SAE that occurs after a study participant has signed the ICF and prior to administration of the first dose of study drug should be recorded as an SAE for the purposes of this protocol.

SAEs and AEOSIs (see Section 12.5.1.3) should be reported to Theorem Global Safety Advantage^{SM} (hereafter Theorem GSA). The investigator should complete and forward the study-specific SAE Report Form to Theorem GSA via fax to +1 866-869-1551 (in USA and Canada) or 00-800-6666-6660 (in Europe) or via email to drugsafety@theoremclinical.com. **SAEs and AEOSIs that are judged to be related to study drug must be reported within 24 hours of learning of the event.** SAEs and AEOSIs that are judged to be not related to study drug may be reported up to the end of the next business day after learning of the event (where permitted by local regulations, else they should also be reported within 24 hours of learning of the event). Additional follow-up information, if required or available, should be detailed on a follow-up SAE Report Form and faxed or emailed to Theorem GSA within 1 business day of receipt of the information, or as instructed by Theorem GSA. Responses to SAE queries should be provided to Theorem GSA within 1 business day of obtaining the information. The additional information, including any responses to SAE queries, and any follow-up SAE Report Forms should be placed with the original SAE information and kept within the appropriate section of the study file. More detailed information on the reporting of SAEs and AEOSIs to Theorem GSA (including contact information) is provided in the SRM.

Chimerix, Inc. (or designee) is responsible for notifying the relevant regulatory authority(ies) of certain events. It is the investigator's responsibility to notify the relevant IRB-REB or IEC of all SAEs that occur at his or her site. Investigators and the chairman of the DSMB will also be notified of all unexpected, serious, drug-related events (i.e., 7- or 15-day expedited safety reports) that occur during the clinical trial; those events will be reported to the site in a blinded fashion. Each site is responsible for notifying its IRB-REB or IEC of these expedited safety reports, in accordance with applicable site practices.

13. TOXICITY MONITORING AND MANAGEMENT

Because of the high rate of complications and intercurrent illnesses experienced by HSCT recipients, subjects in this study will require intensive clinical monitoring and safety assessments. It is expected that thorough clinical management of study participants, including targeted treatment of AEs, will be conducted throughout the entire study period, including the posttreatment phase, by clinical site personnel and according to the site's standard practices.

13.1. Safety Monitoring and Management Plan (SMMP)

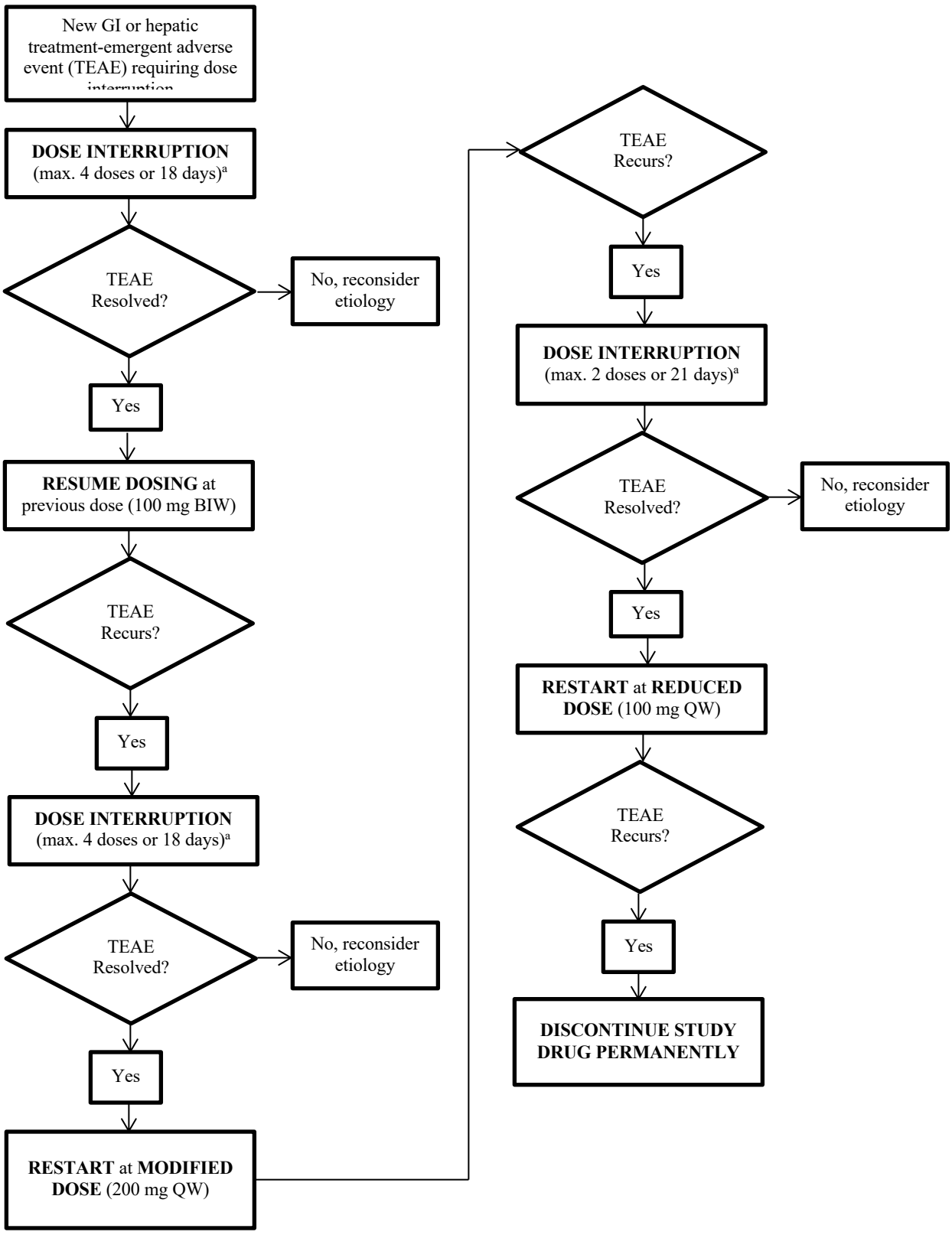
As described previously, the GI effects of CMX001 were first identified in Study CMX001-201. During the dosing of Cohort 4 (200 mg CMX001/placebo BIW) in that study, a cluster of SAEs involving diarrhea as part of the event terms or as part of the symptoms described by the investigators were reported. The onset of these symptoms usually occurred 2 to 4 weeks after the initiation of CMX001/placebo dosing, making it difficult to distinguish drug-related GI events from GVHD of the intestine, which often occurs within 2 to 6 weeks posttransplant, depending on whether the conditioning therapy was myeloablative or of reduced-intensity (Strasser 2009).

After reviewing the data from Cohort 4, Chimerix implemented a program-wide SMMP across all CMX001 studies to help identify, characterize, and mitigate GI and hepatic AEs potentially associated with CMX001 treatment, in particular diarrhea and increases in serum aminotransferases, as well as GI events presenting as possible GVHD. The SMMP describes a method for monitoring, characterizing and managing GI and hepatic symptoms or laboratory abnormalities in subjects enrolled in CMX001 studies. This guidance should be used in combination with the investigator's medical judgment in managing the subjects enrolled in this study, and is reflected in the following sections detailing the currently recommended strategy for managing subjects presenting with GI and hepatic AEs. **While the management of AEs is the responsibility of the investigators using their best medical judgment and local SoC, the rules for study drug interruption or discontinuation set forth in this section must be adhered to.**

A copy of the most current version of the SMMP is provided in the SRM. It is Chimerix's intention to update the SMMP on an ongoing basis as new data become available until there are sufficient data to adequately distinguish AEs related to the use of CMX001 from other causes of GI or hepatic signs or symptoms. Changes to the SMMP will be implemented in consultation with FDA throughout the study prior to IRB-REB/IEC approval, in order to protect subject welfare. Consequently, investigators should refer to the most current version of the SMMP, which may supersede the guidance presented in this protocol. In the event of a conflict between this protocol and the SMMP, the latter document should be followed, in consultation with the Chimerix Medical Monitor (or designee).

A flow chart summarizing the process for the management of treatment-emergent GI and hepatic toxicities requiring dose interruption is provided in Figure 2.

Figure 2: Generalized Flow Chart for the Management of Treatment-emergent Gastrointestinal and Hepatic Toxicities Requiring Dose Interruption



[a] Any subject who misses a cumulative total of 4 weeks of study drug (i.e., 8 doses of a BIW regimen or 4 doses of a QW regimen following dose modification/reduction) should be discontinued from study treatment.

13.1.1. Diagnosis of Cause(s) of Gastrointestinal and Hepatic Symptoms in Subjects with Severe or Serious AEs

Diarrhea is a common symptom in immunocompromised hosts, including HSCT recipients posttransplant, resulting from multiple etiologies including infections (e.g., viral, bacterial, such as *Clostridium difficile* [*C. Difficile*], parasitic, and rarely fungal); drug toxicity (including conditioning regimens for HSCT and immunosuppressant drugs, such as mycophenolate mofetil [MMF]); and GVHD after HSCT, among other causes (Strasser 2009).

In animal studies, the dose limiting toxicity of CMX001 was diarrhea related to alteration of the GI tract starting in the small intestine, particularly the ileum. In human studies, GI symptoms have been attributed to CMX001 and were dose-limiting in the CMX001-201 study when administered at 200 mg BIW to HSCT patients; therefore, particular attention should be paid to GI-related symptoms and the potential cause(s) should be investigated. Below is guidance on explorations suggested to investigate GI or hepatobiliary signs and symptoms.

