An Open-label, Randomized, Multi-center, Parallel Group, Two-arm Study to Assess the Safety, Overall Tolerability, and Antiviral Activity of Brincidofovir versus Standard of Care for Treatment of Adenovirus Infections in High-risk Pediatric Allogeneic Hematopoietic Cell Transplant Recipients

Protocol Number: CXM001-999

Protocol Version/Date: Original, dated 26 September 2017

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BRINCIDOFOVIR (CMX001; BCV)

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Protocol Version/Date: Original, dated 26 September 2017

US IND No.:	110,584
EudraCT No.:	2017-001735-39
Study Sponsor:	Chimerix, Inc. 2505 Meridian Parkway, Suite 100 Durham, North Carolina 27713 USA Tel: +1 919-806-1074
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SPONSOR'S SIGNATURE PAGE

An Open-label, Randomized, Multi-center, Parallel Group, Two-arm Study to Assess the Safety, Overall Tolerability, and Antiviral Activity of Brincidofovir versus Standard of Care for Treatment of Adenovirus Infections in High-risk Pediatric Allogeneic Hematopoietic Cell Transplant Recipients

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

W. Garrett Nichols, MD, MS

Printed Name of Chimerix Medical Officer

_____

Signature of Chimerix Medical Officer

_____

Date

INVESTIGATOR'S AGREEMENT

An Open-label, Randomized, Multi-center, Parallel Group, Two-arm Study to Assess the Safety, Overall Tolerability, and Antiviral Activity of Brincidofovir versus Standard of Care for Treatment of Adenovirus Infections in High-risk Pediatric Allogeneic Hematopoietic Cell Transplant Recipients

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I have received and carefully read the Investigator's Brochure for Brincidofovir (CMX001, BCV). I have carefully read this CMX001-999 study protocol and agree to conduct the study in accordance with the 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 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 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 sponsor medical contacts are provided in Table 1. Emergency, 24-hour, and CRO contacts, as applicable, are provided in the study reference manual (SRM). Any updates to the sponsor medical contacts will also be provided in the SRM.

Table 1: Emergency Contact Information

Role in Study	Name
Study Sponsor	Chimerix, Inc. 2505 Meridian Parkway, Suite 100 Durham, North Carolina 27713, USA Tel: +1 919-806-1074 Fax: +1 919-806-1146
Chimerix Chief Medical Officer	W. Garrett Nichols, MD, MS Chief Medical Officer Chimerix, Inc. Tel: +1 919-287-6006 Cell: +1 919-257-1226 Fax: +1 919-806-1146 Email: gnichols@chimerix.com
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Chimerix Back-up Medical Monitor	Marion Morrison, MD Executive Medical Director Chimerix. Inc. Tel: +1 919-313-2977 Cell: +1 919-886-0830 Fax: +1 919-313-6797 Email: mmorrison@chimerix.com

1. SYNOPSIS

Name of Sponsor/Company: Chimerix, Inc. ("Chimerix")

Name of Investigational Product: Brincidofovir (BCV); hexadecyloxypropyl-cidofovir; CMX001

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: An Open-label, Randomized, Multi-center, Parallel Group, Two-arm Study to Assess the Safety, Overall Tolerability, and Antiviral Activity of Brincidofovir versus Standard of Care for Treatment of Adenovirus Infections in High-risk Pediatric Allogeneic Hematopoietic Cell Transplant Recipients

Short Title: The AdAPT Trial; Adenovirus after Allogeneic Pediatric Transplantation

Study Center(s): This study will be conducted at multiple centers across Europe, North America, and possibly other regions.

Phase of Development: Two (2)

Objectives:

This study is designed to assess the safety, overall tolerability, and antiviral activity of "short course" BCV therapy, as compared with current standard of care (SoC), for the treatment of adenovirus (AdV) infections in high-risk (i.e., T cell-depleted) pediatric allogeneic hematopoietic cell transplant (HCT) recipients. A virologic response-driven approach to the duration of treatment will be evaluated, in which subjects randomized to BCV therapy are treated until AdV viremia is confirmed as undetectable or until a maximum of 16 weeks of therapy, whichever occurs first.

Primary Objective:

The primary objective of the study is to compare the safety, overall tolerability, and virologic response of BCV vs. SoC for the treatment of AdV infection in high-risk pediatric allogeneic HCT recipients.

Secondary Objectives:

- To assess the incidence of and time to all-cause, non-relapse, and AdV-associated mortality in pediatric subjects treated with BCV vs. SoC
- To assess the correlation between virologic response and clinical outcome
- To describe the incidence of and time to virologic relapse in subjects who have previously achieved undetectable AdV viremia
- To assess resolution or progression in clinical symptoms associated with AdV disease (i.e., resolution of all disease to no disease among subjects with probable or definitive AdV disease at baseline and progression from no disease to any probable or definitive AdV disease among asymptomatic subjects at baseline)
- To assess the correlation between AdV hexon "serotype," virologic response, and clinical outcome
- To evaluate the emergence of viral resistance among subjects treated with BCV vs. SoC
- To characterize plasma BCV pharmacokinetic (PK) profiles and evaluate the impact of covariates of interest on PK
- To characterize the potential impact of plasma BCV exposure on clinical safety, virologic, and mortality endpoints, and to evaluate the modifying influence of various covariates of interest on these relationships and endpoints

- To assess virologic response in other non-plasma biologic compartments (urine, stool, respiratory secretions), as well as the association between detectable AdV viral load in these compartments at AdV viremia clearance with subsequent AdV viremia relapse

Exploratory Objectives

- To assess the correlation between baseline HCT co-morbidity index and clinical outcome
- To assess immunologic predictors of virologic response (all subjects) and relapse (among subjects with confirmed AdV clearance from plasma)
- To evaluate exploratory biomarkers for BCV-related gastrointestinal (GI) toxicity (e.g., citrulline, suppression of tumorigenicity-2 [ST2], T cell immunoglobulin mucin-3 [TIM3], and C-reactive protein [CRP])
- To assess healthcare resource utilization

Methodology: This is a randomized, open-label, multi-center study of the safety, overall tolerability, and antiviral activity of BCV, as compared with SoC, in pediatric recipients of high-risk (i.e., T cell-depleted) allogeneic HCT. Pediatric patients with AdV detected in plasma within the previous 21 days and for the first time since their qualifying transplant may be screened for participation in the study. Subjects who meet all applicable entry criteria will be randomized in a 2:1 ratio to receive either BCV or SoC. The day of randomization is defined as Day 1. During randomization, subjects will be stratified based on the following variables: last (non-baseline) screening AdV viremia (≥ 10,000 copies/mL vs. < 10,000 copies/mL), time from transplant to randomization (≥ 28 days vs. < 28 days), and T cell-depletion methodology (receipt of alemtuzumab or ex vivo depletion vs. receipt of anti-thymocyte globulin [ATG]). Subjects randomized to receive BCV will be treated until AdV deoxyribonucleic acid (DNA) is confirmed to be undetectable in plasma, up to a maximum of 16 weeks post-randomization. Subjects randomized to the SoC arm will be managed according to local or institutional practice guidelines for the treatment of AdV infection. All subjects, regardless of treatment assignment, will be followed in the study for a total of 36 weeks post-randomization. Subjects will be assessed on a weekly basis through Week 16, with additional assessments performed at Weeks 24 and 36 post-randomization. The data collected through Week 16 will comprise the primary data set for the study; hence, the primary database will be locked and analyzed following capture of data for all subjects through Week 16. In addition, all subjects (both BCV and SoC recipients) will be encouraged to enroll in the BCV Registry (Study CMX001-333) to assess the longer-term impact of exposure to BCV.

Number of Subjects (Planned):

The study will target the enrollment of a total of approximately 141 subjects, with 94 subjects randomized to the BCV arm and 47 subjects randomized to the SoC arm.

Diagnosis and Main Criteria for Study Eligibility:

Prospective subjects must be:

- aged at least 2 months and less than 18-years-old on Day 1 AND
- have received a T cell-depleted allogeneic (i.e., non-autologous) HCT within the previous 100 days, where "T cell-depleted" describes EITHER:
  - ex vivo T cell depletion via positive selection (e.g., CD34+ cell) or negative selection (e.g., T cell receptor α/β or CD3+ cell removal by column filtration), OR
  - serotherapy with ATG (as cumulative dose of ≥ 3 mg/kg rabbit-derived ATG or ≥ 50 mg/kg of equine-derived ATG) administered within 10 days prior to transplant or at any time post-transplant and prior to Day 1 OR
  - serotherapy with alemtuzumab administered within 30 days prior to transplant or at any time post-transplant and prior to Day 1.

Subjects must have had a first AdV detection in plasma since the qualifying transplant within 21 days prior to Day 1 and have a confirmed plasma AdV viremia of ≥ 1000 copies/mL and rising, defined as two consecutive AdV DNA polymerase chain reaction (PCR) test results ≥ 1000 copies/mL **from the designated central virology laboratory**, with the second result being greater than the first. The second sample must be drawn at least 48 hours after the first sample and no more than 7 days prior to Day 1. Prospective subjects may have multiple samples sent as screening samples, but will need to have two consecutive samples drawn at least 48 hours apart with AdV viremia ≥ 1000 copies/mL and rising as reported by the central virology laboratory to be eligible for randomization.

Key exclusion criteria include:

- Any CTCAE (United States [US] National Institutes of Health [NIH]/National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events) Grade 4 diarrhea (i.e., life-threatening consequences with urgent intervention indicated) within 7 days prior to Day 1
- Any CTCAE Grade 2 or 3 diarrhea (i.e., increase of ≥ 4 stools per day over baseline), unless attributed to AdV, within 7 days prior to Day 1
- NIH Stage 4 acute graft versus host disease (GVHD) of the skin (i.e., generalized erythroderma with bullous formation) within 7 days prior to Day 1
- NIH Stage 2 or higher acute GVHD of the liver (i.e., bilirubin > 3 mg/dL [SI: > 51 μmol/L]) within 7 days prior to Day 1
- NIH Stage 2 or higher acute GVHD of the gut (i.e., diarrhea > 556 mL/m^2/day, or severe abdominal pain with or without ileus) within 7 days prior to Day 1
- Poor clinical prognosis (including active malignancy or use of vasopressors within 7 days prior to Day 1)
- Requirement for mechanical ventilation within 7 days prior to Day 1, or sustained oxygen delivery for > 24 hours within 7 days prior to Day 1, or any oxygen requirement within 48 hours prior to Day 1
- Concurrent human immunodeficiency virus (HIV) infection, or active hepatitis B virus or hepatitis C virus infection
- Specified out of range laboratory results (including alanine aminotransferase [ALT] greater than five times the upper limit of the normal reference range [> 5x ULN], aspartate aminotransferase [AST] > 5x ULN, total bilirubin > 3 mg/dL (SI: > 51 μmol/L), or prothrombin time – international normalized ratio [PT-INR] > 2x ULN) within 7 days prior to Day 1
- Estimated creatinine clearance < 30 mL/min or use of renal replacement therapy within 7 days prior to Day 1
- Previous receipt of BCV at any time or receipt of intravenous (IV) cidofovir (CDV) within 48 hours prior to Day 1
- Received any cell-based anti-AdV therapy within 6 weeks prior to Day 1 or previously received an anti-AdV vaccine at any time

As applicable, female subjects of childbearing potential (i.e., not pre-menarche) must not be pregnant or breastfeeding, and must agree to use two acceptable forms of contraception (one of which must be a barrier method) during heterosexual intercourse while enrolled in the study and for at least 90 days after the last dose of BCV. [Note: For the purposes of this study, acceptable forms of contraception include barrier methods of contraception (e.g., male or female condom, diaphragm), an intra-uterine device, or hormonal contraception (e.g., oral pill, implant, injection, ring or transdermal patch).] Male subjects capable of fathering a child must agree to use a barrier method of contraception during heterosexual intercourse while enrolled in the study and for at least 90 days after the last dose of

BCV.

In accordance with applicable national or local law, and current institutional practice, written informed consent (or assent) to participate in the study will be obtained from each subject and his or her legal guardian(s). Subjects must be available to participate in all required study activities for the entire duration of the study (i.e., through completion of the Week 36 assessment).

Investigational Product, Dosage and Mode of Administration:

Subjects randomized to the BCV arm will receive BCV as follows:

- 2 mg/kg (up to a maximum of 100 mg) twice weekly (BIW) for subjects not receiving concurrent cyclosporine
- 1.4 mg/kg (up to a maximum of 70 mg) BIW for subjects receiving concurrent cyclosporine (i.e., subjects taking cyclosporine on Day 1 or who initiate cyclosporine at any time while taking BCV)

Subjects who discontinue cyclosporine while taking BCV should increase the BCV dose to 2 mg/kg (up to a maximum of 100 mg), starting with the next scheduled BCV dose following discontinuation of cyclosporine.

Each dose of BCV will be administered orally as an oral suspension of 10 mg/mL strength. The dose of BCV to be administered will be calculated using the lowest body weight recorded for the subject in the 30 days prior to Day 1. Whenever possible, the BCV doses should be given with food (with or within 30 minutes after finishing a meal) to potentially improve tolerability. Subjects who are unable to take medicines orally may be dosed through a nasogastric tube, gastrostomy tube, or other feeding tube that allows the dose to be delivered directly into the subject's stomach or duodenum. Intrajejunal delivery is not advised as PK and tolerability data are not available for this route of administration. The BCV doses should be administered at alternating 3- and 4-day intervals unless dosing is modified for tolerability reasons, as described below.

Duration of Treatment/Study:

For subjects randomized to the BCV arm, BCV will be administered for a maximum of 16 weeks, based on virologic response to treatment and tolerance to the drug. In the absence of toxicity requiring dose interruption, BCV will be administered BIW until plasma AdV viremia is confirmed undetectable (two consecutive plasma viral load results of "undetectable" as reported by the designated central virology laboratory), or until Week 16 post-randomization, whichever occurs first. After a subject's first AdV plasma viral load result is reported as "undetectable" by the designated central virology laboratory, a confirmatory blood sample must be drawn no sooner than 7 days (6 full calendar days and no later than 14 days (13 full calendar days) after the first sample was drawn. Once AdV viremia is confirmed as undetectable, BCV will be discontinued.

Until a subject has achieved sufficient immune reconstitution, reactivation of latent virus from the gut may result in a subsequent episode of AdV viremia. Subjects who stop BCV therapy after achieving confirmed undetectable AdV viremia may re-initiate treatment with BCV if AdV viremia is subsequently confirmed at ≥ 1000 copies/mL by the designated central virology laboratory, unless precluded by the BCV toxicity management guidelines. For the purposes of re-initiating BCV therapy, "confirmed AdV viremia ≥ 1000 copies/mL" is defined as two consecutive results ≥ 1000 copies/mL from the designated central laboratory, with the second sample drawn at least 48 hours after the first sample. BCV dosing will be resumed at the same dose and dose frequency the subject was receiving when BCV therapy was stopped (i.e., if BCV dosing had been consolidated to once weekly [QW] administration for toxicity management purposes, the subject would resume at the QW dose).

Subjects who permanently discontinue BCV for toxicity reasons are not eligible to re-initiate BCV therapy.

Treatment with BCV may not be extended past Week 16 under this protocol. Therefore, investigators wishing to extend or re-initiate treatment with BCV for a subject after Week 16 will need to request access to the drug through the local named patient program (NPP) or other expanded access program, where available.

The duration of any therapy administered as part of SoC will be determined by local institutional practice. Subjects randomized to the SoC arm will be managed according to local institutional practice and guidelines and any relevant product labelling. To allow for a meaningful and interpretable comparison of safety and efficacy between treatment arms, subjects randomized to the SoC arm will NOT be eligible to receive BCV therapy prior to Week 16 post-randomization. After completion of the Week 16 assessment, subjects randomized to the SoC arm may be able to access BCV through the local NPP or other expanded access program, as described above.

All subjects will be followed for a period of 36 weeks post-randomization, regardless of treatment assignment, including SoC subjects who begin BCV treatment after Week 16 post-randomization.

Reference Therapy, Dosage and Mode of Administration:

BCV will be compared with local institutional SoC. Subjects randomized to the SoC arm will be managed according to local or institutional practices and any relevant product labelling. The decisions regarding SoC, including administration of therapy, dose and regimen of therapy, modification of immunosuppression, and monitoring will be the responsibility of the clinical team according to institutional guidelines, local practices, and applicable treatment guidelines for the management of AdV infection.

Criteria for Evaluation:

Subjects will be assessed at weekly intervals through the 16-week treatment period, with additional assessments performed at 24 and 36 weeks post-randomization as follows:

- Assessments scheduled for Weeks 1, 2, 3, 4, 6, 8, 12, and 16 must be completed in the hospital or clinic (i.e., subjects who are being treated on an outpatient basis must return to the hospital/clinic).
- For all other assessments (i.e., Weeks 5, 7, 9, 10, 11, 13, 14, 15, 24, and 36):
  - If a subject has detectable AdV in plasma, the subject will be required to return to the hospital or clinic to complete these assessments until such time as the subject achieves confirmed undetectable AdV viremia.
  - Thereafter, every effort should be made to have a subject return to the hospital or clinic for these assessments. However, if return visits to the hospital or clinic are not practical (e.g., because the subject has returned to his or her home region), these visits may be performed through a home healthcare service provider or at a third-party facility that has been pre-approved by the sponsor (for the collection of samples including blood draws for safety and/or virologic analysis). Telephone contact between the investigator and the subject or the subject's caregiver (to assess adverse events [AEs], AdV symptoms, etc.) will need to occur in parallel.
  - If an approved home healthcare services provider or an approved third-party facility capable of performing the required procedures is not available, then all assessments must be performed at the hospital or clinic.

Efficacy: Blood (plasma), urine, stool, and respiratory secretions, and other samples/specimens for virologic evaluations will be collected at screening, on Day 1 (before randomization), and at periodic intervals throughout the treatment and post-treatment periods of the study as follows:

- Blood will be collected during screening, on Day 1 (before randomization), and at each subsequent assessment for real-time analysis of AdV viremia in plasma at the designated central virology laboratory. These samples will also be analyzed in real time for

cytomegalovirus viremia. The Day 1 (baseline) samples will also be analyzed for BK virus (BKV) viremia.

- Urine, stool (where available), and respiratory secretions (nasopharyngeal swab and bronchoalveolar lavage, if appropriate, based on symptoms) will be collected from all subjects on Day 1 (before randomization) and at Weeks 4, 6, 8, 12, and 16. Samples will also be collected from subjects: (1) at the same time that AdV viremia is confirmed as undetectable (i.e., at the time the confirmatory plasma sample is drawn), or (2) if BCV is re-initiated after the recurrence of AdV viremia ≥ 1000 copies/mL (with the samples collected prior to re-initiation of BCV), as applicable. Samples may also be collected at any time on the basis of signs or symptoms suggestive of AdV disease. Based on the clinical status of the subject, in consultation with the Chimerix Medical Monitor (or designee), investigators may request real time analysis of non-plasma specimens for AdV viral load.
- While subjects are inpatient and, where practicable, once subjects are outpatient, stool samples will be collected on Day 1 (before randomization) and each subsequent assessment during treatment and follow-up and stored for possible virologic analyses (e.g., additional AdV or other double-stranded DNA virus viral load analyses, analyses for other viruses, viral genotypic and/or phenotypic assessments).
- Collected samples (blood/plasma, urine, respiratory secretions, and stool) and/or remaining extracted DNA will be stored for possible future virologic/immunologic analyses (e.g., additional AdV or other dsDNA viral load analyses, viral typing, retrospective analyses for other viruses, longitudinal viral genotypic and/or phenotypic assessments, markers of AdV- and other virus specific immunity).

Stored blood (plasma) samples or extracted DNA will be used for AdV typing by PCR amplification and sequencing of the variable region of the hexon gene. Determination of baseline genotype will be carried out by PCR amplification and sequencing of the AdV DNA polymerase gene. Emergence of antiviral-resistant AdV due to virologic failure will be determined by genotyping the AdV polymerase gene from subjects where: (1) confirmed recurrence of AdV viremia ≥ 1000 copies/mL is noted subsequent to viral clearance; (2) confirmed increase in plasma AdV DNA by ≥ 1 $\log_{10}$ after experiencing a ≥ 1 $\log_{10}$ decrease from baseline, and (3) non-responders and/or subjects with detectable plasma AdV DNA at the last on-treatment measurement. Stored samples may also be used for AdV viremia/viral load assessments; additional resistance analyses based on newly available assays, including phenotyping for resistance and deep sequencing; and for retrospective analyses of other dsDNA virus viremia/viral loads. **No stored samples will be used for human genomic analyses.**

Changes in AdV-related disease signs and symptoms will be evaluated throughout the study.

Safety: Safety will be assessed through physical examination findings, vital signs measurements, and the collection of blood and urine samples for routine safety assessments (analyzed by the designated central safety laboratory), including hepatic and renal assessments, determined at periodic intervals through 36 weeks post-randomization. AEs will be recorded from the time of administration of the first dose of BCV or, for subjects randomized to SoC, from the date of randomization, until completion of the Week 16 assessment or premature discontinuation from the study. In addition, any study procedure-related AE that occurs prior to administration of the first dose of BCV (or randomization to SoC) will be recorded as an AE. After the Week 16 assessment, until completion of the Week 36 assessment, only serious adverse events (SAEs) will be recorded. Subjects will also complete electronic diaries (e-diaries) collecting diarrhea symptoms on a daily basis (and date/time for each BCV dose and whether taken with food) through Week 16. Concomitant medication use will be recorded through Week 16.

Specific monitoring and BCV stopping criteria will be followed for targeted GI and hepatic abnormalities, as described below.

Pharmacokinetics: For subjects randomized to BCV, blood samples (5 samples collected pre-dose and up to 48 hours post-dose) will be collected on Day 1 and Week 2 (where blood volume loss limits allow) for analysis of plasma BCV concentrations by the designated bioanalytical laboratory. Samples collected from subjects who are receiving concurrent cyclosporine will also have cyclosporine concentrations analyzed. The Week 2 PK samples will only be collected if the subject remains on BCV therapy.

Safety Monitoring and Safety Reviews:

Prior clinical experience has shown that the main toxicities associated with BCV dosing are GI events, in particular diarrhea, and increase in serum aminotransferase concentrations. Investigators will be specifically trained on the management of BCV toxicity; subjects randomized to BCV therapy will be monitored for GI and hepatic abnormalities and managed as follows:

Treatment-emergent Grade 1 GI-related AEs:

Dosing with BCV may continue, while closely monitoring the subject for worsening of the AE(s).

Symptomatic care may be provided as needed (e.g., anti-emetics, anti-diarrheals). Hydration status should be closely monitored, and liquid and electrolyte intake should be encouraged, if appropriate, to avoid dehydration and the downstream consequences of dehydration on renal function.

In the absence of extra-intestinal involvement, starting or increasing steroids and/or other immunosuppressants for the treatment of GVHD should be delayed if medically feasible for CTCAE Grade 1 diarrhea. If steroid treatment of GVHD cannot be delayed (and BCV is continued) in subjects with Grade 1 symptoms, the subject's response to GVHD therapy should be closely monitored.

If diarrhea persists for > 14 days at CTCAE Grade 1, the complete subject profile should be reviewed, other etiologies for diarrhea considered, and if deemed appropriate, interruption of BCV should be considered in order to determine whether diarrhea resolves.

Treatment-emergent Grade 2 or Higher Diarrhea in Subjects with ≤ Grade 1 Diarrhea at Baseline:

For subjects enrolled with CTCAE Grade 1 diarrhea or no diarrhea at baseline, BCV must be interrupted for treatment-emergent CTCAE Grade 2 or higher diarrhea. This includes new-onset Grade 2 or higher diarrhea or progression from Grade 1 to Grade 2 or higher diarrhea, regardless of the cause of the diarrhea.

In general, changing multiple therapies at the same time (e.g., interrupting BCV and starting steroids for new-onset or worsening GI GVHD) is not recommended. In order to assess response to BCV treatment interruption, start of (or increase in) steroid therapy for new-onset or worsening GI GVHD should be delayed, when possible.

If diarrhea improves to ≤ CTCAE Grade 1 in intensity, subjects may resume dosing of BCV, but no sooner than 7 days (i.e., at least 6 full days off drug) following the last BCV dose administration. If resumed, BCV must be administered in a consolidated QW dose, i.e., 4 mg/kg (up to a maximum of 200 mg) QW in the absence of concurrent cyclosporine or 2.8 mg/kg (up to a maximum of 140 mg) QW for subjects taking concurrent cyclosporine, to potentially improve tolerability, as weekly dosing allows more time for GI mucosal regeneration between doses. Treatment with the consolidated QW BCV dose will be continued through Week 16 post-randomization or until confirmed undetectable AdV viremia in plasma, whichever occurs first.

If diarrhea does not improve to ≤ CTCAE Grade 1 during interruption, BCV must not be resumed. Recurrence of CTCAE Grade 2 or higher diarrhea after restarting BCV requires permanent discontinuation of BCV.

Treatment-emergent Diarrhea AEs in Subjects with Grade 2 or 3 Diarrhea Attributed to AdV at Baseline:

For subjects enrolled with CTCAE Grade 2 or 3 diarrhea at baseline that is attributed to AdV, BCV dosing must be interrupted if:

- the diarrhea has not improved to ≤ CTCAE Grade 1 after 21 days of therapy, or
- the subject experiences on-treatment worsening of one CTCAE grade or more at any time following initiation of BCV (i.e., Grade 2 worsens to ≥ Grade 3, or Grade 3 worsens to ≥ Grade 4), regardless of the cause of the diarrhea

If the diarrhea does not improve during interruption, BCV must not be resumed.

If diarrhea improves to ≤ Grade 1 in intensity during interruption, subjects may resume dosing, but no sooner than 7 days (i.e., at least 6 full days off drug) following the last BCV dose administration. If resumed, BCV must be administered in a consolidated QW dose as described above, i.e., 4 mg/kg (up to a maximum of 200 mg) QW in the absence of concurrent cyclosporine or 2.8 mg/kg (up to a maximum of 140 mg) QW for subjects taking concurrent cyclosporine.

Treatment-emergent Non-diarrheal GI AEs:

BCV dosing must be interrupted for Grade 3 or higher non-diarrheal GI events (e.g., abdominal pain, ileus, nausea, and vomiting). If non-diarrheal GI AE(s) improve to ≤ Grade 2 in intensity, subjects who have interrupted BCV may resume dosing, but no sooner than 7 days (i.e., at least 6 full days off drug) following the last BCV dose administration. If resumed, BCV must be administered in a consolidated QW dose as described above. If non-diarrheal GI AE(s) do not improve during interruption, BCV must not be resumed. In the event of recurrence of CTCAE Grade 3 or higher non-diarrheal GI AEs after restarting BCV, BCV may be allowed to continue only after discussion and agreement with the Chimerix Medical Monitor (or designee).

Increases in Serum Aminotransferases:

Treatment with BCV must be interrupted for at least 7 days (i.e., 6 full days off drug) if any of the following confirmed abnormalities occur:

1. ALT or AST > 8x ULN and ≥ 2x baseline value
2. ALT or AST > 5x ULN and ≥ 2x baseline value for more than 2 weeks
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%)
5. Total bilirubin > 3 mg/dL and ≥ 2x baseline value

If an alternate reason for the laboratory abnormalities is identified and after the abnormalities decrease by ≥ 1 CTCAE grade below the grade that triggered BCV interruption, dosing with BCV may resume at the consolidated weekly dose described above. Generally, subjects with persistent and significant ALT or AST elevations (> 5x ULN) should not resume administration of BCV unless there is clear evidence of a causal association with a viral disease being treated. In these cases, continued treatment with BCV may be allowed after discussion and agreement with the Chimerix Medical Monitor (or designee). Recurrence of the liver abnormalities after reintroduction of BCV requires permanent discontinuation of BCV.

Data and Safety Monitoring Board (DSMB):

A DSMB will be convened according to US Food and Drug Administration and European Medicines Agency guidelines on clinical trial data monitoring committees to monitor safety for this study. The DSMB will review safety data on an ongoing and scheduled basis, as determined by the board and detailed in the DSMB charter.

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

- All SAEs
- CTCAE Grade 3 or higher AEs
- AEs resulting in permanent BCV or other anti-AdV drug discontinuation
- AEs requiring BCV or other anti-AdV drug interruption
- AEs requiring dose modification or consolidation of BCV or other anti-AdV drug
- Incidence of and time to all-cause mortality and non-relapse mortality
- Laboratory parameters predictive of liver abnormalities (e.g., ALT, AST, alkaline phosphatase, PT-INR, and total and direct bilirubin), renal abnormalities (creatinine clearance, estimated glomerular filtration rate [eGFR]), and hematologic cell counts predictive of graft function
- Observed plasma BCV concentrations (as available)

At least two safety reviews will be conducted by the DSMB. The first safety review will be performed after the first 30 subjects enrolled have completed through Week 16. The second safety review will be performed after the first 60 subjects enrolled have completed through Week 16.

Study Drug Withdrawal Criteria:

Subjects randomized to BCV who experience any of the following criteria after initiating treatment in this study will be required to discontinue BCV, but will continue to be followed in the study:

- Subject request to discontinue for any reason
- Treatment-emergent AE (TEAE) that necessitates the discontinuation of BCV as described above
- If the investigator or the subject's primary care provider believes that participation in the study is no longer in the best interests of the subject
- Pregnancy in a female subject

  Female subjects who become pregnant will be immediately discontinued from BCV, but will continue to be followed in the study. Pregnancies in female subjects randomized to the SoC arm must be reported according to local guidelines and relevant product labelling.
- Discontinuation of the study at the request of Chimerix, a regulatory agency, or the governing ethics committee (EC)

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

- Development of an exclusionary condition, including a decrease in eGFR to < 15 mL/min considered related to BCV, or unrelated to BCV but not being dialyzed
- Treatment with, or requirement for treatment with, a prohibited or excluded medication
- Subject is not compliant with the protocol (i.e., significant protocol deviation)

Subjects randomized to the SoC arm in this study will be managed according to local or institutional practice guidelines and any relevant product labelling. Investigators will need to consider the clinical status of the subjects and the local availability of treatment options.

All subjects who are randomized will be followed through Week 36, including subjects who discontinue BCV for any reason and subjects who are randomized but not dosed in either arm. 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.

Subjects who are randomized and who do not complete the study will not be replaced.

Study Endpoints:

Subjects will be assessed on a weekly basis through Week 16, with additional assessments performed at Weeks 24 and 36 post-randomization. The data collected through Week 16 will comprise the primary data set for the study, with a database lock and analysis performed following completion of the last subject through Week 16 (or death or loss to follow-up, as applicable).

Primary Efficacy Endpoint:

The primary efficacy endpoint for this study is the time-averaged area under the concentration-time curve (AAUC) for AdV viremia (log_{10} copies/mL) from randomization through Week 16 post randomization.

Key Secondary Efficacy Endpoint:

The key secondary efficacy endpoint is the incidence of all-cause mortality through Week 16.