1. Diarrhea should be evaluated by measurement of stool volumes and/or number of watery stools per 24 hours; examining a specimen for blood, and evaluation for pathogens, GVHD, and other potential causes.
    a. Infectious causes: Except for CMV, all of the common causes of intestinal infection in immune suppressed patients can be found in stool studies. The spectrum of infecting organisms varies with the extent of environmental exposure:
        – If the onset of symptoms was in a protected hospital environment, the most useful tests are toxigenic *C. difficile*, AdV DNA, viral culture, CMV DNA (in blood), gut biopsy for immunohistochemistry (IHC) and centrifugation culture
        – If symptoms began after hospital discharge, potential exposure to community-acquired organisms should be considered, with tests for rotavirus (EIA), norovirus (RNA), astrovirus (RNA), Giardia antigen, Cryptosporidia PCR, ova and parasites
        – If symptoms began after greater exposure to potential pathogens, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Aeromonas*, *E. coli* H7:O157, and fungi should also be considered.
    b. Acute GVHD in its more severe forms causes diarrhea in volumes as high as 8 to 10 L/day, often accompanied by falling serum albumin as a result of gut protein loss, and sometimes accompanied by abdominal pain and pseudo-obstruction.
        – The consensus definition listed below may be used to assign a stage for a case of suspected GI GVHD, based upon the severity of GI symptoms and signs (Przepiorka 1995). When the exact volume of diarrhea is not recorded, peak daily volumes should be based upon the clinical description.
            - Stage 1, diarrhea 500-999 mL/day or biopsy-proven upper gut involvement

- Stage 2, diarrhea 1,000-1499 mL/day
- Stage 3, diarrhea 1,500-1999 mL/day
- Stage 4, diarrhea ≥ 2,000 mL or severe abdominal pain with or without ileus

– Confirming the diagnosis of GVHD of the intestine depends upon the existence of risk factors, the presence of a drop in serum albumin (which in the setting of diarrhea can be a nonspecific indication of enteropathy), and the endoscopic appearance of the mucosa; histology of mucosal biopsy; and in some cases, intestinal imaging (CT enterography, sonographic ultrasound). The anatomic sites of greatest diagnostic utility for histology are the pyloric gland area in the antrum and the colon; therefore upper GI endoscopy with biopsy should be performed as a first diagnostic method if GVHD is suspected. There is a significant false negative rate in histologic diagnosis of GVHD related to sampling error.

– There are also histologic mimics of GVHD from other causes such as MMF toxicity.

– CMX001 administration has been associated with diarrhea, typically occurring after 2 or more weeks of dosing. In some cases, decreasing serum albumin concentrations have been noted in subjects with persistent, higher volume (Grade 2 to 3) diarrhea. It is unknown at this time whether CMX001 toxicity is associated with histologic changes in the gut or whether it can be differentiated histologically from GVHD. Therefore, in the absence of extra-intestinal signs of GVHD or if the timing/incidence of GVHD is unusual, based on conditioning regimen and risk factors, CMX001 should be considered as a possible cause of diarrhea and, depending upon the severity and persistence of the diarrhea, CMX001 doses should be interrupted before treatment of GVHD is considered (additional guidance is provided below).

c. Medications, other causes: High-volume diarrhea is less likely to be caused by medications and ingestion of disaccharides than GVHD or infections; however, in the presence of diarrhea, oral magnesium supplementation should be interrupted.

2. More severe upper gut symptoms, including anorexia, nausea, vomiting, and early satiety, have a limited differential diagnosis that includes GVHD, herpesvirus infection, medication side effects, and increased intracranial pressure disorders. Endoscopic biopsy for histology and centrifugation culture is the diagnostic method of choice.

3. Severe hepatobiliary problems include cholestatic disorders (cholangitis lenta, GVHD, obstruction) and hepatocellular necrosis (GVHD, DiLI, viral infections, hypoxic hepatitis). Diagnostic methods include hepatobiliary imaging, PCR for relevant viral pathogens, and liver histology in enigmatic cases. Concomitant medications commonly associated with potential hepatobiliary AEs should also be considered (e.g., azoles, Bactrim®, and isoniazid).

13.1.2. Management of Subjects with Gastrointestinal AEs

Investigators should pay particular attention to GI signs and symptoms when questioning subjects about AEs at every study visit. In particular when a decrease in serum albumin level is noted, investigators should intensify their questioning of subjects with respect to symptoms of diarrhea. In order to facilitate this monitoring, serum albumin concentrations that represent a decrease from baseline of ≥ 4g/L (≥ 0.4g/dL) and are ≤ 30 g/L (≤ 3 g/dL) will be systematically flagged by the central safety laboratory on the laboratory report. At each study assessment during the treatment phase, the subject should be specifically asked about GI symptoms.

Any AEs should be graded in accordance with the CTCAE grading scales; additional details regarding the GI symptoms will be collected in the eCRF. For convenience, the CTCAE grading for diarrhea as an AE is listed here:

- Grade 1:
  - Increase of < 4 stools per day over baseline; or mild increase in ostomy output compared to baseline
- Grade 2:
  - Increase of 4 to 6 stools per day over baseline; or moderate increase in ostomy output compared to baseline
- Grade 3:
  - Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; or severe increase in ostomy output compared to baseline; limiting self-care activities of daily living (ADL)
- Grade 4:
  - Life-threatening consequences; urgent intervention indicated

Please refer to the SRM for the most current version of the CTCAE grading scales.

Management of subjects with GI AEs is dependent upon the duration and intensity of signs and symptoms and is described below.

13.1.2.1. For subjects with Grade 1 GI-related AEs:

GI complaints are very frequent in the HSCT patient population immediately post transplantation. Nutritional advice should be given to avoid ingesting food and drink that affect intestinal water transport (e.g., caffeine, alcohol, carminative spices, and concentrated sugar syrups). In addition, some patients with intestinal inflammation may develop down-regulation of intestinal disaccharidases (lactase, sucrase-isomaltase), and should avoid lactose- and sucrose-containing drinks. Consideration should be given to adjusting medications associated with GI side effects (e.g., macrolide antibiotics, magnesium sulfate salts, and MMF). Liquid and electrolyte intake should be encouraged to avoid dehydration if renal function is normal. Symptomatic care may be provided for symptoms as needed (e.g., anti-emetics). Other causes of new GI symptoms should be investigated and treated as appropriate (including infections, GVHD, etc.)

For Grade 1 GI AEs, aggressive treatment of GVHD should be initiated only if the diagnosis is confirmed at another organ site (e.g., skin or liver); anorexia and new onset of lack of appetite/no pleasure in eating may be used as a potential marker of upper-GI GVHD in addition to biopsy results, if endoscopy was felt to be warranted. Standard first line treatments for aGVHD, including steroids and calcineurin inhibitors, are allowed under this protocol. Details of the diagnostic procedures and risk factors will be captured in the eCRF. In the absence of extra-intestinal involvement and of GVHD risk factors, treatment of GVHD should be delayed if medically feasible for Grade 1 diarrhea.

13.1.2.2. For subjects with Grade 2 GI-related AEs:

In addition to the measures described under Grade 1, institution of loperamide, given at regular intervals rather than PRN (pro re nata), for control of diarrhea should be considered, along with antiemetics for nausea and vomiting.

For subjects with diarrhea, oral magnesium supplementation should be interrupted and plasma or blood concentrations of immunosuppressant drugs should be measured.

For intermittent diarrhea symptoms of Grade 2 intensity, no further action on study drug is warranted.

If subjects present with more than one Grade 2 GI AE at the same time or Grade 2 diarrhea for more than 3 consecutive days, **consideration should be given to interrupting study drug dosing in consultation with the Chimerix Medical Monitor (or designee)**, particularly if the symptoms are noted 2 to 8 weeks after the initiation of study drug treatment and when a decrease in serum albumin from baseline of ≥ 4 g/L reaching to serum albumin concentrations of ≤ 30 g/L is noted in the absence of other etiology for hypoalbuminemia.

13.1.2.3. For subjects with Grade 3 or higher GI-related AEs:

For patients with more severe AEs (i.e., Grade 3 or higher), the imperative for a diagnosis becomes greater. Study drug administration should be interrupted; and the treatment recommendations described under Grade 1 and 2 above intensified (including measurement of immunosuppressant concentrations).

1. **For subjects at high risk of GVHD with evidence of extra-intestinal GVHD** (i.e., liver and/or skin):
    - Treatment with steroids or local SoC should be initiated and **study drug administration should be interrupted**.
    - If symptoms improve after steroid therapy, study drug should be resumed at the same dose as soon as feasible (see Section 11.5 for guidance on resuming dosing after study drug interruption).
2. **In the absence of extra-intestinal involvement of GVHD and low risk of GVHD:**
    - **Study drug administration should be interrupted** and treatment with corticosteroids should be withheld, where medically feasible, for at least 3 days.
    - If the signs and symptoms increase in intensity or do not improve after study drug has been withheld for at least 1 dose, then steroid therapy may be introduced if clinically

indicated. If symptoms improve on steroid therapy, study drug can be resumed at the same dose as soon as feasible (see Section 11.5 for guidance on resuming dosing after study drug interruption).

- If the signs and symptoms improve after study drug interruption without additional intervention, study drug dosing may be resumed but at a reduced dose or dosing frequency, in consultation with the Chimerix Medical Monitor (or designee). In the event of reduced dose, new drug supplies will need to be requested through the IV/WRS as described in Section 11.5.
- If after 18 days of study drug interruption (with or without steroid therapy), i.e., 4 missed doses, there is no improvement in the GI symptoms (i.e., the symptoms remain Grade 3 or higher), and no other etiology has been identified the subject should be permanently discontinued from study drug. Subjects who discontinue study drug should follow the same schedule of assessments through Week 24 (Table 9). If another etiology has been identified it should be treated and dosing with study drug should not be resumed until improvement is noted. If the GI AE improves to Grade 2 or lower after up to 14 days of interruption, the subject may resume dosing with study drug. The choice of resuming at the original dose or with a dose or dosing frequency reduction will be made in consultation with the Chimerix Medical Monitor (or designee).

Overall, the dose at which study drug may be restarted can be:

1. The previously administered dose, if symptoms have improved and an alternate cause for the Grade 3 AE has been identified and treated.
2. With a reduced dose or change in dosing frequency if symptoms have improved but no other etiology for the AE has been identified.

If the GI symptoms return to ≥ Grade 3 after the reintroduction of study drug, study drug should be permanently discontinued. Discontinued subjects should remain in the study and should follow the schedule of assessments until resolution of symptoms or study completion, i.e., Week 24, whichever comes later.

13.1.3. Management of Subjects with Serum Elevations in Serum Aminotransferases

Interruption of treatment with study drug should be considered if any of the following confirmed abnormalities are met:

1. ALT or AST > 8x ULN and 2x baseline value
2. ALT or AST > 5x ULN for more than 2 weeks and 2x baseline value
3. ALT or AST > 3x ULN (and 2x baseline value) **and** total bilirubin > 2x ULN **or** PT-INR > 1.5x ULN
4. ALT or AST > 3x ULN (and 2x baseline value) with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% of total WBC count).