Other Secondary Efficacy Endpoints:

- Time to all-cause mortality through Week 16
- Incidence of and time to all-cause mortality through Week 36
- Incidence of and time to non-relapse mortality through Weeks 16 and 36
- Incidence of and time to AdV-associated mortality through Weeks 16 and 36, where mortality is assessed by a blinded endpoint adjudication committee
- Proportion of subjects with undetectable AdV viremia at Weeks 2, 4, 6, 12, and 16
- Proportion of subjects with ≥ 2-log_{10} decline from baseline or undetectable AdV viremia at Weeks 2, 4, 6, 12, and 16
- Proportion of subjects with ≥ 1-log_{10} decline from baseline or undetectable AdV viremia at Weeks 2, 4, 6, 12, and 16
- AAUC at Weeks 2, 4, 6, and 12
- Incidence of and time to first confirmed undetectable AdV viremia
- Incidence of and time to virologic relapse (subsequent confirmed AdV viremia ≥ 1000 copies/mL) among subjects with confirmed clearance of AdV from plasma (overall; by AdV in urine, stool, and respiratory secretions at the time of first undetectable AdV viremia; and by T cell-mediated immune function [e.g., CD4+ cells > or ≤ 50 cells/μL] at the time of first undetectable AdV viremia)
- Maximum pediatric logistic organ dysfunction (PELOD) score through Week 16
- Number of days spent in the hospital through Week 16
- Number of days spent in the intensive care unit (ICU) through Week 16
- Emergence of AdV mutations associated with genotypic resistance and phenotypic resistance (the latter when possible) to BCV or CDV
- Incidence of and time to progression to probable or definitive AdV disease (among asymptomatic subjects at baseline)
- Incidence of and time to resolution of AdV clinical disease (among subjects with probable or definitive AdV disease at baseline)
- Primary model-based PK parameters, such as apparent clearance (CL/F), intercompartmental clearance (Q/F), volume of central compartment (V_c/F), volume of peripheral compartment (V_p/F), absorption rate constant (K_a), and lag time (T_{lag}), secondary PK parameters, such as maximum concentration (C_{max}) and area under the concentration-time curve at steady state

(AUC_{ss}), and identification of covariates that influence these PK parameters

- Relationship between plasma BCV exposure, other covariates of interest, and
  - safety endpoints, including GI AEs, diarrhea, ALT, total bilirubin, and other safety events of interest
  - virologic endpoints, including AAUC, AAUC minus baseline, viral load change from baseline, and other virologic endpoints of interest
  - all-cause and non-relapse mortality through Week 16

Safety Endpoints:

- Incidence of TEAEs, particularly those of ≥ CTCAE Grade 3 severity and SAEs
- Incidence of treatment-related AEs, particularly those of ≥ CTCAE Grade 3 severity and SAEs
- Incidence of AEs resulting in permanent BCV or other anti-AdV drug discontinuation
- Incidence of AEs requiring BCV or other anti-AdV drug interruption
- Incidence of AEs requiring dose modification or consolidation of BCV or other anti-AdV drug
- Incidence of fatal AEs
- Incidence of and time to CTCAE Grade 2 or higher diarrhea
- Incidence of doubling, tripling, or quadrupling of baseline serum creatinine
- Incidence of need for renal replacement therapy
- Incidence of ≥ 1/2/3 CTCAE grade increases from baseline for safety laboratory parameters of interest (by visit, maximum on-treatment, last on-treatment, last on-study)
- Distributions of change from baseline over time for central safety laboratory parameters of interest (by visit, maximum on-treatment, last on-treatment, last on-study)
- Assessment of all deaths that occur through Week 16 and in follow up through Week 36

Exploratory Endpoints:

- Association of HCT co-morbidity index and clinical outcomes
- Change from baseline in exploratory biomarker laboratory parameters (e.g., citrulline, ST2, TIM3, and CRP)
- Association of exploratory biomarkers with treatment-emergent CTCAE Grade 2 diarrhea or GI GVHD
- Number of and reasons for emergency room (A&E) visits; number of, duration, and reasons for hospital admissions; number of days spent in ICU, in isolation, or confined to bed; other infections; receipt of and duration of relevant concomitant medications and therapies; type and number of certain diagnostic or therapeutic procedures; and provision of home healthcare through Week 16
- Association between immune reconstitution and viral response and clinical outcome (e.g., based on measurement and activity of AdV-specific cytotoxic T lymphocytes and other immune reconstitution parameters)

Statistical Methods:

All subjects will be classified into Intent-to-Treat (ITT), modified Intent-to-Treat (mITT), Per Protocol (PP), Safety, and PK analysis sets. The following definitions will be used:

- ITT: The ITT analysis set will include all subjects who are randomized.
- mITT: The mITT analysis set will include all subjects in the ITT analysis set with AdV viremia ≥ 1000 copies/mL measured by the designated central virology laboratory in the last sample on or prior to randomization. Subjects randomized to BCV and not treated will be excluded from the mITT analysis set.
- PP: The PP analysis set will include all subjects in the mITT analysis set who complete the study through Week 16 (or die prior to Week 16) and who do not have any major protocol deviations (defined as significant inclusion/exclusion criteria violation or noncompliance that would be expected to impact the analysis of efficacy).
- Safety: The safety analysis set will include all subjects who are randomized to and receive at least one dose of BCV, and all subjects who are randomized to SoC.
- PK: The PK analysis set will include all subjects who are randomized to and receive at least one dose of BCV, and have at least one blood sample collected for analysis of plasma BCV concentrations.
- Safety Exposure-Response: The safety exposure-response analysis set will include subjects who are in both the safety analysis set and the PK analysis set.
- Efficacy Exposure-Response: The efficacy exposure-response analysis set will include subjects who are in both the mITT analysis set and the PK analysis set.

The ITT analysis set will be used to summarize all efficacy endpoints, including the primary endpoint/analysis. The mITT and PP analysis sets will be determined prior to database lock for the primary analysis, and will be used for supportive primary efficacy analyses and possibly other selected endpoints. All efficacy analyses will use the randomized treatment assignment. The safety analysis set will be used for all safety analyses and the PK analysis set will be used for all PK analyses.

The primary AAUC analysis will utilize all randomized subjects (ITT) in an analysis of covariance (ANCOVA) with all stratification factors included in the model: T cell-depletion method (alemtuzumab or ex vivo cell selection vs. ATG), time from HCT to randomization (< 28 days vs. ≥ 28 days), and baseline AdV viremia (continuous $\log_{10}$ copies/mL). In the ANCOVA, AdV viremia values that are undetectable will be imputed at 99 copies/mL (i.e., one less than the lower limit of detection of 100 copies/mL) and values that are detected but not quantifiable (BLQ) will be imputed at 189 copies/mL (i.e., one less than the lower limit of quantification of 190 copies/mL).

The primary analysis will be supplemented by a number of planned sensitivity analyses to assess the impact of subjects who die prior to Week 16 and other potential influential elements on the primary inference.

In addition, a supportive analysis of overall mortality (adjusting for advanced baseline disease, Matthes-Martin 2008) will examine the non-inferiority of BCV treatment to SoC. No negative impact on mortality will be concluded if the upper bound of the one-sided 95% confidence interval (CI) for the absolute difference between BCV mortality and SoC mortality is < 10%. In the event this supportive analysis concludes non-inferiority and the primary endpoint is met, superiority for overall mortality at Week 16 will be tested at alpha 0.05. Non-relapse mortality will be assessed in a similar fashion.

The primary and all-cause mortality endpoints will be analyzed by various subgroups, including, but not limited to, each of the stratification factors, sex, age, race, transplant characteristics, underlying disease (malignant, non-malignant), advanced disease status, and investigator's intended SoC selected

at the time of randomization. Multivariate modelling will be considered and defined in the Statistical Analysis Plan (SAP).

Continuous secondary efficacy analyses will use the same method used for the primary analysis.

Dichotomous secondary efficacy analyses will be analyzed using a Cochran-Mantel-Haenszel test stratified by each of the stratification factors. Number of failures and failure rates will be presented for each treatment arm. Cochran-Mantel-Haenszel p-values, estimated common odds ratios, and corresponding approximate 95% CIs will be presented for each comparison. The Breslow-Day test will be used to test the homogeneity of the odds ratios. Missing data will be imputed as failure.

Most time-to-event analyses will be performed using Kaplan-Meier methods/plots and Cox models. P-values and hazard ratios along with their 95% CIs will be presented for each treatment comparison. Missing data will be censored, generally at the earlier of the end of study for each subject or the time point for the specific analysis.

Non-relapse mortality will be analyzed with relapse as a competing risk adjusted for baseline strata, with corresponding cumulative incidence plots, Fine-Gray models, and cause-specific and sub-distribution hazard ratios with corresponding 95% CIs.

All safety analyses will be presented by randomized treatment arm using the safety analysis set. Inferential analyses will generally not be performed for safety endpoints.

Sample size calculations were based on the primary endpoint, i.e., AAUC through Week 16. Assuming the observed standard deviation of ~ 1.03 $\log_{10}$ copies/mL in AAUC at Week 16 from a comparable subset of SoC subjects, the study has > 90% power with the currently planned sample size to demonstrate superiority of BCV vs. SoC, given that the true difference in means is > 0.6 $\log_{10}$ copies/mL (i.e., an effect size of ~ 0.58). In addition, the overall mortality at Week 16 non-inferiority comparison will have > 80% power in the event that the expected mortality for SoC is 20% to 30% and there is a true mortality advantage of 6% to 9% in favor of BCV (Feghoul 2015, Hiwarkar 2017, Mynarek 2014).

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

Table 2: List of Abbreviations

Abbreviation	Explanation
AAUC	Time-averaged area under the concentration-time curve
AAUCMB	Time-averaged area under the concentration-time curve minus baseline
ADL(s)	Activity(ies) of daily living
AdV	Adenovirus
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the concentration-time curve from time zero (0) extrapolated to infinity
AUC_{last}	Area under the concentration-time curve from time zero (0) to time of last measurable concentration
AUC_{ss}	Area under the concentration-time curve at steady state
BCV	Brincidofovir (CMX001)
BIW	Twice weekly
BKV	BK virus
BLQ	Below limit of quantitation
CD3/4/8/34	Cluster of differentiation 3/4/8/34
CDV	Cidofovir
CDV-PP	CDV-diphosphate
CI	Confidence interval
C_{max}	Maximum concentration
CMV	Cytomegalovirus
CMX001	Brincidofovir
CRP	C-reactive protein
CTCAE	(NIH/NCI) Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
%CV	Percent coefficient of variation

Abbreviation	Explanation
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded DNA
DSMB	Data and safety monitoring board
EAC	Endpoint adjudication committee
EC	Ethics committee
ECIL	European Conference on Infections in Leukaemia
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FDA	(United States) Food and Drug Administration
GCP	Good clinical practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GVHD	Graft versus host disease
HBV	Hepatitis B virus
HCT	Hematopoietic cell transplant
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
ITT	Intent-to-treat
IV	Intravenous
IV/WRS	Interactive voice/web response system
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
Max	Maximum
Min	Minimum
mITT	Modified intent-to-treat
MMF	Mycophenolate mofetil

Abbreviation	Explanation
N, n	Number of observations or events
NCI	(US) National Cancer Institute
NIH	(US) National Institutes of Health
NPP	Named patient program
OAT1	Organic anion transporter 1
OATP1B1/3	Organic anion transporting polypeptide 1B1 or 1B3
PCR	Polymerase chain reaction
PELOD	Pediatric logistic organ dysfunction
P-gp	P-glycoprotein
PHI	Protected health information
PK	Pharmacokinetic
PP	Per protocol
PT-INR	Prothrombin time-international normalized ratio
Q1	First quartile
Q3	Third quartile
QW	Once weekly
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SD	Standard deviation
SoC	Standard of care
SRM	Study reference manual
ST2	Suppression of tumorigenicity-2
TEAE	Treatment emergent adverse event
TIM3	T cell immunoglobulin mucin-3
UK	United Kingdom
ULN	Upper limit of normal reference range
UND	Undetectable
US(A)	United States (of America)

4. INTRODUCTION

4.1. Background

In immunocompetent individuals, adenovirus (AdV) infections and resulting illnesses are generally mild, typically self-limited and resolve without sequelae (Ison 2002a, Ison 2006, Lenaerts 2008). However, patients who have undergone allogeneic hematopoietic cell transplant (HCT) are at especially high risk for developing AdV disease and, in this susceptible population, the development of AdV infection associated with viremia is much more prevalent and rapidly fatal without treatment (Florescu 2012, Ison 2006, Lion 2014, Sandkovsky 2014). Children are at higher risk of infection and manifestations can be severe among pediatric patients (Lion 2014). Common disease manifestations of AdV infection in immunocompromised patients are serious and include hemorrhagic cystitis, pneumonia and bronchiolitis obliterans, liver failure, severe gastrointestinal (GI) disease (Ison 2006, Legrand 2001) and renal damage, such as nephritis and obstructive nephropathy (Mori 2003).

The incidence of AdV infection and risk of serious disease is generally higher among children (Chakrabarti 2000, Howard 1999, Ison 2002b, Mynarek 2014) as well as recipients of T cell-depleted grafts (Chakrabarti 2002, Lee 2011, Mynarek 2014) and patients with acute graft versus host disease (GVHD) (Flomenberg 1994, Lion 2014, Runde 2001); risk is also high among recipients of unrelated or human leukocyte antigen-mismatched transplants due to profound and persistent immunodeficiency (Baldwin 2000, Bruno 2003, Howard 1999, Lion 2014). Earlier detection of AdV viremia after HCT and higher viral loads have also been correlated with increased risk of fatal outcome (Mynarek 2014). Severe and persistent lymphopenia is also associated with increased incidence of AdV infection, as well as progression to disseminated and often fatal AdV disease (Chakrabarti2002, 2007, Lion 2014). The mortality rate for patients undergoing HCT approaches 26% for all symptomatic patients, and can reach 50% to 80% in pediatric patients with disseminated AdV disease (Lion 2014).

No product has received regulatory approval for the treatment or prevention of AdV infection or disease in the transplant setting. Intravenous (IV) cidofovir (CDV) has been shown to have antiviral activity against AdV in vitro and in pediatric and adult patients with AdV infection and disease (de Pagter 2009, Doan 2007, Feghoul 2015, Legrand 2001, Nagafuji 2004, Refaat 2008, Williams 2009, Yusuf 2006). However, IV CDV is associated with dose-limiting nephrotoxicity which can result in renal failure or death with a single administration (De Clercq 2003, Safrin 1997, Vistide Package Insert [Gilead Sciences 2010]). This is of particular concern for HCT recipients who are at increased risk of acute renal injury during the first 100 days post-transplant, with doubling of serum creatinine reported in 15% to 73% of HCT recipients, and renal failure requiring dialysis in up to 8.5% of HCT recipients (Hingorani 2005, Rajpal 2013). CDV is often given at reduced doses in an apparent effort to reduce the risk of toxicity, with the unintended consequence of selecting for viral resistance.

There remains a major unmet medical need for a safe and efficacious treatment for AdV infection in the post-transplant patient population in whom disseminated AdV disease can be rapidly fatal.

4.2. Brincidofovir

Brincidofovir (BCV, CMX001) is a compound of the antiviral class of drugs and is chemically designated as phosphonic acid, [[(S)-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]mono[3-(hexadecyloxy)propyl] ester. BCV is designed to mimic a natural lipid, lysophosphatidylcholine, to utilize natural lipid uptake pathways to achieve optimal intracellular concentrations of BCV. Inside the cell, BCV is cleaved to release CDV, which is then converted to the active antiviral, cidofovir diphosphate (CDV-PP) by intracellular anabolic kinases. CDV-PP exerts its antiviral effects against herpesviruses, AdV, and orthopoxviruses by acting as an alternate substrate inhibitor for viral deoxyribonucleic acid (DNA) synthesis. Overall, lipid conjugation of CDV results in more efficient intracellular delivery of BCV, which results in lower circulating plasma concentrations of CDV (Cundy 1999). The lower peak plasma concentrations of CDV and the fact that BCV (unlike CDV) is not a substrate for the human organic anion transporter 1 (OAT1) greatly reduces the risk of CDV-like nephrotoxicity following administration of BCV (Tippin 2016).

Because of its broad-spectrum antiviral activity, Chimerix, is developing BCV for the prevention and treatment of clinically significant infection and disease caused by double-stranded DNA (dsDNA) viruses with high unmet medical need, including AdV infections in adult and pediatric HCT recipients and as a possible medical countermeasure against smallpox (variola virus).

4.2.1. Summary of Toxicology Studies with BCV

The nonclinical safety profile of orally-administered BCV has been defined in rodents and non-human primates. Importantly, analysis of systemic exposures in animals administered BCV via oral gavage indicate that human exposure exceeds exposures achieved in preclinical safety models. BCV was negative for mutagenicity in the Ames test, negative for clastogenicity in the mouse micronucleus test and was weakly positive for increased structural aberrations in the absence of metabolic activation in the chromosome aberrations assay. In repeat dose animal studies, transient aminotransferase elevations without a histopathological correlate occurred in rodents and monkeys. These elevations were minor (2- to 5-fold), lacked dose-responsiveness and reversed upon cessation of treatment. Additionally, GI and reproductive toxicity was observed in repeat dose studies up to 26 and 39 weeks' duration in rats and monkeys, respectively. The dose-limiting GI findings, diagnosed as gastropathy and enteropathy or enteritis, were observed following daily oral administration of BCV in rodents and monkeys. However, incidence and severity were significantly reduced when BCV was administered twice weekly (BIW) and recovery was demonstrated after cessation of dosing. The BCV-related effects on the male reproductive system in rats and monkeys was characterized by an effect on the mitotic spermatogonia resulting in maturation depletion. Based on this mechanism of testicular toxicity, the extent of cell types affected throughout the seminiferous tubules and the resumption of spermatogenesis upon cessation of dosing is dependent on the duration of exposure and the length of the spermatogenic cycle. While recovery was not demonstrated in rats during a 12-week off-dose period after 13 weeks of BIW dosing, in monkeys, spermatogenesis resumed during a 26-week off-dose period after 39 weeks of BIW dosing.

Additional BCV-related reproductive findings included embryo toxicity and fetal morphological changes in rabbits and decreased fertility, embryonal viability and growth and development of

pups, as well as delayed sexual maturation in rats. Based on these data, BCV should be considered a potential teratogen and may affect female fertility.

Mammary gland adenocarcinomas and squamous cell carcinomas were observed in rats approximately 9 weeks after the cessation of 13 weeks of BIW BCV dosing and additional tumors, including carcinomas, adenocarcinomas and hemangiocarcinomas in a variety of tissues were observed after 26 weeks of BIW dosing. While tumors occurred in rats with extremely high frequency after as few as 26 doses of BCV and with peak BCV plasma concentrations (C_{max}) as low as 0.4 ng/mL, neither masses nor neoplastic or preneoplastic lesions were detected in monkeys following administration of BCV at doses which achieved peak plasma concentrations > 80-fold higher than concentrations recorded in rat. Furthermore, no BCV-related malignancies have been reported in any of the > 2000 patients who have received BCV treatment since the clinical program began in 2006. Like the monkey, plasma exposure in humans also significantly exceeded exposures which resulted in tumors in rat. Based on these data, BCV is considered a potential human carcinogen.

Additional details on toxicology studies may be found in the BCV Investigator's Brochure.

4.2.2. Pharmacokinetics of BCV

In virally-infected subjects, plasma BCV exposure increased dose proportionally after single oral dose administration over the range of 100 to 200 mg in adult subjects and greater than dose proportional over the range of 2 to 4 mg/kg in pediatric subjects. In multiple-dose studies in healthy subjects and HCT recipients with adequate renal function, neither BCV nor CDV concentrations accumulate in plasma following once weekly (QW) or BIW oral dosing. In contrast, CDV-PP concentrations accumulate intracellularly; intracellular peripheral blood mononuclear cell CDV-PP area under the concentration time curve from time zero (0) to time of last measurable concentration (AUC_{last}) measured 2 weeks after initiation of BCV treatment was associated with 3- and 6-fold accumulation for the 200 mg QW and 100 mg BIW oral regimens compared with AUC_{last} on Day 1. Exposure to CDV-PP in peripheral blood mononuclear cells appears to trend with plasma BCV exposure.

Following oral administration, median time of maximum plasma concentration is approximately 4 hours for BCV and 12 hours for CDV and geometric mean elimination half-life is approximately 8 to 12 hours for BCV and 50 hours for CDV in plasma. Administration of BCV as an oral suspension resulted in slightly higher (17%) plasma BCV exposure (as measured by AUC) compared with administration as a tablet. Administration of BCV tablets (200 mg dose) with a low-fat meal or a moderate-fat meal (compared to the fasted state) reduced area under the plasma concentration time curve extrapolated to infinity (AUC_{inf}) by 29% and 31%, respectively, and C_{max} by 32% and 49%, respectively.

BCV is a substrate of organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3 and increased plasma BCV concentrations are observed when cyclosporine, a potent inhibitor of these transporters, is co-administered; see Section 4.3.3 for BCV dose adjustment for subjects receiving concurrent cyclosporine.

After oral administration, BCV is eliminated through metabolism via multiple pathways; CDV represented 5% of total plasma radioactivity. Major metabolites, CMX103 (3-hydroxypropyl ester of CDV) and CMX064 (4-[3-propoxy]butanoic acid ester of CDV), have little to no

measurable activity against dsDNA viruses. CDV (minor metabolite) was active against dsDNA viruses in vitro; however, it was 25- to 380-fold less potent than BCV. Thus, the major circulating BCV metabolites and CDV are not expected to substantially contribute to antiviral activity observed following administration of BCV.

4.2.2.1. Pharmacokinetics of BCV in Subjects with Hepatic or Renal Impairment

Among subjects with moderate or severe hepatic impairment, there was no observed clinically meaningful effect on plasma BCV pharmacokinetics (PK); therefore, no dose adjustment based on hepatic function is recommended.

Following oral BCV administration, plasma CDV concentrations were significantly increased in subjects with renal impairment, but plasma CDV C_{max} values remained well below values observed with IV CDV. Detailed information on plasma BCV and CDV PK in subjects with renal impairment is provided in the BCV Investigator's Brochure. Because BCV and CDV share the same active moiety, surveillance and assessment for known adverse effects of CDV (i.e., nephrotoxicity) have been part of the BCV clinical development plan. However, due to the lipid conjugation of CDV which results in the improved delivery of activated drug intracellularly there is a significantly lower peak plasma concentration of CDV following administration of BCV. That, and the inability of BCV to be effectively transported by OAT1 have significantly reduced CDV-like nephrotoxicity. Due to the shared active moiety with CDV, careful monitoring of renal function and hydration status (when subjects are experiencing diarrhea) is warranted during treatment with BCV. In cases where the glomerular filtration rate (GFR) decreases to < 15 mL/min, the benefit:risk proposition of continuing treatment with BCV must be re-evaluated in each subject, because even with dialysis there remains a risk of increased CDV exposure. Given the lack of alternative therapy for treatment of AdV in the setting of end stage renal disease, continuation of BCV in a subject receiving dialysis remains a reasonable option. Detailed information on reports of renal events is provided in the BCV Investigator's Brochure.

4.2.2.2. Pharmacokinetics of BCV across Age Groups

Following oral administration of 2 mg/kg BIW, plasma BCV C_{max} was consistent across the age groups (Table 3). Plasma BCV AUC was lowest in children < 2 years of age and highest in adolescents; on average (based on comparison of geometric means), plasma BCV AUC values observed in each pediatric age group were within 25% of adult values.

Table 3: Summary of Dose-normalized Plasma BCV PK by Age Group

Age Group	N	Dose-normalized Weekly AUC (ng.h/mL)	N	Dose-normalized C_{max} (ng/mL)
< 2 years	38	3772 (3103, 4585) [65]	37	187 (156, 264) [98]
2 to < 6 years	57	3953 (3188, 4901) [96]	49	172 (136, 216) [88]
6 to < 12 years	47	4140 (3437, 4987) [70]	41	157 (152, 226) [92]
12 to < 18 years	33	5313 (4177, 6759) [77]	32	157 (116, 199) [110]
Adult	104	4771 (4214, 5401) [71]	96	161 (126, 176) [86]

Note: Data presented as geometric mean (95% CI) [%CV] of post hoc PK parameters for subjects with AdV infection enrolled in Studies CMX001-202, CMX001-304, and CMX001-350.

Dose-normalized Weekly AUC: normalized to 200 mg/week for adults; normalized to 4 mg/kg/week for pediatric subjects weighing < 50 kg and to 200 mg/week for pediatric subjects weighing ≥ 50 kg.
Dose-normalized C_{max}: normalized to 100 mg for adults; normalized to 2 mg/kg for pediatric subjects weighing < 50 kg and to 100 mg for pediatric subjects weighing ≥ 50 kg subjects.
Abbreviations: AUC = area under the plasma concentration-time curve; CI = confidence interval; %CV = percent coefficient of variation.

Additional details on clinical pharmacology studies may be found in the BCV Investigator's Brochure.

4.2.3. Clinical Experience with BCV

As of 21 June 2017, 1554 patients and healthy subjects have been enrolled in the BCV clinical development program; of these, 1239 have received one or more oral doses of BCV and 30 have received a single IV dose of BCV in 21 completed or closed clinical studies. Additionally, an estimated 1361 patients have been treated with BCV under expanded access or compassionate use regulations, including a completed expanded access study for the treatment of serious or life-threatening infections with dsDNA viruses (CMX001-350, N = 210), one ongoing expanded access protocol for the treatment of serious AdV infection or disease (CMX001-351, N = 123), as well as under Emergency Investigational New Drug Application regulations in the United States (US) and under foreign equivalent regulations outside of the USA, including the current Named Patient Program (NPP, N = 1028). Approximately one-half of those through the NPP are pediatric patients and approximately 40% of the patients have been treated in Europe.

Fifteen of the 21 clinical studies were Phase 1/clinical pharmacology studies, which enrolled healthy subjects, subjects with hepatic or renal impairment, or kidney transplant and HCT recipients with BK virus (BKV) viruria. Two were Phase 2 clinical studies, one of which evaluated the safety and efficacy of BCV for the prevention of cytomegalovirus (CMV) infection in adult HCT recipients (CMX001-201), while the other evaluated BCV for the pre-emption of AdV disease in pediatric and adult HCT recipients (CMX001-202), and two were Phase 3 studies. One Phase 3 study (CMX001-301) evaluated the safety and efficacy of BCV for the prevention of CMV infection in CMV-seropositive adult HCT recipients, while the other, an open-label, single arm study (CMX001-304), assessed BCV in subjects with AdV infection or disease. Two other Phase 3 studies of BCV for the prevention of CMV infection in adult kidney transplant recipients (CMX001-303 and CMX001-307) were initiated, but terminated early in March 2016 following completion of a 60-day post-last dose of study drug follow-up period. These studies were terminated after review of the top-line results from CMX001-301 showed no statistically significant difference in the incidence of clinically significant CMV infection through Week 24 between the BCV and placebo arms (Marty 2016).

4.2.3.1. Overview of Key BCV-related Toxicity: GI Events (Diarrhea)

In preclinical and clinical studies, GI events (primarily diarrhea, but also nausea, vomiting, and abdominal pain) have been observed in conjunction with the use of BCV, particularly in adults at doses of 200 mg BIW or higher for more than 2 to 4 weeks. In the CMX001-201 study, diarrhea, frequently associated with other GI symptoms, and sometimes ascribed to a presumptive diagnosis of GI GVHD, was reported at a higher incidence in subjects receiving BCV at doses > 200 mg/week. These diarrheal events were considered dose limiting in the HCT study population at the 200 mg BIW dose. While events of diarrhea in the 100 mg BIW cohort were

also more frequent and severe than in placebo subjects, these events only infrequently led to permanent discontinuation of study drug. Approximately one-third of subjects in the 100 mg BIW cohort (17 of 50) temporarily interrupted study drug dosing due to a diarrheal event, but the vast majority were able to resume study drug dosing. These findings led to the development of toxicity management guidelines which focused on the differentiation of potentially drug-related diarrhea from GI GVHD, and to provide safety surveillance and toxicity management strategies to enable early identification of and intervention (including study drug interruption, if appropriate) for potential drug-related toxicities, as well as resumption of study drug dosing once adverse events (AEs) have subsided. Dose interruption thresholds were also established for treatment-emergent liver laboratory abnormalities.

In Study CMX001-202, which evaluated BCV as treatment for asymptomatic AdV viremia, acute GVHD and diarrhea were the most frequently reported serious adverse events (SAEs). None of the cases of acute GVHD were considered by the investigators to be treatment-related, and treatment-emergent diarrhea (reported at a higher incidence rate for subjects randomized to BCV BIW [57%] than to placebo [28%]) was generally considered mild-to-moderate in severity. Grade 3 or higher diarrhea was reported by 14% (2 of 14) subjects in the BCV BIW treatment group, compared with 6% (1 of 18) subjects in the pooled placebo group; no subjects were permanently discontinued from therapy due to diarrhea in the BCV BIW subject group. At the time, this was interpreted as being due, at least in part, to successful implementation of the toxicity management guidelines developed following the CMX001-201 study, as well as administration of BCV with a low-fat meal which had been anecdotally reported as mitigating the GI-related events.

In Study CMX001-301, a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3 study of the safety, tolerability, and efficacy of BCV for the prevention of CMV in adult CMV-seropositive allogeneic HCT recipients, GI events were the most commonly reported AEs (61% in BCV arm vs. 36% in placebo arm) and the most common reason given for the interruption and/or permanent discontinuation of study drug. Overall, more than three times as many subjects in the BCV arm permanently discontinued treatment early due to AEs, as compared with the placebo arm (26% vs. 7% placebo, $p < 0.001$); the most frequent AEs leading to permanent discontinuation of study drug in the BCV treatment arm were acute GVHD (9% vs. 2% placebo) and GI events (overall, 10% vs. 0% placebo), led by diarrhea (7% vs. 0% placebo).

The primary endpoint in Study CMX001-301, the incidence of clinically significant CMV infection through Week 24, was not met, with no difference in the incidence of clinically significant infection between the BCV and placebo treatment arms through Week 24 (51% BCV vs. 52% placebo, $p = 0.805$) (Marty 2016). Higher overall and non-relapse related mortality was observed among BCV-treated subjects, although the difference was not statistically significant. These differences between arms in both CMV infections and mortality appeared to be driven by higher rates of reported acute GVHD (57% in BCV-treated subjects, compared with 32% in placebo recipients), illustrating the importance of proper management of diarrhea when the differential diagnosis includes acute GI GVHD, given the overlapping timing and nature of BCV-related diarrhea and the development of GVHD post-transplant. This was more evident than in the CMX001-201 study, likely due to the earlier initiation of study drug after HCT in Study CMX001-301 (median Day 15), compared with initiation of study drug after engraftment (typically around Day 28 post-HCT) in the CMX001-201 study. Initiation of study drug before the gut had fully recovered from pre-HCT chemotherapy and conditioning regimens is thought to

have led to the earlier development of gut-related AEs, including those labelled as acute GI GVHD.

Acute GVHD events in BCV-treated subjects were more likely to be severe, assessed as serious, and to prove fatal in Study CMX001-301. Closer scrutiny of the acute GVHD data after adjudication by an independent committee suggests that the excess acute GI GVHD in the BCV treatment arm was likely drug-related diarrhea mimicking the signs and symptoms of acute GI GVHD; in many cases, diagnosis of GVHD was based on biopsy results, and a post hoc independent pathology review concluded that GI biopsy was not able to discern between GI GVHD and BCV-related diarrhea. Treatment of diarrhea with corticosteroids while BCV therapy continued (with the rationale that subjects were at even greater risk for CMV reactivation) resulted in continued diarrhea, which was interpreted as refractory GVHD. The subsequent increased steroid use in BCV recipients (median 8-fold higher cumulative use compared with placebo recipients through Week 24, median 5-fold higher cumulative use compared with placebo recipients through Week 14) and/or the addition of second-line therapies, including T cell-depleting antibodies and other biologics, further increased the net state of immunosuppression, which had a negative impact on outcomes. Subjects with diarrhea who were managed more conservatively with treatment interruptions had better outcomes, including improved overall mortality, when compared with subjects managed less conservatively (i.e., continued study drug dosing in the setting of persistent or worsening diarrhea attributed to GI GVHD).

In Study CMX001-304, subjects were treated with 12 weeks of BCV for AdV, and GI events, in particular diarrhea, were still the most commonly reported AEs, although reports of acute GVHD were lower than in the CMX001-301 study. Diarrhea is a common manifestation of AdV disease in patients with AdV infection post HCT; further, pediatricians are less likely to aggressively treat presumptive GVHD in the presence of AdV viremia, as reduction of steroids and other immunosuppressants is typically employed. As a result, AdV is almost always treated in favor of GVHD, suspected or otherwise.

Serious events of diarrhea were reported by 21 subjects (10% of dosed subjects) in the CMX001-304 study. GI events were the most frequently reported AEs that led to BCV discontinuation (16% adults, 5% pediatric subjects); more specifically, diarrhea prompted BCV discontinuation in 9% adults and 5% of pediatric subjects, followed by abdominal pain (6% adults vs. < 1% pediatric subjects). Overall, more adult subjects (34%) than pediatric subjects (19%) discontinued treatment with BCV due to any AE.