Confirmed abnormalities of the magnitude described above should lead to study drug interruption. These values should be confirmed at the central safety laboratory as soon as

feasible, if clinically acceptable. A sample can be drawn in parallel for local laboratory analysis if deemed necessary by the investigator. If awaiting confirmation is not deemed clinically appropriate, then study drug should be interrupted, pending further investigation of the laboratory abnormalities. If confirmed, administration of study drug should be interrupted and the following investigations conducted including, but not limited to, imaging, identification of potential hepatotropic infections, evaluations for GVHD, review of other concomitant medications and possibly liver biopsy, as appropriate. Lactic acidosis should also be ruled out. For subjects receiving an azole, interruption of the azole should be considered if criterion 2 is the only criterion met, i.e., there is no bilirubin elevation.

If an alternate reason for the abnormalities is identified and after the abnormalities decrease by one grade below that which triggered the study drug interruption criteria listed above, dosing with study drug may resume at a similar or lower dose after discussion with the Chimerix Medical Monitor (or designee).

Generally resumption of dosing in subjects with ALT or AST elevations remaining at levels > 5x ULN should not be attempted unless an alternative etiology for the aminotransferase elevations is confirmed. Recurrence of the liver abnormalities after reintroduction of study drug should lead to permanent discontinuation of study drug.

13.1.4. Cidofovir-associated Events: Nephrotoxicity, Neutropenia, Ocular Hypotony, and Carcinogenesis

Because CDV is a metabolic product of CMX001, surveillance for AEs associated with the use of Vistide injection (i.e., nephrotoxicity, neutropenia, and ocular hypotony) is recommended, although none of these toxicities have been observed in either preclinical or clinical studies of CMX001 performed to date.

As a precaution, BUN and serum creatinine measurements, calculation of eGFR, and urinalysis will be performed weekly during the treatment phase of the study. In addition, subjects who experience a decrease in eGFR to < 15 mL/min or who experience a new or persistent requirement for renal dialysis will be required to discontinue study drug, if the eGFR change or the requirement for dialysis is considered to be study drug-related. For subjects with an on-treatment decrease in eGFR to < 15 mL/min that is not related to study drug, then study drug treatment may be continued if dialysis or other RRT is initiated. RRT must be continued for as long as the subject's eGFR remains < 15 mL/min and the subject remains on study drug.

Neutropenia has been associated with the use of CDV. Management of neutropenia should follow the site SoC; however, in the case of persisting severe neutropenia with no other reasonable explanation, study drug should be discontinued. Hematology panels, including differential white blood counts, will be performed weekly during the treatment phase of the study. The use of growth factors is permitted during the study, as clinically appropriate. Such use should be documented on the concomitant medication page of the eCRF.

To screen for possible ocular events, staff should question any subject reporting any eye pain and/or vision problems. If hypotony, uveitis, or retinitis is suspected, the subject should be referred to an ophthalmologist for consultation. In cases of uveitis or ocular hypotonia with no other reasonable explanation, discontinuation of study treatment should be considered.

CMX001 and CDV are both considered potential carcinogens to humans. Subjects who complete the CMX001-301 study will be followed for at least 10 weeks after the last dose of CMX001 and will be encouraged to additionally enroll in the "Chimerix Registry for CMX001" (Study CMX001-333: A Prospective Observational Study for the Long-term Follow-up of Subjects Previously Enrolled in Selected Clinical Studies of CMX001) to assess the long-term impact of exposure to CMX001 following completion of the CMX001-301 study.

14. STATISTICS

All summaries and analyses will be presented in tabular or graphical form. Statistical methods will be described in detail in the Statistical Analysis Plan (SAP), which will be finalized prior to unblinding the study for analysis. All statistical analyses will be conducted using SAS®, unless otherwise specified in the SAP.

14.1. Determination of Sample Size

A total of approximately 450 subjects will be enrolled into this study. Sample size calculations were based on the primary endpoint, i.e., the development of clinically significant CMV infection. Prior data indicate that the proportion of placebo subjects developing clinically significant CMV infection is at least 0.30. A clinically meaningful relative risk for CMX001 subjects relative to placebo is 0.5 (i.e., a 50% reduction). A two group continuity corrected chi-squared test with a 0.05 two-sided significance level will have > 85% power to detect the difference between a CMX001 proportion of 0.15 and a placebo proportion of 0.30 when 360 subjects are allocated 2:1 between the two treatment groups (CMX001:placebo). In order to account for an estimated 20% dropout rate, 300 subjects will be randomized to CMX001 and 150 subjects will be randomized to placebo, i.e., a total of 450 subjects.

14.2. Analysis Sets

All subjects will be classified into Intent-to-Treat (ITT), modified Intent-to-Treat (mITT), Per Protocol (PP), and Pharmacokinetic (PK) analysis sets. The following definitions will be used:

- **ITT:** The ITT analysis set will include all subjects who receive at least one dose of study drug.
- **mITT:** The mITT analysis set will include all subjects in the ITT who are CMV viremia negative on the FDD, i.e., excluding subjects subsequently found to have been CMV viremia positive (a CMV PCR ≥ 100 copies/mL [≥ LLOD]) on the FDD.
- **PP:** The PP analysis set will include all subjects in the mITT analysis set who complete the study through Week 24 (or die on study) and do not have any major protocol deviations (defined as significant inclusion/exclusion criteria violation, study drug noncompliance, or the use of a prohibited concomitant medication unless initiated post-FDD as anti-CMV PrT per protocol).
- **PK:** The PK analysis set will include all randomized subjects who take at least one dose of CMX001 and have at least one blood sample collected for analysis of plasma CMX001/CDV concentrations.

The ITT analysis set will be used to summarize all endpoints and will be used for the primary inferential efficacy analysis. The mITT and PP analysis sets will be determined prior to unblinding the study. All analyses will use the actual treatment received by the subject. In the event that a meaningful number of subjects (e.g., ≥ 3%) are either (a) randomized and not treated, or (b) first treated with the incorrect study drug, the primary endpoint will be analyzed with all randomized subjects and using randomized treatment to assess the impact on the results.

14.3. Interim Analyses

No formal interim analyses are planned. Safety will be monitored by an independent DSMB periodically, as described in Section 6.5.1. There are no plans to stop the study for efficacy; hence, no alpha-adjustment for DSMB monitoring is made. However, if the DSMB changes this intent and recommends early stoppage for overwhelming efficacy, a p-value of < 0.0001 would be required in order to preserve the overall alpha level of the study at 0.05, two-sided.

14.4. Efficacy Analyses

14.4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is a composite endpoint for the development of clinically significant CMV infection measured through Week 24 (± 14 days). The proportion of subjects meeting this endpoint will be compared between CMX001 and placebo using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline CMV risk category ("higher" vs. "lower" risk of disease progression). Number of failures and failure rates will be presented for each treatment. CMH p-values, estimated common odds ratios, and corresponding approximate 95% confidence intervals (CIs) will be presented for each comparison. The Breslow-Day test will be used to test the homogeneity of the odds ratios. A Mantel-Haenszel test for risk difference will be conducted as a supportive analysis.

The primary analysis will include subjects who receive anti-CMV PrT as failures (except those receiving preemptive therapy prematurely one time, as described in Section 8.1), regardless of whether or not preemption was initiated according to protocol-specified criteria. In the event that any subjects initiate anti-CMV PrT outside of protocol-specified criteria, a sensitivity analysis will be conducted in which these subjects are excluded from the analysis set. In the event that any subjects do not initiate anti-CMV PrT when meeting protocol specific criteria, a sensitivity analysis will be conducted in which these subjects are counted as failures.

Subjects for whom the primary endpoint is missing will be considered failures. Sensitivity analyses will be conducted to investigate the impact of this missing data imputation on the primary endpoint. Conclusions regarding the investigation of possible bias introduced by dropouts and/or the handling of missing data using the primary method of data imputation will be included in the clinical study report. The first of these analyses will utilize the method of multiple imputation (MI) to impute missing data using the following approach:

- The number of missing values (nmiss) will be calculated (e.g., if 450 subjects are included in the ITT analysis set and 5% of these subjects are missing data, then nmiss = 23).
- The missing values will be filled in '5 x nmiss' times to generate '5 x nmiss' complete data sets (e.g., 115 sets of imputations will be performed if 450 subjects are included in the ITT analysis set and 5% of these subjects are missing data. The imputation model used will be a logistic regression with treatment group and risk group as independent factors.
- Each complete data set will be analyzed with a logistic regression with treatment group and risk group as independent factors.

- The results from these analyses will be combined into a single inference.

The second sensitivity analysis will use a repeated measures logistic regression model (generalized estimating equations [GEEs]), with dichotomized clinically significant CMV infection as the dependent variable and treatment, risk group, and visit (Week 1, Week 2, Week 3, and so on) as independent factors. In this analysis, data from all post-baseline visits will be included with no imputation for missing data.

14.4.2. Secondary Efficacy Endpoints

Dichotomous secondary endpoints will be analyzed using the same method (i.e., CMH test) as used for the primary endpoint. Missing data will be imputed as failure.

Time-to-event analyses will be performed using Kaplan-Meier methods/plots and log rank tests. P-values and hazard ratios along with their 95% CIs will be presented for each treatment comparison. Missing data will be censored.

Duration and number of courses of PrT will be summarized descriptively using counts/ percentages and/or summary statistics.

In the event that the primary analysis is statistically significant, specific secondary endpoints will be tested sequentially as follows:

- The incidence of any non-CMV dsDNA virus end-organ disease (i.e., AdV, BKV, EBV, HSV-1/2, HHV-6, and VZV), through Week 24 will be tested at 5% alpha.
- In the event that the preceding test is statistically significant, the incidence of end-organ disease due to each of the six individual viruses through Week 24 will be tested using the Hochberg method.

Further adjustments will not be made for multiple comparisons.

14.5. Viral Load Analyses

Only data analyzed by the central virology laboratories will be used for any viral load analyses. Viral load data (CMV only) obtained from local virology laboratories will be listed.

14.6. Pharmacokinetic Analyses

Concentrations of CMX001 and CDV in plasma will be determined using a validated bioanalytical assay(s).