Based on learnings to-date, it is recommended that BCV be interrupted for treatment-emergent diarrhea of ≥ CTCAE (National Institutes of Health/National Cancer Institute Common Terminology Criteria for Adverse Events) Grade 2, with a treatment interruption of at least 7 days (i.e., at least 6 full days off drug) and until symptoms improve to ≤ Grade 1. In doing so, interruption of BCV treatment serves as both a diagnostic test and, if the diarrhea is related to BCV, the time off drug also allows the gut epithelium an opportunity to regenerate. If the diarrhea improves, BCV may be safely reintroduced thereafter. A dose consolidation approach (administering the same total weekly dose at weekly dosing intervals to allow more time between doses for GI mucosal regeneration) is also recommended at re-introduction of BCV. If there is no improvement following interruption of BCV, the likely etiology of diarrhea is not BCV;

nevertheless, BCV should not be reintroduced until the diarrhea improves, regardless of the underlying etiology.

In conclusion, oral administration of BCV is associated with known GI toxicity, which cannot be reliably differentiated from GI GVHD histopathologically or based on GI symptoms. Though clinical evaluation of other organ systems also affected by GVHD, namely the skin, may assist in determining the most appropriate patient management strategy, treatment-emergent diarrhea of Grade 2 or higher severity, regardless of etiology, should prompt BCV treatment interruption for at least 7 days (i.e., 6 full days off drug). Initiation of steroid therapy for GVHD should be delayed, if clinically appropriate, in order to assess whether symptoms improve as a result of BCV withdrawal. Resumption of BCV as a consolidated QW dose is possible if symptoms improve.

Further details of this and other BCV-related toxicities are provided in the BCV Investigator's Brochure.

4.3. Overview of Study CMX001-999 Design and Rationale

This study is a randomized, open-label, parallel group, two-arm, multi-center assessment of BCV compared with SoC in high-risk (i.e., T cell-depleted) pediatric allogeneic HCT recipients with AdV viremia. A virologic response-driven approach to the duration of treatment will be evaluated, in which subjects randomized to BCV therapy are treated until AdV viremia is confirmed as undetectable or until a maximum of 16 weeks of therapy, whichever occurs first. All subjects will be followed in the study for a total of 36 weeks post-randomization, regardless of treatment assignment. Subjects will be assessed on a weekly basis through Week 16, with additional assessments performed at Weeks 24 and 36 post-randomization. The data collected through Week 16 will comprise the primary data set for the study; hence, the primary database will be locked and analyzed following capture of data for all subjects through Week 16.

4.3.1. Study Rationale

Allogeneic HCT recipients are at risk of AdV infection and disease progression. Published guidelines recommend screening of high-risk HCT recipients and the application of antiviral therapy pre-emptively before AdV disease occurs. However, there is currently no approved antiviral therapy for AdV.

BCV is an investigational antiviral which has demonstrated activity against AdV in vitro and in clinical investigations. In previous studies of oral BCV for AdV infection, initiation of therapy early in the course of infection (when plasma viral load was less than 10^4 or 10^5 copies/mL) was associated with rapid clearance of viremia.

As described previously, diarrhea is the most common AE associated with oral BCV administration with typical onset in pediatric subjects from 4 to 6 weeks after initiating treatment with BCV. In the context of HCT, BCV-related diarrhea can mimic symptoms of GI GVHD, which can confuse accurate diagnosis and management of patients (Detweiler 2016). GI toxicity management that was conservative (i.e., specifically withholding further BCV dosing until symptoms resolved) appeared to be an effective and straightforward toxicity management approach, and was associated with better subject outcomes in Study CMX001-301 (Marty 2016). As described in Section 4.2.3.1, these clinical findings have led to further refinement of the

subject safety monitoring and management guidance for oral BCV to promote a more conservative management approach with clear and mandated stopping criteria. The assessment of the effectiveness of these revised guidelines as a critical component in optimally managing subjects is a primary objective of this study.

Therefore, this study is designed to assess the safety and overall tolerability of oral administration of BCV using defined safety monitoring and management criteria (Section 8.3) and to assess the impact of BCV in reducing AdV viremia in HCT recipients relative to the current SoC. By studying the proposed treatment paradigm and toxicity management in a subject population likely to benefit from treatment, a more refined approach to overall treatment strategies can be established.

4.3.2. Rationale for Subject Population

Pediatric patients who have received a T cell-depleted allogeneic (i.e., not autologous) HCT within the last 100 days and have confirmed AdV DNA detectable in the blood will be considered for participation in this study. For the purposes of this study, "T cell-depleted" describes:

1. Ex vivo T cell depletion via positive (e.g., CD34+ cell) selection or negative selection (e.g., T cell receptor α/β or CD3+ cell removal by column filtration);
2. Serotherapy with anti-thymocyte globulin (ATG, as cumulative dose of ≥ 3 mg/kg rabbit-derived ATG or ≥ 50 mg/kg of equine-derived ATG) administered within 10 days prior to transplant or at any time post-transplant and prior to Day 1, or
3. Serotherapy with alemtuzumab administered within 30 days prior to transplant or at any time post-transplant and prior to Day 1.

These subjects are among the highest risk for AdV infection and progression to disease and are also among those with the highest unmet medical need.

Among patients who have undergone HCT, there are well-defined risk factors for AdV infection and progression; these include younger age, allogeneic transplant, cord blood transplants, and T cell depletion (Chakrabarti 2002, Kampmann 2005). These subjects are at high risk for developing AdV disease due to profound and persistent immunodeficiency (Tromblyn 2009) and in this susceptible population, the development of AdV infection associated with viremia is much more prevalent, severe, often disseminated, and rapidly fatal without treatment (Florescu 2012, Ison 2006, Lion 2014, Sandkovsky 2014).

Published European Conference on Infections in Leukaemia (ECIL) Treatment Guidelines (Matthes-Martin 2012) recommend routine monitoring of pediatric patients, especially pediatric patients with at least one defined risk factor for AdV viremia. Identified cases of AdV viremia are recommended to decrease immunosuppression where possible (e.g., in patients without ongoing GVHD), together with the initiation of "off-label" treatment with IV CDV. This population is at especially high risk, with adenoviral clearance intrinsically linked under normal circumstances to T cell recovery, which typically does not occur for many months post allogeneic HCT. IV CDV is reportedly less effective in patients who have not reconstituted effective T cell function (Hiwarkar 2017).

Pediatric subjects have responded to BCV therapy. Study CMX001-304 enrolled 201 subjects (130 pediatric, 71 adult) with disseminated AdV disease or with asymptomatic viremia or localized AdV infection who were at risk for progression to disseminated AdV disease. Subjects were treated with BCV for 12 weeks. In this study, pediatric subjects had improved clinical outcomes compared with adult subjects (all-cause mortality at Week 36 was 39% in pediatric subjects vs. 63% in adults). Key differences between these two groups at baseline suggest that the adults who enrolled in this trial had poorer prognoses than the children (e.g., indication for transplantation, frequency of T cell depletion). Additionally, the time from transplant to BCV initiation was longer for adults (median 94 days) than pediatric subjects (median 53 days), which may reflect earlier diagnosis in the setting of screening protocols that are common at pediatric transplant centers. Pediatric subjects tolerated BCV better than adults and had longer median duration of BCV therapy (78 days vs. 38 days in adults).

Because pediatric recipients of T cell-depleted allogeneic HCT are at very high risk for AdV infection and progression to serious disease, they are among the most in need of new treatment options, and have demonstrated reasonable tolerability and responses with BCV-based therapy. Accordingly, this study will focus enrollment on this population most likely to benefit from treatment with BCV.

Subjects to be excluded are those with baseline comorbidities AdV who are unlikely to survive to Week 4, such as subjects with renal failure or a need for renal replacement therapy, those with pre-existing coagulopathy, sepsis requiring vasopressors, or the need for ventilator support.

4.3.3. Rationale for BCV Dosage Regimen and Treatment Duration

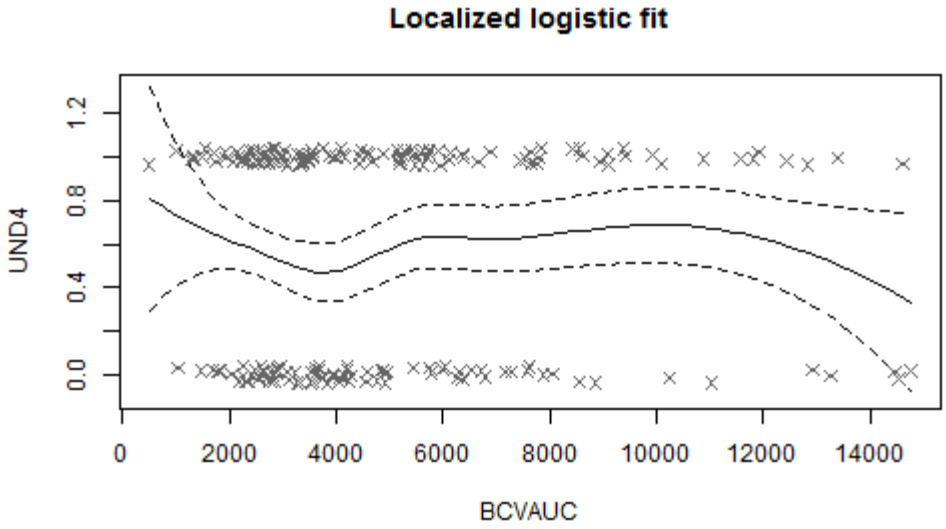
Subjects will receive a BCV dosage regimen based on their lowest body weight measurement within 30 days prior to Day 1 (to best represent dry weight) and concurrent cyclosporine use. Subjects not receiving concurrent cyclosporine will receive BCV at a dose of 2 mg/kg (up to a maximum of 100 mg) BIW. Subjects receiving concurrent cyclosporine will receive 1.4 mg/kg (up to a maximum of 70 mg) BIW; the BCV dose is adjusted to account for increased exposures observed with cyclosporine co-administration. See Section 8.2 for additional dosing details.

4.3.3.1. Rationale for BCV Dosage Regimen

BCV 2 mg/kg (up to 100 mg) BIW has been selected as the dosage regimen for this study. In the Phase 2 AdV pre-emption study (CMX001-202), there were trends for improved antiviral effect and survival (through 4 weeks post-end of treatment) with BCV 2 mg/kg (up to 100 mg) BIW compared with BCV 4 mg/kg (up to 200 mg) QW and placebo (Grimley 2017). In the subsequent open-label, single arm AdV treatment study (CMX001-304), BCV 2 mg/kg (up to 100 mg) BIW was associated with rapid virologic response; in the subset of pediatric HCT recipients remaining on-study at Week 4 and Week 6 (69 and 66 of 100 enrolled, respectively), 59% achieved undetectable plasma AdV viral load by Week 4 and 68% achieved undetectable plasma AdV viral load by Week 6 (Section 4.3.7). Rapid virologic response was associated with improved survival in subjects with disseminated AdV disease, and there were trends for an association between rapid virologic response and improved survival in subjects with asymptomatic or localized AdV disease (Section 4.3.7.1 and Section 4.3.7.2). Similar rapid virologic responses were observed with BCV 2 mg/kg BIW in the compassionate use setting (Hiwarkar 2017).

Efficacy and safety exposure-response analyses suggest that high plasma BCV exposures are not required for antiviral activity for AdV (Figure 1) and that lower oral doses may be associated with lower BCV-associated AEs (see the BCV Investigator's Brochure for details). Actions taken to minimize PK variability and avoid high plasma BCV exposures in this study include BCV dose reduction for subjects receiving concurrent cyclosporine to account for drug interaction (Section 8.6). Overall exposure will be decreased by applying treatment only until AdV DNA is cleared from the plasma, as explained below.

Figure 1: Relationship between Weekly Plasma BCV AUC and Achievement of Undetectable Plasma AdV Viral Load



Abbreviations: BCV AUC = brincidofovir weekly area under plasma concentration-time curve; UND4 = undetectable plasma AdV viral load at Week 4 (0 = no, 1 = yes).

4.3.3.2. Rationale for Virologic Response-Driven BCV Treatment Duration

Because of the observed toxicities associated with BCV therapy (primarily GI/diarrhea and elevations in liver enzymes), there is the recognized need to balance potential side effects against potential therapeutic benefit of BCV therapy. Because of the rapid virologic response to BCV, a shorter course of BCV may be adequate for the treatment of AdV, while minimizing the risk of GI AEs. Therefore, subjects randomized to BCV in this study will be managed according to a virologic response-driven approach, in which BCV therapy is administered until AdV plasma viremia is confirmed to be undetectable, up to a maximum of 16 weeks, contingent on their not meeting pre-defined tolerability thresholds requiring interruption or discontinuation of treatment (Section 8.3).

A virologic response-driven approach for BCV is supported by the rapid antiviral response observed in clinical trials. In Study CMX001-304, subjects treated with BCV overall demonstrated rapid declines in AdV plasma viremia, typically after 1 to 4 weeks of therapy with a median time to undetectable AdV viremia of 12 to 22 days among pediatric subjects; clearance of AdV respiratory secretions and urine as well as plasma was seen in the majority of subjects after 4 weeks of BCV. Pediatric subjects with lower AdV viral loads at baseline (< 10,000 copies/mL) cleared within a median 8 days of BCV initiation. Among pediatric

subjects with AdV DNA < 5 $\log_{10}$ (< 100,000 copies/mL), 72% cleared within 4 weeks (Prasad 2017). Furthermore, subjects with an early virologic response had better outcomes (data presented in Section 4.3.7). Similar rapid virologic responses were observed with BCV among patients treated in the expanded access setting (Florescu 2012, Hiwarkar 2017).

A virologic response-driven approach is well established for the treatment of infectious diseases during the post-transplant period. It is the current standard practice for the pre-emptive treatment of CMV, a virus that targets the same at-risk populations. For CMV disease, the choice of medication, i.e., (val)ganciclovir or foscarnet, as well as the duration of treatment is determined based on the patient's overall status and need for treatment and the known toxicities of each of the medications (Boeckh 2009). In general, antiviral therapy is continued until clearance of CMV from the blood, followed by continued regular monitoring for CMV DNA by polymerase chain reaction (PCR). Should CMV viremia recur, pre-emptive therapy is restarted.

Because subjects participating in this study are likely to have persistent immune compromise, putting them at risk for recurrence of AdV viremia, subjects will be allowed to re-initiate BCV if AdV viremia recurs. Details for initiating, stopping and restarting BCV dosing are in Section 8.

4.3.4. Rationale for Safety Monitoring and Toxicity Management Guidance

Pro-active identification and management of AEs potentially associated with BCV treatment (e.g., diarrhea and other GI events, as well as increases in serum liver enzymes) is critical to the optimal dosing of BCV. To that end, the protocol specifies close surveillance, diagnosis and characterization of AEs, as well as definitive thresholds for interruption, or if necessary, discontinuation of BCV treatment. Thresholds for interruption have been set to promote early recognition and action for specified events that reach a certain severity grade (using the CTCAE grading scales). In cases of BCV-related toxicity, interruption at these times is generally associated with improvement or resolution of symptoms while the subject is off BCV therapy, allowing for possible resumption of BCV. This approach allows differentiation between BCV-related toxicities and other toxicities or processes (such as GVHD). Specific safety monitoring and toxicity management guidelines are detailed further in Section 8.3.2.

Critical to the success of implementing and assessing a robust safety monitoring plan is accurate and timely collection of relevant information. In this study, GI symptoms will be recorded daily on electronic diaries (e-diaries) provided to the subjects. The e-diaries will promote subject awareness and vigilance, as well as alert study staff in order that they may intervene promptly, as clinically appropriate. E-diaries will prove particularly useful for monitoring subjects when they are outpatients.

Finally, a Data and Safety Monitoring Board (DSMB) will be chartered for this study to independently oversee the safety information obtained during the conduct of this study, and will be chartered to recommend any changes to the management of subjects to improve their outcomes over the course of the study (Section 4.5).

4.3.5. Rationale for Standard of Care Comparator

In this study, BCV will be compared with local institutional standard of care (SoC). A standard placebo-controlled design is not considered to be an ethical or practical option because AdV infection or disease can be rapidly fatal in this population. Similarly, an active control study design, in which patients would be randomized to BCV or IV CDV, is problematic because CDV

is not approved for this indication, is not standardly administered to all patients with AdV infection, and is not licensed for any indication in some countries. Furthermore, when IV CDV is used to treat AdV in HCT recipients, the dose, regimen and duration of treatment are not standardized, with regimens varying between 5 mg/kg QW to 1 mg/kg three times weekly, which may be modified according to patient response. The use of pre- and post- dose IV hydration and the use of probenecid are also variably applied. Finally, a significant percentage of patients with AdV infection have renal insufficiency, which is a noted contraindication for IV CDV (Mori 2003, Vistide Package Insert [Gilead Sciences 2010]). Therefore, physician-selected SoC represents the optimal comparator for this study, providing an opportunity to observe the efficacy and safety/tolerability of oral BCV vs. usual care for this condition, for which there are no approved therapies.

4.3.6. Rationale for Open Label Design

Blinding a study in which subjects are randomized to either oral BCV or a SoC arm that could include IV CDV is prohibitively difficult. Co-administration of probenecid is recommended to reduce renal toxicity (Vistide Package Insert [Gilead Sciences 2010]). Probenecid would, therefore, need to be provided under double-blind, double-dummy conditions. However, at the doses required, probenecid is associated with side effects, such as nausea, which would functionally unblind the treatment assignment. Administration of IV CDV also typically requires pre- and post-dose IV hydration which would have to be administered to all subjects to maintain the blind. This IV fluid load is associated with its own risks, particularly for small children, which raises ethical concerns for subjects randomized to oral BCV.

For these reasons, this study will be conducted as an open-label investigation. SoC will be according to local guidelines and institutional practice and may include administration of IV CDV, reduction in immunosuppression or other approaches not prohibited by this protocol. Given that the primary endpoint of the study is objective (clearance of AdV DNA from the plasma), biased assessment of the primary endpoint is unlikely.

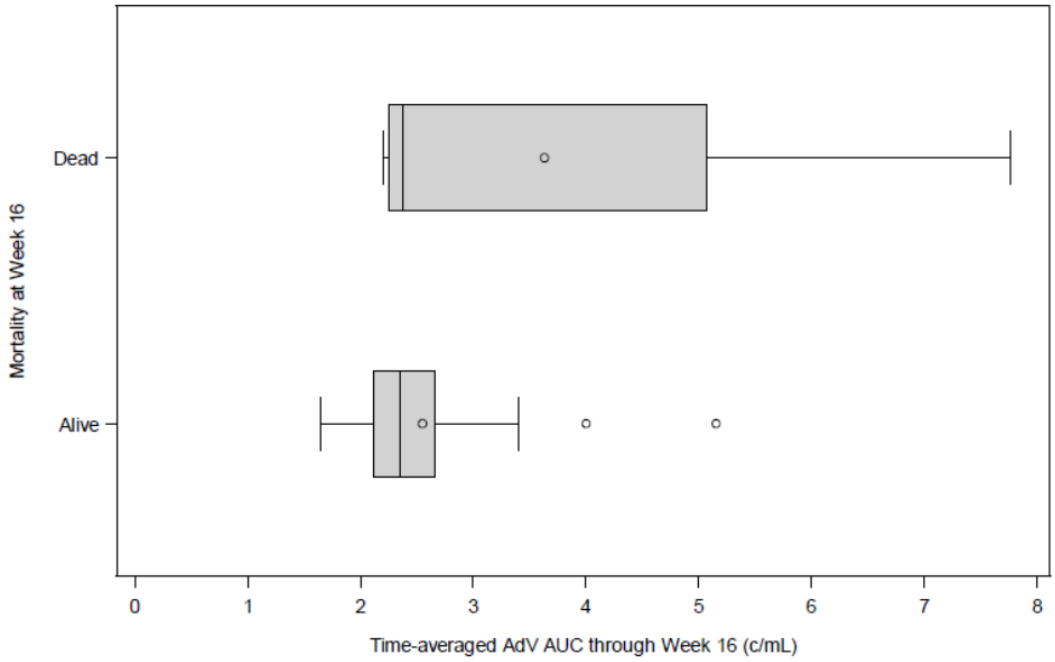
4.3.7. Rationale for Primary Efficacy Endpoint and Secondary Endpoints

Powering a study for superiority on the basis of mortality was not considered ethical or feasible due to the large number of subjects that would need to be included. Multiple non-mortality clinical outcomes were considered as potential primary endpoints (such as progression of AdV disease or infection) and were rejected for a variety of reasons, including: (1) lack of consensus definitions of AdV disease and progression; (2) multiple etiologies that can result in similar signs/symptoms, and (3) the reluctance to require invasive diagnostic procedures to document progressive AdV disease (e.g., liver biopsy to document AdV hepatitis). For example, respiratory compromise can be the result of worsening AdV disease, the sequelae of the patient's conditioning regimen, or another infectious etiology; and renal dysfunction can be the culmination of multiple nephrotoxic insults, including AdV disease, and is commonly observed after CDV administration as well other known nephrotoxic medications. Gut injury is perhaps even more complicated with clinical, gross pathology and even histopathologic analysis unable to differentiate from progression of AdV disease, gut GVHD, and injury related to prolonged oral administration of BCV. In contrast, a primary endpoint based on control of AdV viremia is considered to be both feasible and clinically relevant.

The primary efficacy endpoint selected for this study is the time-averaged area under the concentration-time curve (AAUC) for plasma AdV viremia (log_{10} copies/mL) through Week 16 post-randomization. This viral AAUC endpoint was selected based on evidence collected from prior BCV clinical trials and expanded access programs, as well as data from the literature evaluating SoC, showing that virologic response is predictive of clinical outcomes. AdV viremia has been demonstrated in natural history studies to be a valid predictor of disease-related outcomes, with thresholds of peak viremia identified which predict significant changes in expected survival, thus supporting the use of AdV viremia as a surrogate that is reasonably likely to predict clinical benefit. In addition, the positive impact on survival has been noted with reductions in AdV viral load following investigational interventions, including with adoptive T cells (Feucht 2015), IV CDV, and BCV (see Section 4.3.7.1 and Section 4.3.7.2).

To illustrate the clinical relevance of this endpoint, Chimerix has analyzed the data from pediatric HCT subjects enrolled in Cohorts A and B in the CMX001-304 study with AdV viral load ≥ 1000 copies/mL at baseline who were within 100 days of transplant (n = 40). In this group, 28% (11 of 40) subjects died by Week 16. A boxplot looking at distribution of AAUC through Week 16 by vital status (i.e., alive or dead) at Week 16 shows that survivors had reduced AAUC when compared with non-survivors (t-test p = 0.11) (Figure 2).

Figure 2: Study CMX001-304: AAUC through Week 16, Mortality at Week 16



Similar analyses have been conducted for two retrospective patient cohorts: a historical dataset dating back more than 10 years from Royal Manchester Children's Hospital in the United Kingdom (UK) (the "Manchester Cohort") (Figure 3) and preliminary data from three countries (France, Spain, and UK) from the AdVance study (Figure 4), which is a natural history study sponsored by Chimerix that will explore the association of AdV viremia, response to SoC therapy, and clinical outcomes (including overall survival and non-relapse mortality) in a contemporary multicenter cohort. The results from these two retrospective patient cohorts also support the correlation between the proposed endpoint (viral AAUC) and mortality under SoC

treatment with IV CDV (Manchester Cohort n = 24, p = 0.0032; AdVance n = 51, p = 0.007). (Note that a Manchester Cohort analysis looking at AAUC vs. mortality was not available in time to contribute; therefore, a previous analysis looking at time-averaged area under the curve minus baseline, or AAUCMB, is presented.)

Figure 3: Manchester Cohort: AAUCMB through Week 16, Mortality at Week 16

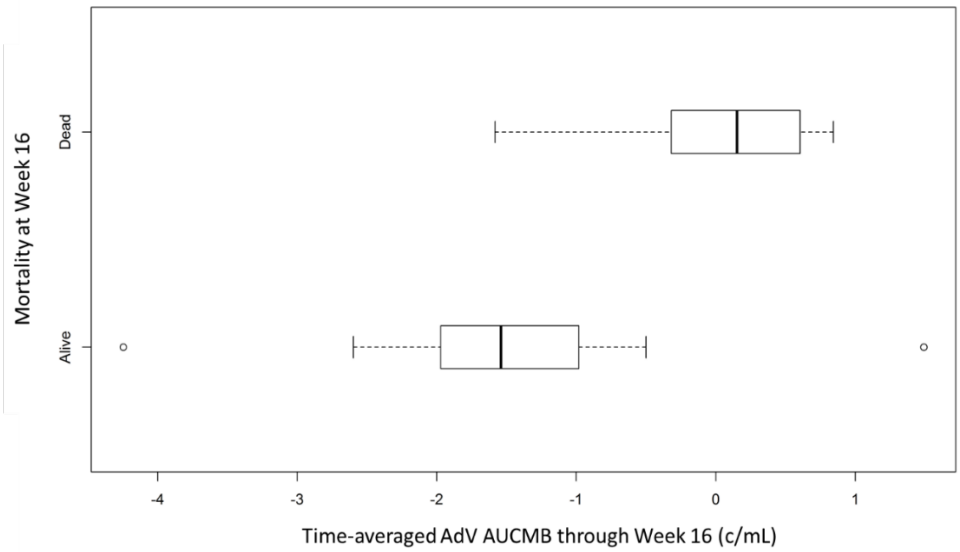
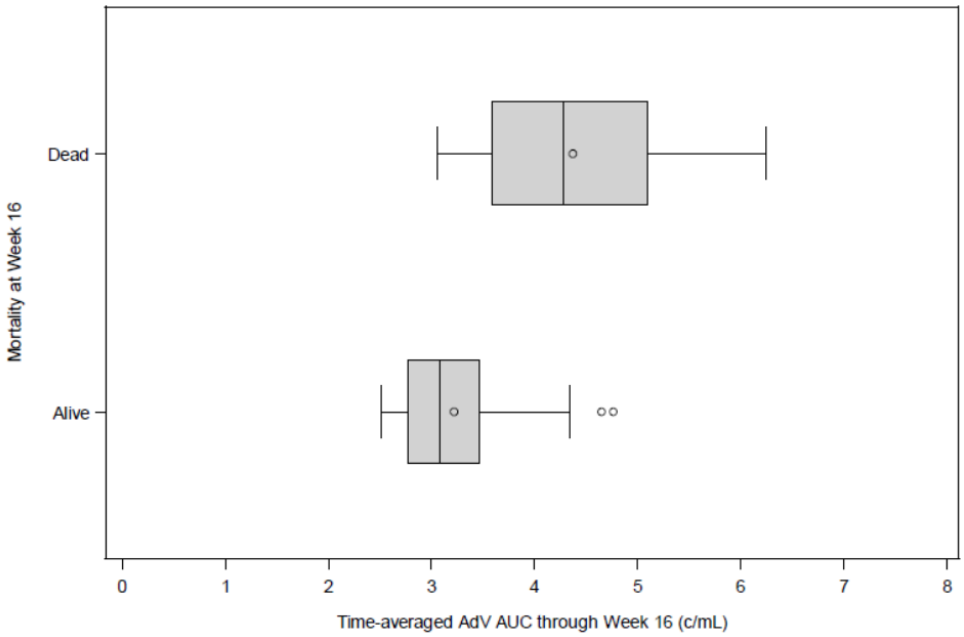


Figure 4: AdVance Study: AAUC through Week 16, Mortality at Week 16 (Preliminary Data from UK, Spain, and France)



A viral AAUC endpoint also provides the opportunity to correlate total viral burden with secondary endpoints of clinical outcomes, including all-cause and non-relapse mortality, as well as other clinical benefits, such as decreased progression to AdV pneumonia, and decreased number of days spent in the hospital or intensive care unit (ICU).

The study will also provide a holistic assessment of safety that includes the known side effects of oral BCV (GI toxicity) and IV CDV (renal injury). Immunosuppressant therapies utilized in the study will be recorded to document that short course BCV therapy and updated safety management guidance has mitigated the overuse of steroids observed in the CMX001-301 study (Section 4.2.3.1). Though it is anticipated that control of AdV replication will limit resulting organ damage and numerically improve survival in patients treated with oral BCV, a non-inferiority analysis of overall mortality at Week 16 between the BCV and SoC arms is included as a key secondary efficacy endpoint in order to rule out an untoward effect of BCV on outcomes.

4.3.7.1. Study CMX001-304

In a landmark analysis of data from Study CMX001-304, lower mortality outcomes were observed among subjects with early virologic response across both Cohort A (localized or asymptomatic AdV infection) and Cohort B (disseminated disease). Specifically, improved survival was observed among pediatric subjects with an undetectable viremia result at Week 4 (mortality 24% Cohort A and 29% Cohort B vs. 44% and 47%, respectively among non-responders who did not achieve undetectable AdV viremia at Week 4) (see Table 4). Pediatric subjects with disseminated disease (Cohort B) who achieved undetectable AdV viremia by Week 6 also had an improved overall survival (25% mortality vs. 54% mortality in pediatric subjects who did not achieve undetectable AdV viremia at Week 6). Similar observations were made in adult subjects, although overall survival rates were lower.

Table 4: Study CMX001-304: Early Virologic Response and Mortality Outcome

Responder Definition	Pediatrics			Adults		
	Proportion Responder[a]	Mortality among Responders	Mortality among Non-responders	Proportion Responder[a]	Mortality among Responders	Mortality among Non-responders
Cohort A (localized or asymptomatic AdV infection)						
Undetectable at Week 4	17/26 (65%)	4/17 (24%)	4/9 (44%)	7/13 (54%)	3/7 (43%)	5/6 (83%)
Undetectable at Week 6	17/25 (68%)	5/17 (29%)	2/8 (25%)	8/13 (62%)	4/8 (50%)	4/5 (80%)
Cohort B (disseminated AdV disease)						
Undetectable at Week 4	24/43 (56%)	7/24 (29%)	9/19 (47%)	9/26 (35%)	5/9 (56%)[b]	15/17 (88%)
Undetectable at Week 6	28/41 (68%)	7/28 (25%)[b]	7/13 (54%)	10/24 (42%)	5/10 (50%)[b]	13/14 (93%)

[a] Denominator reflects subjects with baseline AdV viremia still on study at Week 4 or Week 6.
[b] $p < 0.05$ vs. non-responders, Cox model for time to death.
Note: Cohort A total n (pediatric n, adult n): Enrolled 65 (42, 23), Week 4: 39 (26, 13), Week 6: 38 (25, 13).
Note: Cohort B total n (pediatric n, adult n): Enrolled 93 (58, 35), Week 4: 69 (43, 26), Week 6: 65 (41, 24).

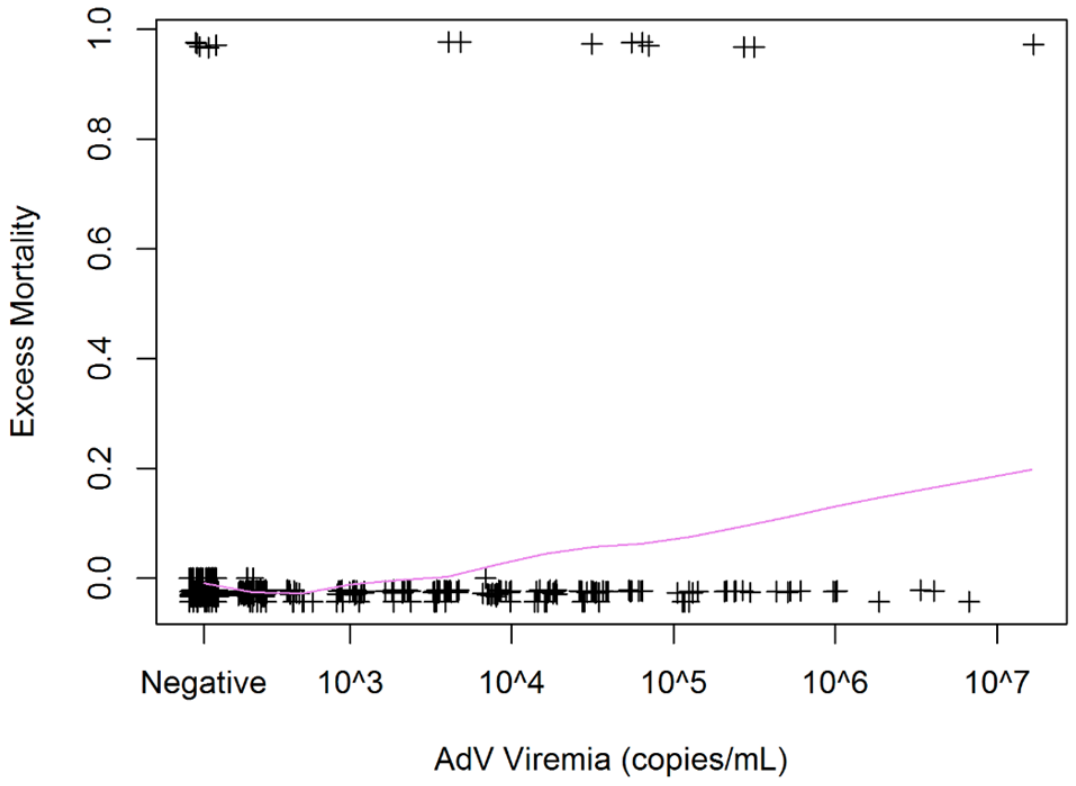
4.3.7.2. Data from Literature

Reports in the literature suggest that viral dynamics are correlated to risk of mortality for AdV; AdV infection has been established as an independent risk factor for death (Hiwarkar 2013,

Lion 2010, Mynarek 2014, Symeonidis 2007). Overall survival was associated with lowest peak AdV viremia levels; patients with peak AdV viremia < 1000 copies/mL had an overall survival similar to AdV viremia-negative patients (Mynarek 2014). In this same study, patients with peak AdV viremia levels > 10,000 copies/mL had poorer survival (hazard ratio=3.81; p=0.003). Hiwarkar and colleagues demonstrated in a retrospective cohort of 291 high-risk children (years 2005 to 2010) that AdV viremia was a major independent predictor of mortality ($p < 0.05$) (Hiwarkar 2013). In this cohort, AdV reactivation caused prolonged hospitalization ($p < 0.05$) and accounted for 15% of all mortality. Recently, Hiwarkar and colleagues have shown that death from disseminated adenoviral disease may be associated with failure to respond to therapy, as measured by cumulative viral load despite treatment with IV CDV (Hiwarkar 2017).