Plasma CMX001 and CDV concentrations obtained at 3 (± 1) hours after the first dose, and for weekly samples thereafter will be summarized using descriptive statistics (including N, mean, SD, CV%, median, minimum, and maximum). Concentrations below the limit of quantitation (BLQ) will be treated as zero (0) for the purposes of descriptive statistics.

14.7. Health Economics Analyses

AEs, SAEs, number and duration of hospitalizations, concomitant therapies and procedures collected through Week 24 will be used to assess the health economics impact of treatment with CMX001, as compared to treatment with placebo. Since cost information is not being collected

directly, the impact on cost will be assessed via assumed fixed costs per type of procedure or concomitant therapy.

Change from baseline HE/HRQL scores will be analyzed using an analysis of covariance (ANCOVA) model with factors of baseline score, treatment, and risk category. P-values and 95% CIs will be presented. Binary endpoints will be assessed via CMH test as used for the primary endpoint.

14.8. Safety Analyses

A primary objective of this study is to evaluate the safety of CMX001 compared to placebo. All safety analyses will be presented by treatment group using the ITT analysis set. Safety endpoints include AEs and laboratory results. Inferential analyses will not be performed for safety endpoints.

14.8.1. Adverse Events

Treatment-emergent AEs (TEAEs) are those that begin on or after the date of the first dose of study drug and on or before 7 days after the date of the last dose of study drug. Follow-up AEs are those that begin beyond 7 days after the last dose of study drug.

Summaries (number and percent of subjects) of TEAEs and follow-up AEs (by system organ class and preferred term) will be provided as follows (* = treatment-emergent only):

- All AEs,
- All severe, life-threatening, and fatal AEs,
- All treatment-related AEs*,
- All severe, life-threatening, and fatal treatment-related AEs*,
- All SAEs,
- All treatment-related SAEs*,
- All AEs that cause discontinuation from study drug*,
- All AEs that cause study drug dose reduction or interruption*, and
- All AEs leading to death.

14.8.2. Laboratory Results

Descriptive statistics (N, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided for each continuous laboratory test as follows:

- Baseline values,
- Values at each post-baseline analysis window, and
- Change from baseline at each post-baseline analysis window.

Laboratory tests will also be descriptively analyzed by grade and visit using counts and percentages.

The last on-treatment value and grade (on/before the end of 1-week follow-up window) will also be summarized. Missing data will not be imputed.

In addition, the proportion of subjects with a ≥ 1 grade, ≥ 2 grade, and ≥ 3 grade increase from baseline at any point during treatment will be presented. Laboratory tests with criteria for both increased and decreased levels will be analyzed for each direction (i.e., increased and decreased).

14.9. Other Analyses

14.9.1. Subject Enrollment and Analysis Sets

The number and percent of subjects treated by each investigator will be summarized overall and by treatment group. The denominator for this calculation will be the number of ITT subjects.

A summary of analysis sets will present the number of subjects screened, randomized, and included in each analysis set (with summary of reasons for exclusion from each analysis set) by treatment group.

14.9.2. Demographics and Baseline Characteristics

Subject demographic data (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, body mass index [BMI], CMV viral load, disease for which HSCT was conducted, pre-transplant conditioning regimen, source of graft, type of graft, donor CMV serostatus [i.e., D+ or D-], and baseline AdV/BKV/EBV viral serology) will be summarized by treatment group and overall using descriptive statistics (N, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and using the number and percent of subjects for categorical data. Age is calculated as age in years at first dose of study drug. The summaries of demographic data and baseline characteristics will be provided for each analysis set.

14.9.3. Prior and Concomitant Medications

Medications started prior to the FDD and those started on or after the FDD will be summarized separately (number and percentage of subjects) by treatment group and WHO generic name.

14.9.4. Exposure and Subject Disposition

Duration of exposure to study drug will be defined as: last dose date – first dose date +1, regardless of temporary interruptions in study drug administration, and will be expressed in days. Duration of exposure to study drug will be summarized using descriptive statistics (N, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percent of subjects exposed for bi-weekly durations (decreasing cumulative). Dose modifications and reductions will also be summarized.

A summary of subject disposition will be provided by treatment group. This summary will present the number and percent of subjects who:

- complete the study treatment period,
- do not complete the study treatment period (with summary of reasons for not completing the study treatment period),
- complete the treatment-free follow-up period,

- do not complete the treatment-free follow-up period (with summary of reasons).

14.10. Subgroup Analyses

The primary efficacy endpoint, incidence of TEAEs, and selected laboratory values (e.g., serum aminotransferases, albumin, and creatinine) will be summarized by age (tertiles), race/ethnicity (separate categories for racial/ethnic groups contributing at least 10% of study enrollment plus "other"), sex (male vs. female), weight (tertiles), and baseline CMV risk category ("higher" vs. "lower" risk of disease progression).

15. RESPONSIBILITIES

15.1. Quality Controls and Study Monitoring

Quality controls include all project management activities by Chimerix, Inc. in addition to the monitoring of study events and verification of data.

Before an investigational site can enter a subject into the study, a representative of Chimerix, Inc. (or designee) will visit the study center to:

- Determine the adequacy of the facilities
- Discuss with the investigator and other site personnel their responsibilities with regard to protocol adherence, and the responsibilities of Chimerix, Inc. or its representatives.

During the study, a monitor from Chimerix, Inc. or representative will have regular contacts with each investigational site for the following:

- Provide information and support to the investigator
- Confirm that site facilities remain acceptable
- Confirm that the investigator is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's clinic charts and other records relevant to the study.
- Record and report any protocol deviations not previously sent to Chimerix, Inc. and confirm that the deviations have been forwarded to the relevant IRB-REB or IEC, as applicable.
- Confirm that AEs and SAEs have been properly documented on eCRFs and confirm that any SAEs have been forwarded to Chimerix, Inc. and to the relevant IRB-REB or IEC, as applicable.

The investigator will allocate time, including study staff, to the monitor as required during on-site monitoring visits. The monitor will be available between visits if the investigator or study staff needs information or guidance.

15.2. Quality Assurance Audits and Regulatory Inspections

Authorized representatives of Chimerix, Inc. (or designee), a regulatory authority, or the applicable IRB-REB or IEC may visit the site to perform audits or inspections, including source data verification. The purpose of such an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. If such an audit or inspection occurs, the investigator will allow the auditor(s) or inspector(s) direct access to all source documents, eCRFs, and other study documentation for source data check and/or on-site

audit/inspection, and will allocate his or her time and the time of his or her staff to the auditor or inspector, as required. The investigator should contact Chimerix, Inc. immediately if contacted by a regulatory agency about an inspection.

16. ETHICS

16.1. Ethics Review

It is the investigator's responsibility to ensure that this protocol is reviewed and approved by an appropriate IRB-REB or IEC which conforms to the regulations set forth in Title 21 of the US Code of Federal Regulations (CFR), Part 56, and other national regulations, as applicable. The investigator must also submit the ICF, any other written documentation provided to the subject, and all advertisements that may be used for study-specific recruitment to the IRB-REB or IEC for review and approval. Formal documentation of the IRB-REB's or IEC's initial approval, and all materials submitted to the IRB-REB or IEC for this study, including the ICF and subject recruitment materials, and all correspondence regarding approvals and non-approvals by the IRB-REB or IEC must be maintained by the investigator and made available for inspection. The investigator must submit written approval from the IRB-REB or IEC to Chimerix, Inc. before (s)he can perform any study-specific screening or enroll any subject into the study.

The investigator is responsible for informing the IRB-REB or IEC of any amendment to the protocol in accordance with local requirements before implementation of the amended study procedures. The protocol must be re-approved by the IRB-REB or IEC upon receipt of amendments and annually, as local regulations require.

Sites are responsible for abiding by their IRB-REB or IEC's rules and regulations for recording and reporting protocol deviations. All deviations reported to the IRB-REB or IEC must be recorded as deviations and documented in the site's study file.

The investigator is also responsible for providing the IRB-REB or IEC with expedited safety reports from any other study conducted with the investigational product. Chimerix, Inc. will provide this information to the investigator.

Progress reports and notifications of expedited safety reports will be provided to the IRB-REB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH-GCP, and applicable regulatory requirements.

16.3. Written Informed Consent of Study Subjects

Before participation in this study, the informed consent of the subject must be obtained in accordance with FDA regulations as set forth in 21CFR, Part 50, and all other national regulations, as applicable. The investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject must be given the opportunity to ask questions and allowed time to consider the information provided.

The ICF must contain all US FDA-required elements (as allowable by foreign agencies), ICH-required elements, and HIPAA (US Health Insurance Portability and Accountability Act)

authorization (and/or other local requirements for data protection/privacy laws, as applicable) in language that is understandable to the subject. At the discretion of the study site, the HIPAA authorization may be contained in a separate document. The subject's signed and dated ICF must be obtained before conducting any study procedures, including any study-specific screening procedures.

The investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

17. DATA HANDLING AND RECORDKEEPING

17.1. Data Collection

All observations relating to the study will be recorded by site personnel in source documents. In addition, eCRFs will be provided for this study. An eCRF must be completed for every subject entered into the study. The eCRF must be completed according to the eCRF completion instructions provided in the SRM. After each subject has completed the study, the investigator must review and electronically sign the eCRFs indicating that (s)he has reviewed the completed eCRFs and pertinent clinical data for the subject and that, to the best of his/her knowledge, all data recorded in the eCRFs accurately reflects the subject's performance in the study.

17.2. Inspection of Records

Chimerix, Inc. (or designee) will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records related to study conduct.

17.3. Retention of Records

The investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Chimerix, Inc. or any regulatory authority (e.g., FDA) to review any documentation relating to the study, the investigator must permit access to such records.

17.4. Confidentiality

Subject names will remain confidential and will not be supplied to Chimerix, Inc. or its designee. If the subject name appears on any other document collected (e.g., clinic discharge summary), it must be redacted before the document is transmitted to Chimerix, Inc. or its designee. All study findings will be stored in electronic databases. Subjects will give explicit permission for representatives of Chimerix, Inc. or its designee, regulatory authorities, and the relevant IRB-REB or IEC to inspect their medical records to verify the information collected. Subjects will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with HIPAA (in USA) or local data protection/privacy laws (outside USA).