Ongoing work at the Royal Manchester Children's Hospital in the UK to explore the impact of AdV viremia upon outcomes has shown the clear impact of increasing AdV viremia (in spite of the application of pre-emptive IV CDV therapy) on increasing mortality (Figure 5).

Figure 5: Relationship between AdV Viremia and Mortality (Viremia Modelled as Time-varying Covariate)



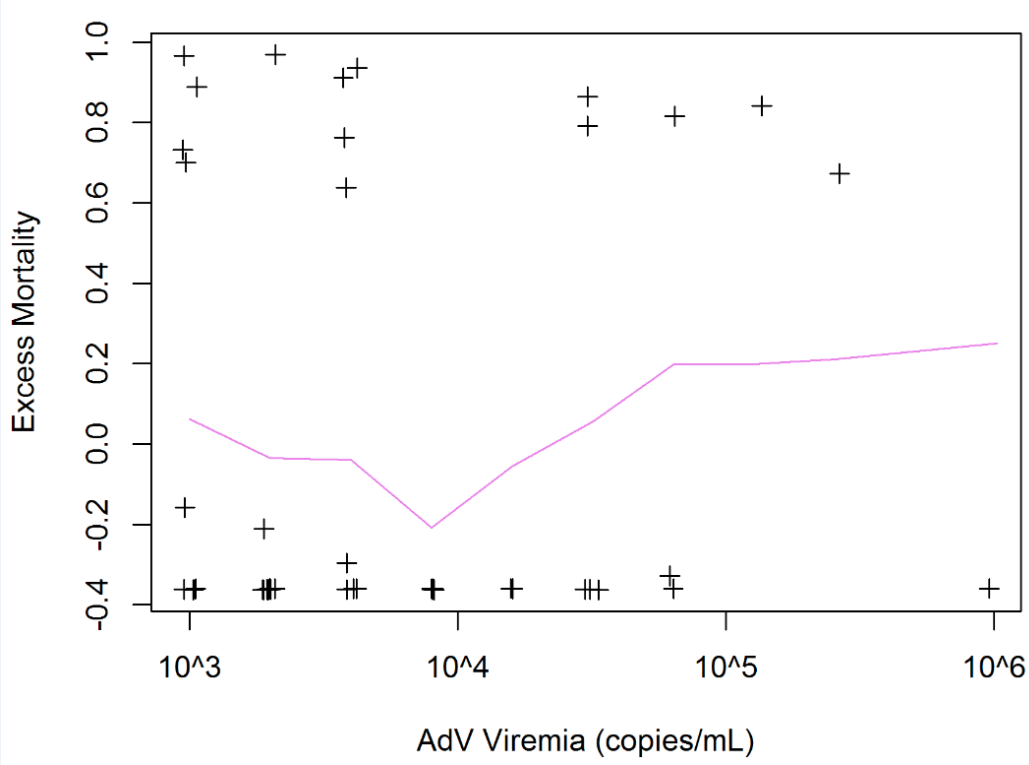
Source: Professor Robert Wynn, Royal Manchester Children's Hospital, unpublished data.

Each point ("+") on the plot represents an individual viral load measurement, plotted against its Martingale residual (i.e., "excess mortality"), which is defined as observed mortality minus expected mortality. Observed mortality is "0" for censored observations (i.e., alive at next measurement or censored prior to next measurement) and "1" for events (i.e., dead prior to next measurement or censored). Expected mortality is the integrated hazard obtained from a Cox

model with viral load included as a time-varying covariate. A non-parametric smoothing line is used to show the relationship.

Figure 6 represents a similar analysis using viremia at the time of initial diagnosis of significant AdV. While the trend is less clear, even with this small sample size, there is still evidence to suggest that higher viremia is associated with higher mortality.

Figure 6: Relationship between Baseline Viral Load and Mortality (Viral Load as Time of Initial Viremia > 1000 copies/mL)



Source: Professor Robert Wynn, Royal Manchester Children's Hospital, unpublished data.

4.3.8. Rationale for Limiting Access to BCV for SoC Subjects to after Week 16 Post-randomization

While a BCV crossover option for subjects who fail to respond to SoC therapy would be expected to have support from physicians who have used BCV for IV CDV failures via the NPP, subjects who are randomized to the SoC arm in this study must remain in their assigned treatment arm without the option for BCV treatment through a minimum of Week 16 post-randomization to allow for a meaningful and interpretable comparison of safety and efficacy between the treatment arms. The aim of this study is to show a positive risk-benefit for BCV when compared with SoC-based preemptive therapy for AdV viremia in pediatric HCT recipients. This will only be possible if SoC-treated subjects are not allowed to switch to BCV in the event of failure during the 16-week virologic response-driven treatment period. Crossover in a substantial proportion of SoC-treated patients has the potential to negatively impact interpretation of the planned efficacy comparisons for BCV vs. SoC by decreasing the sample size available in the SoC arm after the switch for several of the secondary efficacy endpoints, including time to clearance of AdV viremia and sustained virologic response. Similarly, early

switching could also potentially complicate interpretation of the safety and tolerability assessments of BCV vs. SoC. Attribution of events such as SAEs and all-cause and non-relapse mortality in this complicated post-HCT patient population could also be more difficult. There would also be the potential for significant differences in the duration of BCV vs. antiviral exposure in the SoC arm and follow-up times.

4.3.9. PELOD Scoring

Because the pathogenesis of AdV infection is related to lysis of cells in key organs, such as the lungs, liver and gut (and viral load in plasma is thought to reflect the extent of cellular lysis, supported by correlations between peak viral load and mortality; Heim 2011), capturing decreased viral burden (as viral AAUC) is highly likely to correlate with decreased organ damage. Maximum pediatric logistic organ dysfunction (PELOD) score has been added as a validated surrogate outcome measure for severely-ill pediatric ICU patients (Leteurtre 2003). It quantifies the degree of dysfunction across several organ systems (neurologic, cardiovascular, renal, respiratory, hematologic, and hepatic) and has been shown to correlate with mortality in pediatric HCT recipients (Balit 2016), thus offering an opportunity to quantify the effect of BCV vs. SoC in limiting the occurrence of organ dysfunction by AdV infection.

4.3.10. Exploratory Biomarker Analyses

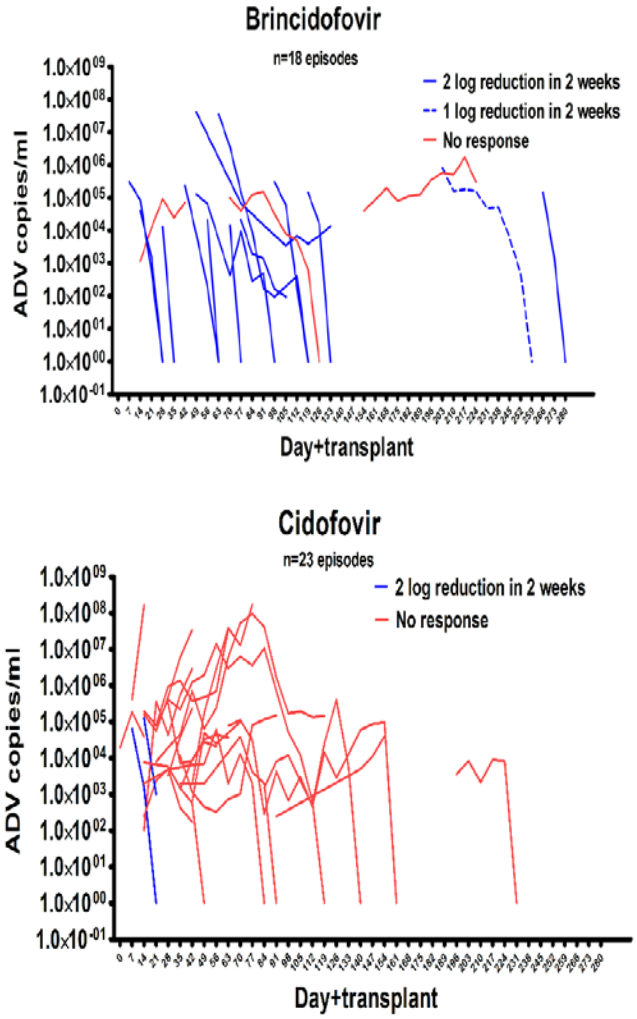
Because early detection of BCV-related GI AEs could allow early intervention, several exploratory biomarkers are proposed for potential use in these patients, including citrulline as a marker of GI toxicity (van der Velden 2010), suppression of tumorigenicity-2 (ST2) and T cell immunoglobulin mucin-3 (TIM3) as markers of GVHD (McDonald 2015), and C-reactive protein (CRP) concentrations as a non-specific marker of inflammation (Clyne 1999). Because of the unknown effect of BCV on these markers, they are considered exploratory. Analysis of these biomarkers may support their use in future clinical studies of BCV.

4.4. Benefit:Risk Assessment

There is no approved therapy for the treatment of AdV infection. The current SoC may include reducing immunosuppression or off-label use of IV CDV; ribavirin is not recommended by ECIL and is rarely used. The efficacy of IV CDV for the treatment of AdV viremia in HCT recipients has not been formally established, with some reports in the literature describing high success rates in controlling viremia and others describing very poor response rates (Ganapathi 2016, Lion 2014). The ECIL Treatment Guidelines note that while pre-emptive treatment of AdV with CDV has been reported in several studies, the "evidence concerning the effectiveness on mortality is inconsistent," with AdV-related mortality rates varying from 23% to 50% despite pre-emptive treatment, and an AdV-related mortality of 18% has been reported for patients not receiving pre-emptive therapy (Matthes-Martin 2012).

Hiwarkar and colleagues have recently reported their experience with oral BCV, obtained via the NPP (Hiwarkar 2017). They compared virologic response amongst BCV recipients (generally applied in the setting of IV CDV contraindications or failure of IV CDV therapy) vs. those that were treated with IV CDV, as shown in Figure 7.

Figure 7: Virologic Responses after BCV or CDV Treatment in Pediatric HCT Recipients



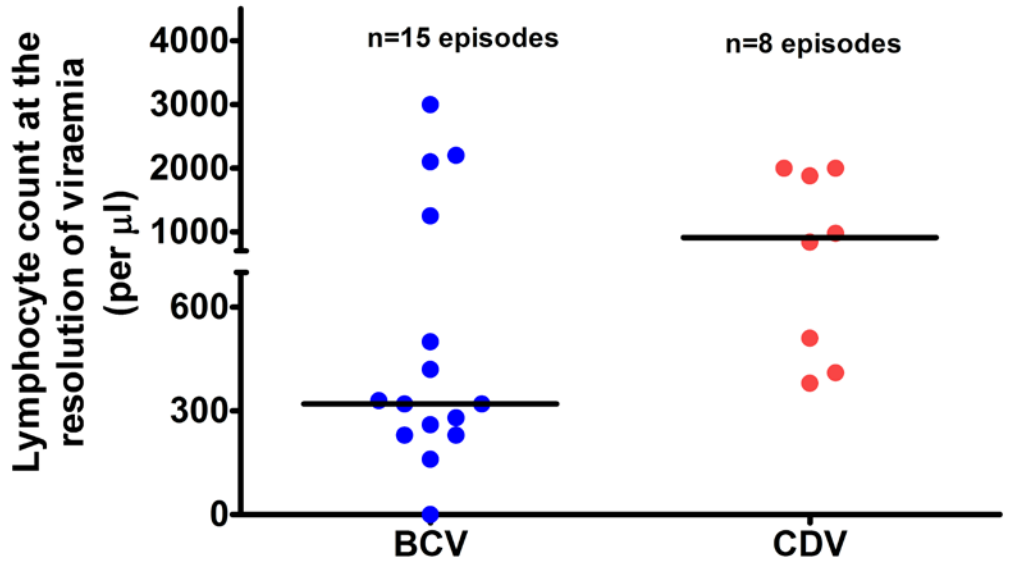
Abbreviations: ADV = adenovirus.
Source: Hiwarkar 2017.

Rapid virologic response in pediatric HCT recipients (defined by the authors as ≥ 2 $\log_{10}$ copies/mL decline in AdV viremia at two weeks) was more common with oral BCV (13/18, 72%) when compared with IV CDV (2/23, 9%). Patients were treated until viremia cleared; the median time to clearance of viremia with BCV was 4 weeks (range: 2 to 9 weeks) compared with 9 weeks (range: 3 to 15 weeks) with IV CDV ($p < 0.005$). The rapid antiviral response reported in these cohorts is consistent with the responses observed in interventional clinical trials with BCV (see Section 4.3.7 and the BCV Investigator's Brochure for more details). Furthermore, the lymphocyte count at the time of resolution of viremia was lower in patients receiving BCV than for those who received CDV. It is also noteworthy that many of the BCV patients had previously failed CDV.

Figure 8 shows the lymphocyte count at the resolution of viremia with BCV (n = 15) and CDV (n = 8). The median lymphocyte count at the resolution of viremia after BCV was 320 cells/µL and after CDV was 910 cells/µL. Thus, the resolution of viremia occurred in the BCV group

despite significant lymphopenia, while resolution of viremia occurred in the CDV group when lymphocyte count was > 300/µL ($p < 0.05$). The academic consortium also concluded that BCV was generally well tolerated: only 1 of 18 patients temporarily interrupted oral BCV for GI AEs, while renal toxicity was observed in 9 of 23 patients treated with IV CDV. The lower GI toxicity may in part be attributable to the shorter courses of BCV therapy used in these cohorts.

Figure 8: Lymphocyte Count at Resolution of Viremia Following Treatment with BCV (n = 15) or CDV (n = 8)



Abbreviations: BCV = brincidofovir; CDV = cidofovir.
Source: Hiwarkar 2017.

The primary risk associated with IV CDV is nephrotoxicity, which can result in renal failure or death (De Clercq 2003, Safrin 1997, Vistide Package Insert [Gilead Sciences 2010]). This is of particular concern for HCT recipients who are at increased risk of acute renal injury during the first 100 days post-transplant, with doubling of serum creatinine values reported in 15% to 73% of HCT recipients, and renal failure requiring dialysis in up to 8.5% of HCT recipients (Hingorani 2005, Rajpal 2013).

Cohort studies have shown that kidney injury is associated with poorer prognosis and mortality in pediatric HCT patients (Bhadri 2009, Ljungman 2003, Vora 2015). One retrospective cohort of pediatric patients who received IV CDV for the treatment of AdV demonstrated significant association of acute kidney injury (defined as ≥ 0.3 mg/dL [SI: ≥ 27 µmol/L] increase in serum creatinine) and mortality. All 6 subjects who met this threshold died, whereas, all 17 subjects who did not meet this threshold survived (Vora 2015).