Individual subject medical information obtained during this study is confidential and its disclosure to third parties other than those mentioned in the preceding paragraph is prohibited. Medical information obtained during this study may be provided to the subject's personal physician or other appropriate medical personnel when required in connection with the subject's continued health and welfare and with the subject's prior knowledge and permission.

18. PUBLICATION POLICY

It is the intention of Chimerix, Inc. to publish the results of this study in their entirety within a reasonable period of time following the completion of the study. Chimerix, Inc. will determine when and where data will be first disclosed.

All information generated from this study is the proprietary property of Chimerix, Inc. Chimerix, Inc. reserves the right, among other things, to:

- Modify or amend study material to ensure that no confidential or proprietary information is disclosed.
- Ensure that the reported data are factually correct.
- Utilize the information generated from or as a result of this study in any manner it deems appropriate, including but not limited to regulatory submissions, annual reports, and other scientific or business affairs of the company.
- Modify the publication or disclosure or delay it a sufficient time to allow Chimerix, Inc. to seek patent protection of any invention contained therein.

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20. APPENDICES

20.1. Appendix 1: Acute Graft Versus Host Disease Grading Scale

The following table excerpted from Przepiorka et al (Przepiorka 1995) should be used for grading GVHD under this protocol:

Table 13: Staging and Grading Scales for Acute Graft versus Host Disease

	Extent of Organ Involvement		
	Skin	**Liver**	**Gut**
Stage			
1	Rash on < 25% of skin[a]	Bilirubin 2 to 3 mg/dL[b]	Diarrhea > 500 mL/day[c] or persistent nausea[d]
2	Rash on 25 to 50% of skin	Bilirubin > 3 to 6 mg/dL	Diarrhea > 1,000 mL/day
3	Rash on > 50% of skin	Bilirubin > 6 to 15 mg/dL	Diarrhea > 1,500 mL/day
4	Generalized erythroderma with bullous formation	Bilirubin > 15 mg/dL	Severe abdominal pain with or without ileus
Grade[e]			
I	Stage 1 or 2	None	None
II	Stage 3	Stage 1	Stage 1
III	-	Stage 2 or 3	Stages 2 to 4
IV[f]	Stage 4	Stage 4	-

[a] Use 'Rule of Nines' or burn chart to determine extent of rash.

[b] Range given as total bilirubin. Downgrade 1 stage if an additional cause of elevated bilirubin has been documented.

[c] Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Gut staging criteria for pediatric patients was not discussed at the Consensus Conference. Downgrade 1 stage if an additional cause of diarrhea has been documented.

[d] Persistent nausea with histologic evidence of GVHD of the stomach or duodenum.

[e] Criteria for grading given as a minimum degree of organ involvement required to confer that grade.

[f] Grade IV may also include lesser organ involvement but with extreme decrease in performance status.

Any updates to the staging/grading table will be provided in the SRM.

20.2. Appendix 2: Double-stranded DNA Virus Infections

The following table lists possible disease manifestations and potential sample collections for CMV and other dsDNA viruses. It is not intended to be an exhaustive list of permissible dsDNA viruses or sample collections.

Table 14: Disease Manifestations and Potential Samples for CMV and Other dsDNA Virus Infections

Virus	Disease Manifestations	Potential Samples
AdV	Viremia, hepatitis, encephalitis, pneumonitis, enteritis	Plasma, urine, stool, bronchoalveolar lavage (in pneumonitis), nasal swab, sputum, tissue biopsy, CSF (in encephalitis)
BKV	Viremia, thrombotic microangiopathy, nephritis, cystitis	Plasma, urine
CMV	Viremia, nephritis, retinitis, encephalitis, hepatitis, enteritis, pneumonitis	Plasma, urine, tissue biopsy, CSF (in encephalitis), bronchoalveolar lavage (in pneumonitis)
EBV	Viremia, posttransplant lymphoproliferative disorder (PTLD), hepatitis, myocarditis, hairy leukoplakia, severe infectious mononucleosis	Plasma, tissue biopsy, bone marrow, CSF
HSV-1	Viremia, encephalitis, skin and mucous membrane disease, keratitis	Plasma, lesion swabs and/or tissue biopsy, CSF (in encephalitis)
HSV-2	Viremia, encephalitis, skin and mucous membrane disease, keratitis	Plasma, lesion swabs and/or tissue biopsy, bronchoalveolar lavage (in pneumonitis), CSF (in encephalitis)
HHV-6	Viremia, encephalitis, pneumonitis	Plasma, CSF (in encephalitis), bronchoalveolar lavage (in pneumonitis), bone marrow, tissue biopsy
HHV-8	Viremia, Kaposi sarcoma, encephalitis, pneumonitis	Whole blood, CSF (in encephalitis), bronchoalveolar lavage (in pneumonitis), tissue biopsy
JCV	Viremia, progressive multifocal leukoencephalopathy (PML, i.e., vision loss, cognitive impairment, focal neurologic deficits), cystitis	Plasma, CSF (in encephalitis), urine
VZV	Viremia, dermatomal skin lesions, disseminated disease, encephalitis	Plasma, lesion swabs and/or tissue biopsy

20.3. Appendix 3: Viral Cystitis Grading Scale

The following table provides a grading scale for assessing the severity of viral cystitis (AdV, BKV, etc.). Non-viral cystitis should be graded using the appropriate CTCAE scale.

Table 15: Grading Scale for Assessing the Severity of Viral Cystitis

Grade 1	Asymptomatic or mild symptoms; microscopic hematuria; only OTC pain medications; clinical or diagnostic observation only; intervention not indicated.
Grade 2	Localized; oral antimicrobial intervention indicated; non-narcotic pain medications only; urinary catheter or bladder irrigation indicated.
Grade 3	IV intervention indicated (antibiotic or transfusion); narcotic pain medications; gross hematuria; radiologic, endoscopic, or operative intervention indicated.
Grade 4	Life-threatening consequences; narcotic pain medications; gross hematuria with visible clots; urgent intervention indicated.
Grade 5	Fatal; death related to AE.

Refer to the SRM for updates to this grading scale and for the most current version of the CTCAE grading scales.

Summary of Changes for Protocol Amendment 1

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study of the Safety, Tolerability, and Efficacy of CMX001 for the Prevention of Cytomegalovirus (CMV) Infection in CMV-seropositive (R+) Hematopoietic Stem Cell Transplant Recipients

PROTOCOL No. CMX001-301

AMENDMENT 1, DATED 02 SEPTEMBER 2014 (FINAL)

The revision history for Protocol CMX001-301 is summarized in Table 1 below. An overview of the more substantive changes described in Protocol Amendment 1 is provided in Table 2 overleaf. Minor changes, such as the correction of typographic errors and the standardization of data presentation or formatting, within the document are not described.

Table 1: CMX001-301 Protocol Revision History

Protocol Version	Version Date
CMX001-301 Original Protocol	30 April 2013
CMX001-301 Protocol Amendment 1	02 September 2014

Table 2: Summary of Changes under CMX001-301 Protocol Amendment 1

Change No.	Description of Change	Section(s) Affected
1	The EudraCT (European Union Drug Regulating Authorities Clinical Trials) number (2013-004795-35) is added to the title page.	Title page
2	Table 1 (Emergency Contact Information) is updated to: 1. Provide contact information for the Theorem Clinical Research Global Safety Advantage group in the UK for use by European study sites when reporting serious adverse events (SAEs) and adverse events of special interest (AEOSI). 2. Require SAEs and AEOSIs that are judged to be unrelated to study drug to be reported within 24 hours of learning of the event (instead of by the end of the next business day) where expedited reporting is required by local regulation. The same change is also made to Section 12.5.3 (Reporting Serious Adverse Events and Adverse Events of Special Interest).	Table 1 (and Section 12.5.3)
3	Reference to the number of participating countries is expanded to include Canada and also to countries in Europe.	Protocol summary: Study center(s)
4	A new study objective and corresponding secondary endpoint are added to compare reconstitution of the anti-cytomegalovirus (CMV) immunological response between CMX001- and placebo-treated subjects. A blood sample will be collected from subjects at Weeks 5, 9, 14, and 24 and tested using the T-Spot.® *CMV* Test (Oxford Immunotec Ltd., Abingdon, UK), which determines the number of CMV-sensitive effector T cells among peripheral blood mononuclear cells. These samples will be collected from individual study participants where the investigator believes the additional blood loss resulting from the collection of the samples (estimated at approximately 12 mL per sample) is medically acceptable. For those individuals where the investigator feels that the additional blood loss is not medically acceptable, e.g., because the subject is markedly anemic, then some or all of these samples may be omitted, as necessary. A collection window of up to +2 weeks from the scheduled collection date is provided to allow for additional flexibility in the collection of these samples. These data will be used to evaluate the incidence of the emerging anti-CMV immune response at each of the specified time points, as well as the potential impact of	Protocol summary and Sections 6.3.5.1, 7.2, 7.3.2, 8.1.1 (Table 9), and 12.4.6.2 (Table 12)

Change No.	Description of Change	Section(s) Affected
	other anti-CMV preemptive therapies (PrTs) on the observed response. The presence or absence of CMV-specific cellular immunity may be used as a subject characteristic during analysis of the incidence of clinically significant CMV infection during the posttreatment phase.	
5	To better reflect how negative CMV viremia test results are being reported to study sites, the definition of a negative CMV viremia test result for study qualification purposes is revised to refer to the reporting by the central virology laboratory of a "Not Detected" result for the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test. This language replaces the previous definition of a negative CMV viremia test result as CMV DNA in plasma below the lower limit of detection for the Roche assay. In addition, the existing language requiring prospective subjects to have negative results for any other CMV viremia testing performed since the qualifying transplant under local standard of care is revised to make it clearer that this encompasses all prior CMV viremia testing, including other CMV polymerase chain reaction (PCR) and pp65 antigenemia test results.	Protocol summary and Sections 5.0, 8.1, 8.1.1 (Table 9), 9.1, and 9.3 (inclusion criterion 3)
6	The definition of "high-dose steroid therapy" used throughout the study protocol is revised from the previous > 1 mg/kg prednisone equivalent to ≥ 1 mg/kg prednisone equivalent to be more consistent with accepted clinic practice.	Protocol summary and Sections 5.0, 6.3.1, 6.3.5 (Figure 1), 7.3.2, 8.1, 8.1.1 (Table 9) and 10.4
7	The text describing the minimum procedures that must be completed for subjects who are unable to return to the transplant center during the posttreatment phase is revised to additionally describe the collection of blood (plasma) and urine samples for storage at the central virology laboratory.	Protocol summary and Section 8.1
8	Following the opening of the 'Chimerix Registry for Former CMX001 Study Participants' (Protocol No. CMX001-333) to former CMX001-301 study participants, the previous text outlining the proposed design of the Registry is now superfluous and has been removed from the amended study protocol.	Protocol summary and Section 8.1
9	The text describing the submission of blood (plasma) and urine samples for virologic evaluation to the central virology laboratory has been revised to:	Protocol summary and Sections 8.1.1

Change No.	Description of Change	Section(s) Affected
	1. Reflect the addition of a second central virology laboratory (for European sites). 2. Note that the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test used by the central virology laboratories has been CE (Conformité Européene)-marked. 3. Reworked the reference to using the stored blood (plasma) samples for "CMV specific immunity" testing to describe using those samples for possible analysis of other biomarkers of CMV-specific immunity since specific blood samples are now being collected for this purpose (using the T-Spot.® *CMV* Test; see change no. 4). 4. Emphasize that other relevant biological samples (e.g., stool, cerebrospinal fluid, sputum, etc., as appropriate) "should" (rather than "may") be collected and sent to the central virology laboratory when CMV or another double-stranded DNA (dsDNA) viral syndrome or disease is suspected.	(Table 9), 12.1.1, 12.1.1.1, and 14.5
10	All subjects have a single timed blood sample for analysis of plasma concentrations of CMX001 and cidofovir collected at 3 (± 1) hours postdose on the FDD. To afford greater flexibility for the collection of this sample, it may be collected after administration of the second dose of study drug where collection on the FDD is not practical (e.g., to accommodate a scheduling conflict or resource issue).	Protocol summary and Sections 8.1.1 (Table 9), 9.2, and 12.2
11	The requirement that study drug be discontinued when a subject experiences a treatment-emergent decrease in estimated glomerular filtration rate (eGFR) to < 15 mL/min or a new or persistent requirement for dialysis is restated to make it clearer to the reader that these events have to be assessed by the investigator as study drug-related to require study drug discontinuation. If there is an alternative explanation for the decrease in eGFR or the requirement for dialysis, the investigator should contact the Chimerix Medical Monitor (or designee) to discuss the subject's condition and the most appropriate course of action. For subjects with an on-treatment decrease in eGFR to < 15 mL/min that is not related to study drug, then study drug treatment may be continued if dialysis or other renal replacement therapy is initiated. Renal replacement therapy must be continued for as long as the subject's eGFR remains < 15 mL/min and the subject remains on study drug.	Protocol summary and Sections 9.5 and 13.1.4

Change No.	Description of Change	Section(s) Affected
12	The table summarizing the risk factors and CMV viremia thresholds to be used when determining whether to initiate anti-CMV PrT and the supporting text are revised as follows: 1. To emphasize that investigators are expected to draw a confirmatory blood sample for measurement of CMV viremia prior to initiating anti-CMV PrT in subjects who meet the criteria for aggressive anti-CMV viremia management. The decision not to wait for the second, confirmatory result before starting anti-CMV PrT is, however, left to the investigator's discretion. 2. To emphasize that both the initial and confirmatory blood samples for CMV viremia testing are to be sent to the central virology laboratory for analysis. In addition, whenever a sample is collected for CMV viremia testing in a local virology laboratory, a sample should also to be collected and sent to the central virology laboratory for analysis in parallel. The requirement for parallel sample collection and analysis applies to both protocol-scheduled CMV viremia assessments and any unscheduled CMV viremia assessments performed per local SoC. 3. Restate the clinical risk factor that subjects who have "an indication for" concomitant therapy with high-dose systemic steroids, anti-thymocyte globulin (ATG), or alemtuzumab should be considered for aggressive CMV viremia management to describe subjects who (a) are currently receiving, have received within the prior 14 days, or are anticipated to receive within 1 day therapy with high-dose (≥ 1 mg/kg prednisone equivalent) systemic steroids, or (b) are currently receiving, have received, or are anticipated to receive within 1 day either ATG or alemtuzumab. The revised language is thought to be less ambiguous than the original text. 4. Require investigators to make a decision on the initiation of anti-CMV PrT as soon as practicable, but preferably within 4 days after the initial CMV viremia result triggering the initiation of anti-CMV PrT. The original protocol language required investigators to make their decision on the initiation of anti-CMV therapy within 4 days after the initial CMV viremia result. 5. The supporting text describing subjects resuming study drug treatment where anti-CMV	Protocol summary and Section 5.0, 6.3.5 (including Table 5 and Figure 1), 8.1, 12.1.1.1, and 14.4.1

Change No.	Description of Change	Section(s) Affected
	PrT is determined to have been initiated "in error" has been replaced with language describing resuming study drug treatment where the anti-CMV PrT was initiated "prematurely," since the decision to initiate therapy was made in good faith based on the available data.	
13	The stated criterion of a ≥ 30% decrease in renal function from baseline, as measured by eGFR using the Modified Diet in Renal Disease equation 4 (MDRD4), as one symptom of possible BK virus (BKV) end-organ disease is modified to: 1) require both a ≥ 30% decrease in eGFR from baseline and a decrease in eGFR to a value < 60 mL/min/1.73 m^2, and 2) describe the use of the Chronic Kidney Disease Epidemiology (CKD-EPI) equation to calculate eGFR rather than MDRD4 for the study analysis. The MDRD4 equation will continue to be used by the central safety laboratory to determine study eligibility and to monitor the renal function of study participants in real-time.	Protocol summary and Sections 6.3.5.1 and 7.3.2
14	The references to the specific version (4.02) of the National Institutes of Health (NIH)/National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) that will be used to grade the severity of adverse events (AEs) have been deleted from the amended protocol. That version of the NIH/NCI CTCAE grading tables has been superseded (by version 4.03) and not including the version number in the amended protocol will avoid the need to update the protocol again in the event of future revisions to the CTCAE grading tables. A copy of the NIH/NCI CTCAE grading tables is included in the study reference manual (SRM) provided to investigators.	Protocol summary and Sections 7.3.3, 12.5.2, and 13.1.2
15	The "other" clinical endpoint assessing the incidence and severity of non-CMV infections is revised to include protozoal infections (in addition to bacterial, fungal, and viral etiologies).	Protocol summary and Section 7.3.3
16	The Protocol Summary (Statistical Methods: General Considerations) is updated to remove an erroneous reference to "one-sided" statistical tests. Consistent with the existing text in Section 14 (Statistics), unless otherwise stated, all statistical tests will be two-sided, with a p-value of < 0.05 considered statistically significant.	Protocol summary
17	The Protocol Summary (Statistical Methods: Secondary Efficacy Endpoints) is revised to describe the sequential testing of specific secondary endpoints based on the incidence of any non-CMV	Protocol Summary and Section 14.4.2

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	dsDNA virus end-organ disease in the event that the primary analysis is statistically significant. This will allow testing of CMX001 for the prevention of other dsDNA viruses in a way that controls for the type I error rate. The same change is also made to the equivalent text in Section 14.4.2 (Secondary Efficacy Endpoints).	
18	Section 5: Glossary of Terms is revised as follows: 1. To update the definitions for "CMV Viremia Negative" and "CMV Viremia Positive" to provide additional guidance to investigators on how to interpret these terms when determining study eligibility and whether to initiate anti-CMV PrT based on how CMV viremia tests results are being reported by the central virology laboratory to the study sites. 2. To add a new entry, "Initiation of Anti-CMV Preemption Therapy (Standard vs. Aggressive CMV Management)" which describes using the subject's baseline characteristics and/or emergent signs and symptoms and the stated CMV viremia thresholds to determine when to discontinue study drug and initiate anti-CMV PrT. 3. The definition of "(Likelihood of) CMV Disease progression" is revised to explain that the stratification of subjects between the "lower likelihood" and "higher likelihood" of disease progression at the time of randomization is different from the categorization of subjects to standard and aggressive CMV management strategies for the purposes of determining the appropriate threshold for discontinuation of study drug and initiation of anti-CMV PrT. 4. To avoid confusion between primary and secondary graft failure, the definition of "(Secondary) Graft Failure/Rejection" is deleted. 5. The definition of "Treatment Phase" is revised to describe the period from the FDD through Week 14 (replacing the previous definition of Week 1 through Week 14; see also change no. 28).	Section 5.0
19	Section 6.1 (Background) and Section 6.2 (CMX001) are revised to include the generic name for CMX001, brincidofovir.	Sections 6.1 and 6.2
20	Section 6.2.1 (Preclinical Pharmacokinetics and Metabolism of CMX001) is revised to include a statement that CYP4F2 is the primary enzyme responsible for cytochrome P450 (CYP)-mediated	Section 6.2.1

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	metabolism of CMX001, with no significant contribution by other CYP enzymes.	
21	Reflecting recent changes requested by the US Food and Drug Administration (FDA) to the Investigator's Brochure for Brincidofovir (CMX001), Edition 9.1, Section 6.2.2 (Summary of Toxicology Studies with CMX001) is revised to restate the findings from the previously completed 13-week toxicology study in rats to better contextualize the potential carcinogenic risk from exposure to CMX001.	Section 6.2.2
22	Section 6.2.3 (Summary of Clinical Experience with CMX001) is revised to state that Studies CMX001-108, CMX001-114, CMX001-202, and CMX001-350 are now considered complete, i.e., the results of final analyses of the study results have been submitted to FDA.	Section 6.2.3
23	Section 6.2.3.1 (Summary of Clinical Pharmacology [Phase 1] Studies with CMX001) is updated to: 1) include a summary of the results from completed Study CMX001-108, and 2) delete reference to "preliminary," "pending," or "ongoing" when discussing Studies CMX001-114, CMX001-202, and CMX001-350.	Section 6.2.3.1
24	Section 6.2.3.3 (Study CMX001-202) and Section 6.2.3.4 (Study CMX001-350) are updated to include statements directing the reader to the Investigator's Brochure for CMX001 for summaries of the final safety and efficacy results for both studies.	Sections 6.2.3.3 and 6.2.3.4
25	Figure 1 in Section 6.3.5 (Rationale for Primary Efficacy Endpoint) is reworked to provide a flowchart that uses the reader's responses to questions about the subject's baseline characteristics and emergent signs and symptoms and his or her measured CMV viremia to determine whether to initiate anti-CMV PrT.	Section 6.3.5 (Figure 1)
26	Section 6.4 (Potential Risks and Benefits) is revised to include an expanded discussion of the risk:benefit analysis that: (1) highlights the potential benefits from using CMX001 to prevent the indirect effects of uncontrolled CMV replication, as well as other dsDNA viruses, and (2) discusses the potential risk from CMX001 as a possible human carcinogen when used for CMV prevention in the hematopoietic cell transplant patient population based on the clinical experience with cidofovir following FDA approval of Vistide® for injection.	Section 6.4
27	Section 6.5.1 (Data and Safety Monitoring Board [DSMB]) is revised to state that the DSMB for	Section 6.5.1

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	CMX001-301 will be convened according to both FDA- and European Medicines Agency (EMA)-issued guidelines on clinical trial data monitoring committees as reflected in the DSMB charter.	
28	Section 8.1.1 (Study Visit Schedule) is revised to: 1. Update the number of treatment phase assessments to reflect the removal of the "Week 1" column from the Schedule of Study Assessments (Table 9). With all Week 1 assessments already covered under the "FDD" column, the Week 1 column in Table 9 is redundant. References to "Week 1" elsewhere in the study protocol are changed to "FDD". 2. Include guidance on which of the first three scheduled study assessments following the FDD (i.e., the Week 2, Week 3, and Week 4 visits) should be omitted depending on when each subject initiates his or her treatment relative to the date of transplant. This guidance is summarized in tabular form in new Table 7. 3. In order to maximize the opportunity for data collection and minimize the loss to follow-up of study participants after discharge from the care of the transplant center, the amended protocol allows for some or all of the scheduled study assessments (including the collection of blood and other samples, as appropriate) to be performed by a third party providing remote (home) visits by suitably-qualified personnel. Investigators must contact the Chimerix Medical Monitor to request prior approval to use such a service and agree on an action plan detailing which of the scheduled study assessments can be reasonably completed in this manner.	Section 8.1.1 (Table 7, Table 9) (and Protocol summary and Sections 5.0 and 8.1.2 [Table 8])
29	The Schedule of Study Assessments (Table 9) is revised to remove an inconsistency with the body text (Section 9.1, Section 9.4, and Section 12.4.6.4). Footnote 'l' should refer to pre-existing HIV serology and/or hepatitis B or C PCR test results being acceptable for the purposes of study qualification if collected within 6 months prior to the qualifying transplant, not within 6 months prior to the FDD.	Section 8.1.1 (Table 9, footnote 'l')
30	The Schedule of Study Assessments (Table 9) is revised to allow investigators more flexibility with the dispensing of the second card of study drug to take into account the actual duration of the individual subject's treatment, dose interruptions due to AEs, other missed doses, logistical issues	Section 8.1.1 (Table 9, footnote 's')

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	(public holidays, vacation), etc.	
31	Section 8.1.2 (Study Windows) is revised to replace the original text describing study visits being scheduled during the treatment and posttreatment phases within the relevant calendar week with new text describing the visits being scheduled within the relevant week posttransplant. In addition, the text in this section describing the rounding of study data has been deleted as this was thought to be unnecessary in a study protocol.	Section 8.1.2 (Table 8)
32	Section 9.3 (Subject Inclusion Criteria) is revised as follows: 1. Inclusion criterion 1 is revised to reflect the updated definition of a CMV viremia negative result described in change no. 5 (i.e., CMV viremia reported by the central virology laboratory as "Not Detected" for the Roche assay). 2. Inclusion criteria 3 and 4 are revised to clarify that the use of contraception is intended primarily to encompass the use of contraception during heterosexual intercourse with a partner of reproductive potential. The existing note to both inclusion criteria is also revised to include language requiring investigators to caution female subjects of reproductive potential, and male subjects with female partners of reproductive potential, who discontinue the study prior to Week 24 to continue their current contraceptive method(s) for at least 90 days following administration of the last dose of study drug. 3. Inclusion criterion 6, which requires prospective subjects to be able to ingest and absorb oral medication (in the judgment of the investigator and based on lack of significant gastrointestinal (GI) events/medical history), is revised to include explicit reference to subjects being able to "comfortably" ingest oral medication to clarify that forcible oral administration of the study drug was not intended under the original language of this criterion.	Section 9.3
33	Section 9.4 (Subject Exclusion Criteria) is revised as follows: 1. A typographical error in exclusion criterion 1 is corrected, clarifying that female subjects who are planning to become pregnant during the anticipated duration of their participation in the "entire study (i.e., through Week 24)" should be excluded from the study.	Section 9.4

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	2. Exclusion criterion 5 is revised to expand the existing prohibition on the use of other antiviral agents to include not just prior receipt of the listed medications within the stated windows, but also to exclude subjects who are anticipated to need future treatment with such medications. In addition, reflecting the language of Section 10.2.1 (Prohibited Medications), the stated prohibition on the prior receipt of cidofovir at any time posttransplant is revised to make it clearer that this applies to the intravenous administration of cidofovir and not to topical treatments, such as intravesical administration for hemorrhagic cystitis. 3. Exclusion criterion 6 is revised to restate the limitation on subjects receiving intravenous acyclovir therapy on the FDD from the current > 5 mg/kg administered three times a day (TID) to a total daily dose (TDD) of > 15 mg/kg to take account of other acyclovir dosage regimens. 4. Exclusion criterion 7 is revised to additionally exclude subjects receiving ketoconazole treatment (other than topical formulations) at the FDD or who are anticipated to need treatment with ketoconazole during the treatment phase of the study. This change is based on newly available *in vitro* data suggesting that CYP-mediated metabolism of CMX001 is primarily mediated by CYP4F2, so there is a theoretical possibility of a drug-drug interaction mediated by modulators of CYP4F2 activity such as ketoconazole. 5. Exclusion criterion 9 is revised to allow the Chimerix Medical Monitor to approve the enrollment (randomization) of a subject with negative hepatitis B virus (HBV) and/or hepatitis C virus (HCV) PCR results performed at a local laboratory in lieu of pending results from the relevant central laboratory. 6. Exclusion criterion 11 is revised to refer to renal dialysis rather than hemodialysis. 7. Exclusion criterion 13 is revised to clarify that any subject whose baseline serum chemistry tests (i.e., based on blood drawn prior to initiating study treatment on the FDD) shows elevated serum aminotransferase and/or elevated total or direct bilirubin concentrations that meet any of the thresholds for dose interruption as described in Section 13.1.3 of the study protocol should have their study treatment interrupted until those abnormalities have	

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	improved sufficiently to allow treatment to be resumed. These subjects are not required to be discontinued from the study.	
34	For each concomitant immunosuppressant medication being taken by a subject, the investigator is currently required to record the following information: immunosuppressant dose, concentration value and units, matrix analyzed, date and time of collection, and the type of time point relative to last dose (e.g., trough, 4 hours postdose, etc.) Under the amended protocol, investigators are no longer required to record the type of time point relative to last dose, but instead to capture the actual date and time of the last dose administration of each immunosuppressant medication prior to collection of the blood sample for the reported concentration value.	Sections 8.1.1 (Table 9, footnote 'q'), 10.2, and 12.4.6.6
35	Section 10.2 (Concomitant Medications) is revised to include guidance on the recording of prior and concomitant medications, which is summarized as follows: 1. Prior medications to be recorded are those taken within 30-day period prior to the FDD, and are limited to anti-infectives, immunosuppressants, GI medications, steroids, and the subject's conditioning regimen. 2. Concomitant medications to be recorded are all medications (both over-the-counter and prescription drugs) taken during the course of the study, i.e., from the FDD through study completion. However, IV fluids, vitamins, and nutritional or electrolyte supplements (other than oral magnesium) do not need to be entered in the electronic case report form (eCRF). Herbal supplements are considered medications for the purpose of this study. 3. Non-steroid medications, including medications that qualify a subject for "high likelihood of CMV infection" stratification or "aggressive CMV management", and all anti-CMV PrT medications, should be recorded on the Prior and Concomitant Medications eCRF. 4. Steroid medications (both topical and systemic), including any steroids that qualify a subject for "high likelihood of CMV infection" stratification or "aggressive CMV management", should be recorded on the Prior and Concomitant Steroid Medications eCRF. 5. For each recorded medication, the indication should be the condition necessitating the use	Section 10.2

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	of the medication and not the therapeutic class of the drug. For indications of acute or chronic GVHD, the indication must indicate whether the treatment is for prophylaxis, presumptive treatment, or treatment of GVHD. For anti-CMV PrT medications, the recorded indication should be “Preemptive therapy CMV".	
36	Section 10.2.1 (Prohibited Medications: Other) is revised to: 1. Include ketoconazole (other than when administered as topical formulations) as a prohibited medication and explain that no interactions are expected with other azole antifungal agents, such as voriconazole, fluconazole, or posaconazole, based on *in vitro* data demonstrating that these drugs do not inhibit CYP4F2 at relevant physiological concentrations, thereby providing therapeutic alternatives to ketoconazole. Topical formulations of ketoconazole are permitted. 2. Consistent with the previously stated change to exclusion criterion 6, restate the limitation on subjects receiving intravenous acyclovir therapy on the FDD from > 5 mg/kg TID to subjects receiving a TDD of > 15 mg/kg to take account of acyclovir regimens other than TID regimens.	Section 10.2.1
37	Section 10.3.1 (Study Diary Card) is revised to make it clearer to the reader that the main purpose of the study diary card is to serve as an aide-mémoire for the subjects to complete and for the study sites to use when discussing possible signs and symptoms with subjects during their study visits.	Section 10.3.1
38	Section 11.2 (Study Drug Packaging and Labeling) is revised as follows: 1. Update the label contents for study drug cards intended for Europe to include the “For clinical trial use only” statement and expiration (repass) date required by European law. 2. Add statements that European distribution activities will be completed by Biotec Services International (Bridgend, UK), including Qualified Person (QP) batch release.	Section 11.2
39	Section 11.5 (Study Drug Administration: Missed Doses) is revised to add an explicit statement that in the event that a subject does interrupt dosing with study drug (for whatever reason), the	Section 11.5

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	subject should continue with the study schedule, completing all planned assessments (including PK sample collection) except for study drug administration.	
40	Section 11.7 (Study Drug Handling and Disposal) is revised to clarify that Biotec Services International will be the vendor responsible for accepting returned unused study drug sent from sites in Europe, while Xerimis, Inc. will continue to receive shipments of unused study drug supplies from sites in the USA and Canada.	Section 11.7
41	Section 12.1.1.1 (CMV Viremia in Plasma) is revised to include the range of quantitation in human plasma for the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in international units per milliliter (i.e., 137 to 9.1 x 10^6 IU/mL). In addition, the lower limit of quantification (LLOQ) of 137 IU/mL for the Roche assay is restated as 150.7 copies/mL (previously stated as 150 copies/mL), based on the manufacturer's conversion factor of 1.1. This is reported to investigators as 151 copies/mL, after rounding.	Section 12.1.1.1 (and Section 5.0)
42	Section 12.1.1.2 (Virologic Data obtained from Local Virology Laboratories) is revised to expand the reference to recording the results of local qPCR CMV test results in the eCRF to include the results of both qualitative and quantitative CMV PCR testing.	Section 12.1.1.2
43	Section 12.1.3.1 (BKV-associated Urinary Symptoms) is revised to include reference to new Appendix 3 which provides a grading scale for viral-related cystitis. Cystitis not associated with dsDNA viral infection should continue to be assessed using the appropriate CTCAE scale.	Section 12.1.3.1 and Appendix 3
44	Section 12.1.3.2 (HHV-6-associated Symptoms) is revised to remove reference to performing a mini-mental state examination (MMSE) at specific time points on treatment, reflecting the changes to Section 12.4.5 (Neurocognitive Assessments) described in change no. 45.	Section 12.1.3.2
45	Section 12.4.5 (Neurocognitive Assessments) is revised as follows: 1. To describe the addition of a more detailed assessment of neurocognitive function to be performed at selected sites as part of the Week 24 assessment. At participating sites, subjects will be asked to undergo a more detailed neurocognitive assessment using the validated Brief Test of Adult Cognition by Telephone (BTACT) and Oral Trail Making Test (OTMT-B) instruments. The assessment will be performed one time over the	Section 12.4.5 (and Table 9)

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	telephone by trained research staff from Seattle Children's Research Institute. The assessment will take approximately 30 minutes and the subject responses will be recorded, for scoring purposes, using audio recording software. Subjects who agree to undergo the more detailed assessment of neurocognitive function will not need to complete the MMSEs scheduled for Weeks 6, 10, 15, and 24. 2. The statement that additional MMSEs will be performed on individual subjects based on their responses to the screening questions on the study diary card/aide-mémoire is modified to require an unscheduled assessment only when it is deemed clinically appropriate to do so by the investigator. Unscheduled assessments should be performed regardless of whether the subject is participating in the more detailed assessment of neurocognitive function at Week 24.	
46	Section 12.4.6.1 (Hematology and Serum Biochemistry) is revised to clarify that a lymphocyte subset evaluation will be performed during the Week 4 assessment, not during the Week 2 assessment. The requirement for performing the lymphocyte subset evaluation during Week 4 (as well as during the assessments scheduled for Weeks 6, 10, 15, and 24) is supported by the Schedule of Study Assessments (Table 9). The same change is made to Table 12 (Clinical and Virologic Laboratory Evaluations). This section and Table 12 are also revised to clarify that white blood cell differential and lymphocyte subsets will be reported as both percent and absolute (total) counts.	Section 12.4.6.1 and Table 12
47	Section 12.4.6.4 (Non-dsDNA Viruses) is revised as follows: 1. To allow for any serological testing for human immunodeficiency virus (HIV) infection and/or measurement of HBV DNA and/or HCV RNA viral loads needed at screening to be performed by the central safety laboratory or by the central virology laboratory. 2. To allow the Chimerix Medical Monitor to approve the enrollment (randomization) of a subject with negative HBV and/or HCV PCR results performed at a local laboratory in lieu of pending results from the relevant central laboratory.	Section 12.4.6.4
48	Section 12.5.1.1 (Adverse Event [AE]) is revised to update the existing text that excludes disease-	Section 12.5.1.1

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	specific signs and symptoms that do not "worsen (i.e., increase in frequency or severity) unexpectedly post-study drug administration" from being reported as AE by redefining worsening as an "increase in frequency or severity by at least one grade post-study drug administration."	
49	Section 12.5.1.3 (Adverse Events of Special Interest) is revised to: 1. Clarify that only reported AE terms of diarrhea, abdominal pain, ileus, nausea, vomiting, jaundice, elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST), increased total serum bilirubin, or new onset of or exacerbation of acute graft versus host disease of the gut (GI-GVHD) or acute GVHD of the liver which meet the prespecified criteria are to be reported as AEOSIs and not every reported diagnosis that may encompass one or more of these events as signs/symptoms. For example, Grade 3 diarrhea would be reported as an AEOSI, whereas, Grade 3 diarrhea secondary to *C. difficile* colitis would be reported as a diagnosis of "*C. difficile* colitis," rather than diarrhea, and would, therefore, not be considered an AEOSI. 2. Clarify that acute GI-GVHD or acute GVHD of the liver that meet the criteria for a clinical organ Stage 3 or 4 event per the NIH scale (as opposed to a Grade 3 or 4 event per the CTCAE grading scale) are to be reported as AEOSIs.	Section 12.5.1.3
50	Section 12.5.1.3.1 (Diarrhea and GVHD) is revised to: 1. Make it clearer to the reader that only events of acute GVHD, i.e., not chronic GVHD, are to be captured on the GVHD eCRF. 2. Revise the statements about the information that should be captured for diarrhea and acute GVHD events to align with the final eCRF modules. 3. Add an explicit statement that the results of any diagnostic procedures performed for diarrhea and acute GVHD events meeting the criteria for reporting as an SAE or AEOSI may be requested for possible adjudication by the GVHD Adjudication Committee (GAC).	Section 12.5.1.3.1
51	Section 12.5.2 (Recording Adverse Events) is revised to remove reference to capturing the onset and resolution times of AEs. This information is not being captured in the Adverse Events eCRF.	Section 12.5.2

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52	Section 12.5.3 (Reporting Serious Adverse Events and Adverse Events of Special Interest) is revised to remove reference to site personnel telephoning Theorem GSA to notify them of SAEs/AEOSIs. SAEs and AEOSIs are to be reported only by site personnel faxing or e-mailing the completed SAE Report Form to Theorem GSA. In addition, a second fax number is provided for use by study sites in Europe (see also change no. 2).	Section 12.5.3
53	Section 13.1.1 (Safety Monitoring and Management Plan) is revised to clarify that the flow chart summarizing the management of treatment-emergent toxicities presented in Figure 2 applies (1) only to GI and hepatic toxicities, and (2) only to those events requiring treatment interruption and not to all GI and hepatic toxicities. In addition, Figure 2 is revised to include a footnote reminding the reader that, in addition to the maximum-permitted consecutive dose interruptions (i.e., 4 doses/18 days for twice-weekly [BIW] dosing and 2 doses/21 days for once-weekly [QW] dosing following dose modification or reduction), any subject who misses a cumulative total of 8 doses of a BIW regimen or 4 doses of a QW regimen should also be discontinued from study drug.	Section 13.1.1 (Figure 2)
54	Section 13.1.3 (Management of Subjects with Serum Elevations in Serum Aminotransferases) is revised to replace the previous reference to not resuming dosing in subjects with "significant ALT or AST elevations (> 5x ULN)" to not resuming dosing in subjects with "ALT or AST elevations remaining at levels > 5x ULN". The revised text better reflects the original intent of this language to prevent dosing from being resumed in subjects with persistent ALT/AST elevations and not in individuals with an isolated elevated ALT/AST value.	Section 13.1.3
55	Section 13.1.4 (Cidofovir-associated Events: Nephrotoxicity, Neutropenia, Ocular Hypotony, and Carcinogenesis) is updated at the request of the European Federal Agency for Medicines and Health Products to more clearly highlight the carcinogenic potential of CMX001 and cidofovir. See also the changes to Section 6.2.2 (Summary of Toxicology Studies with CMX001) and Section 6.4 (Potential Risks and Benefits) described in change nos. 21 and 26.	Section 13.1.4
56	Section 14.4.1 (Primary Efficacy Endpoint) is revised to replace the erroneous reference to complete data sets being analyzed with a logistic regression with "treatment group and analysis center" as independent factors to analysis with "treatment group and risk group" as the	Section 14.4.1

Change No.	Description of Change	Section(s) Affected
	independent factors.	
57	Section 14.5 (Viral Load Analyses) is revised by deleting the original text describing how the CMV and other dsDNA viral load data would be summarized and presented as it was not appropriate for a study designed to assess the effect of drug on the prevention of infection. Specific details on how the viral load data will be summarized and presented will be provided in the final statistical analysis plan (SAP) for the CMX001-301 study.	Section 14.5
58	Section 14.9.2 (Demographics and Baseline Characteristics) is revised to: 1) remove reference to the reporting of viral serology for non-dsDNA viruses (e.g., HBV, and HCV) at baseline, and 2) remove reference to summarizing emergent dsDNA viral infections at baseline since by definition these infections would not be "emergent". Viral serology for adenovirus, BKV, and Epstein-Barr virus will be summarized, where known.	Section 14.9.2
59	Table 14 (Disease Manifestations and Potential Samples for CMV and Other dsDNA Virus Infections) in Appendix 2 (Double-stranded DNA Virus Infections) is updated to: (1) add human herpes virus type 8 (HHV-8) to the list of dsDNA viruses, and (2) provide additional guidance on possible disease manifestations and potential sample types that may need to be collected. In addition, text is added clarifying that this table should not be construed as providing an exhaustive list of permissible dsDNA viruses or sample collections, but is intended to provide guidance to investigators on the types of samples that may be collected for the more common disease manifestations of each dsDNA virus.	Section 20.2 (Appendix 2) and Table 14
60	Appendix 3 (Viral Cystitis Grading Scale) is added to provide a specific grading scale for viral-related cystitis.	Section 20.3 (Appendix 3)