The primary clinical risks associated with BCV therapy are GI in nature, particularly diarrhea, and elevations in serum aminotransferases. The emergence of diarrhea in the early post-HCT period is problematic due to mimicry of the symptoms of GI GVHD (Detweiler 2016, Marty 2016), which led to a significantly higher use of immunosuppressants on the BCV arm that resulted in poor outcomes in Study CMX001-301. Based on clinical trial experience to-date, the monitoring and management stopping rules for BCV therapy have been refined to include

clear and mandated thresholds at which BCV should be temporarily withheld and when BCV should be permanently discontinued, regardless of the suspected etiology of the diarrhea (see Section 8.3.2). Further, a response-driven approach to shorten BCV treatment duration, supported by the early and rapid antiviral response observed with BCV treatment, will be assessed to minimize exposure and the risk of BCV toxicity by treating until AdV viremia is cleared (see Section 8.3).

Safe and effective therapy for treatment of AdV is currently not available. The BCV response-driven treatment strategy, combined with clear and definitive toxicity management guidelines, informed by clinical trial and cohort data available to-date, are intended to maximize potential benefit to subjects, while decreasing the risk. As a result, the benefit:risk profile is considered sufficiently favorable for the continued assessment of oral BCV in pediatric recipients of T cell-depleted allogeneic HCT with AdV viremia. A DSMB will be chartered to evaluate the PK, safety, tolerability, and mortality data by treatment arm on an ongoing basis throughout the conduct of the trial (Section 4.5).

All sites will be encouraged to enroll their subjects in the "Chimerix Registry for BCV" (Study CMX001-333: A Prospective Observational Study for the Long-term Follow-up of Subjects Previously Enrolled in Selected Clinical Studies of BCV) to assess the long-term impact of exposure to BCV. Both BCV and SoC recipients will be invited to participate, with the latter serving as a control group for the BCV treated group.

More detailed information about the known and expected benefits and risks of BCV, including the Reference Safety Information, is provided in the BCV Investigator's Brochure.

4.5. Independent Safety Oversight

4.5.1. Data and Safety Monitoring Board

A DSMB will be convened according to US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines on clinical trial data monitoring committees to monitor safety for this study. The DSMB will review safety data on an ongoing and scheduled basis, as determined by the board and detailed in the DSMB charter. The DSMB Chair will be allowed to convene ad hoc meetings, as necessary, and meetings may be convened more frequently if unexpected safety issues arise.

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
- CTCAE Grade 3 or higher AEs
- AEs resulting in permanent BCV or other anti-AdV drug discontinuation
- AEs requiring BCV or other anti-AdV drug interruption
- AEs requiring dose modification or consolidation of BCV or other anti-AdV drug
- Incidence of and time to all-cause mortality and non-relapse mortality

- Laboratory parameters predictive of liver abnormalities (e.g., ALT, aspartate aminotransferase [AST], alkaline phosphatase, prothrombin time-international normalized ratio [PT-INR], and total and direct bilirubin), renal abnormalities (creatinine clearance, eGFR), and hematologic cell counts predictive of graft function
- Observed plasma BCV concentrations (as available)

At least two safety reviews will be conducted by the DSMB. The first safety review will be performed after the first 30 subjects enrolled into the study have completed through Week 16 (or have died or are lost to follow-up). The second safety review will be performed after the first 60 subjects enrolled have completed through Week 16 (or have died or are lost to follow-up).

The DSMB Chair will receive copies of all expedited safety reports issued for BCV at the same time these reports are submitted to investigators, 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, regulatory authorities will be consulted, as appropriate, prior to implementation.

4.5.2. Endpoint Adjudication Committee

A blinded endpoint adjudication committee (EAC) will be convened to provide an independent assessment of whether the deaths in the study are attributable to AdV. The EAC will adjudicate all deaths following procedures defined in the EAC charter. The EAC will comprise at least two members who are experts in the field of AdV infection and/or HCT and not otherwise involved in the study.

5. STUDY OBJECTIVES AND OUTCOME MEASURES

5.1. Primary Objective and Primary Efficacy Endpoint

The primary objective of this study is to compare the safety, overall tolerability, and virologic response of BCV vs. SoC for the treatment of AdV infection in high-risk pediatric allogeneic HCT recipients. A virologic response-driven approach to the duration of treatment will be evaluated, in which subjects randomized to BCV therapy are treated until AdV viremia is confirmed as undetectable or until a maximum of 16 weeks of therapy, whichever occurs first. The primary efficacy endpoint is the AAUC for AdV viremia (log_{10} copies/mL) from randomization through Week 16 post-randomization.

5.2. Secondary and Exploratory Objectives

5.2.1. Secondary Objectives:

- To assess the incidence of and time to all-cause, non-relapse, and AdV-associated mortality in pediatric subjects treated with BCV vs. SoC
- To assess the correlation between virologic response and clinical outcome
- To describe the incidence of and time to virologic relapse in subjects who have previously achieved undetectable AdV viremia
- To assess resolution or progression in clinical symptoms associated with AdV disease (i.e., resolution of all disease to no disease among subjects with probable or definitive AdV disease at baseline and progression from no disease to any probable or definitive AdV disease among asymptomatic subjects at baseline)
- To assess the correlation between AdV hexon "serotype," virologic response, and clinical outcome
- To evaluate the emergence of viral resistance among subjects treated with BCV vs. SoC
- To characterize plasma BCV PK profiles and evaluate the impact of covariates of interest on PK
- To characterize the potential impact of plasma BCV exposure on clinical safety, virologic, and mortality endpoints, and to evaluate the modifying influence of various covariates of interest on these relationships and endpoints
- To assess virologic response in other non-plasma biologic compartments (urine, stool, respiratory secretions), as well as the association between detectable AdV viral load in these compartments at AdV viremia clearance with subsequent AdV viremia relapse

5.2.2. Exploratory Objectives

- To assess the correlation between baseline HCT co-morbidity index and clinical outcome
- To assess immunologic predictors of virologic response (all subjects) and relapse (among subjects with confirmed AdV clearance from plasma)

- To evaluate exploratory biomarkers for BCV-related GI toxicity (e.g., citrulline, ST2, TIM3, and C-reactive protein)
- To assess healthcare resource utilization

5.3. Secondary and Exploratory Endpoints

5.3.1. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the incidence of all-cause mortality through Week 16.

5.3.2. Other Secondary Efficacy Endpoints

- Time to all-cause mortality through Week 16
- Incidence of and time to all-cause mortality through Week 36
- Incidence of and time to non-relapse mortality through Weeks 16 and 36
- Incidence of and time to AdV-associated mortality through Weeks 16 and 36, where mortality is assessed by a blinded EAC
- Proportion of subjects with undetectable AdV viremia at Weeks 2, 4, 6, 12, and 16
- Proportion of subjects with $\geq$ 2-$\log_{10}$ decline from baseline or undetectable AdV viremia at Weeks 2, 4, 6, 12, and 16
- Proportion of subjects with $\geq$ 1-$\log_{10}$ decline from baseline or undetectable AdV viremia at Weeks 2, 4, 6, 12, and 16
- AAUC at Weeks 2, 4, 6, and 12
- Incidence of and time to first confirmed undetectable AdV viremia
- Incidence of and time to virologic relapse (subsequent confirmed AdV viremia $\geq$ 1000 copies/mL) among subjects with confirmed clearance of AdV from plasma (overall; by AdV in urine, stool, and respiratory secretions at the time of first undetectable AdV viremia; and by T cell-mediated immune function [e.g., CD4+ cells > or $\leq$ 50 cells/µL] at the time of first undetectable AdV viremia)
- Maximum PELOD score through Week 16
- Number of days spent in the hospital through Week 16
- Number of days spent in the ICU through Week 16
- Emergence of AdV mutations associated with genotypic resistance and phenotypic resistance (the latter when possible) to BCV or CDV
- Incidence of and time to progression to probable or definitive AdV disease (among asymptomatic subjects at baseline)
- Incidence of and time to resolution of AdV clinical disease (among subjects with probable or definitive AdV disease at baseline)

- Primary model-based PK parameters, such as apparent clearance (CL/F), intercompartmental clearance (Q/F), volume of central compartment (V_c/F), volume of peripheral compartment (V_p/F), absorption rate constant (K_a), and lag time (T_{lag}), secondary PK parameters, such as C_{max} and area under the plasma concentration time curve at steady state (AUC_{ss}), and identification of covariates that influence these PK parameters
- Relationship between plasma BCV exposure, other covariates of interest, and
  - safety endpoints, including GI AEs, diarrhea, ALT, total bilirubin, and other safety events of interest
  - virologic endpoints including AAUC, AAUCMB, viral load change from baseline, and other virologic endpoints of interest,
  - all-cause and non-relapse mortality through Week 16

5.3.3. Safety Endpoints

- Incidence of treatment-emergent AEs (TEAEs), particularly those of ≥ CTCAE Grade 3 severity and SAEs
- Incidence of treatment-related AEs, particularly those of ≥ CTCAE Grade 3 severity and SAEs
- Incidence of AEs resulting in permanent BCV or other anti-AdV drug discontinuation
- Incidence of AEs requiring BCV or other anti-AdV drug interruption
- Incidence of AEs requiring dose modification or consolidation of BCV or other anti-AdV drug
- Incidence of fatal AEs
- Incidence of and time to CTCAE Grade 2 or higher diarrhea
- Incidence of doubling, tripling, or quadrupling of baseline serum creatinine
- Incidence of need for renal replacement therapy
- Incidence of ≥ 1/2/3 CTCAE grade increases from baseline for safety laboratory parameters of interest (by visit, maximum on-treatment, last on-treatment, last on-study)
- Distributions of change from baseline over time for central safety laboratory parameters of interest (by visit, maximum on-treatment, last on-treatment, last on-study)
- Assessment of all deaths that occur through Week 16 and in follow up through Week 36

5.3.4. Exploratory Endpoints

- Association of HCT co-morbidity index and clinical outcomes

- Change from baseline in exploratory biomarker laboratory parameters (e.g., citrulline, ST2, TIM3, and CRP)
- Association of exploratory biomarkers with treatment-emergent CTCAE Grade 2 diarrhea or GI GVHD
- Number of and reasons for emergency room (A&E) visits; number of, duration, and reasons for hospital admissions; number of days spent in ICU, in isolation, or confined to bed; other infections; receipt of and duration of relevant concomitant medications and therapies; type and number of certain diagnostic or therapeutic procedures; and provision of home healthcare through Week 16
- Association between immune reconstitution and viral response and clinical outcome (e.g., based on measurement and activity of AdV-specific cytotoxic T lymphocytes [CTLs] and other immune reconstitution parameters)

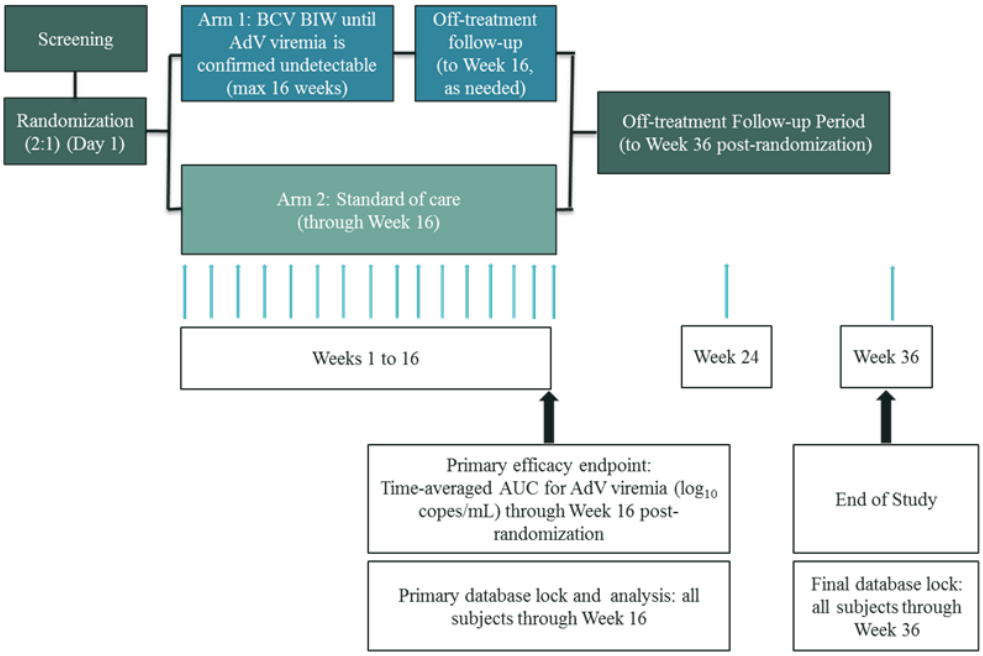
6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a randomized, open-label, multi-center study of the safety, overall tolerability, and antiviral activity of BCV, as compared with SoC, in pediatric recipients of a high-risk (i.e., T cell-depleted) allogeneic (i.e., non-autologous) HCT. Pediatric patients with AdV detected in plasma within the previous 21 days and for the first time since their qualifying transplant may be screened for participation in the study. Approximately 141 subjects who meet all applicable entry criteria will be randomized in a 2:1 ratio to receive either BCV or SoC. The day of randomization is defined as Day 1. Subjects randomized to receive BCV will be treated until AdV DNA is confirmed to be undetectable in plasma, up to a maximum of 16 weeks post-randomization. During randomization, subjects will be stratified based on the following variables: last (non-baseline) screening AdV viremia (≥ 10,000 copies/mL vs. < 10,000 copies/mL), time from transplant to randomization (≥ 28 days vs. < 28 days), and T cell-depletion methodology (receipt of alemtuzumab or ex vivo depletion vs. receipt of ATG). Subjects randomized to the SoC arm will be managed according to local or institutional practice guidelines for the treatment of AdV infection. All subjects, regardless of treatment assignment, will be followed in the study for a total of 36 weeks post-randomization. Subjects will be assessed on a weekly basis through Week 16, with additional assessments performed at Weeks 24 and 36 post-randomization. The data collected through Week 16 will comprise the primary data set for the study; hence, the primary database will be locked and analyzed following capture of data for all subjects through Week 16.

A schema of the overall study design is provided in Figure 9.

Figure 9: Study Design Schema for CMX001-999



Abbreviations: AUC = area under curve; BCV = brincidofovir; BIW = twice weekly.

6.2. Schedule of Assessments/Procedures

Subjects will be assessed at weekly intervals through the 16-week treatment period, with additional assessments performed at 24 and 36 weeks post-randomization as follows:

- Assessments scheduled for Weeks 1, 2, 3, 4, 6, 8, 12, and 16 must be completed in the hospital or clinic (i.e., subjects who are being treated on an outpatient basis must return to the hospital/clinic).
- For all other assessments (i.e., Weeks 5, 7, 9, 10, 11, 13, 14, 15, 24, and 36):
  - If a subject has detectable AdV in plasma, the subject will be required to return to the hospital or clinic to complete these assessments until such time as the subject achieves confirmed undetectable AdV viremia.
  - Thereafter, every effort should be made to have a subject return to the hospital or clinic for these assessments. However, if return visits to the hospital or clinic are not practical (e.g., because the subject has returned to his or her home region), these visits may be performed through a home healthcare service provider or at a third-party facility that has been pre-approved by the sponsor (for the collection of samples including blood draws for safety and/or virologic analysis). Telephone contact between the investigator and the subject or the subject's caregiver (to assess AEs, AdV symptoms, etc.) will need to occur in parallel.
  - If an approved home healthcare services provider or an approved third-party facility capable of performing the required procedures is not available, then all assessments must be performed at the hospital or clinic.

Subjects who interrupt or discontinue BCV (for any reason) will remain on the same schedule of assessments/procedures through completion of the final study assessment at Week 36. Subjects randomized to the SoC arm will follow the same schedule of assessments/procedures through Week 36 as subjects randomized to BCV with the exception of BCV dosing and PK sample collections.

Unless otherwise specified, all study-required laboratory assessments will be performed at the designated central laboratories.

The time schedule described for weekly assessments should be followed as closely as possible. Allowable time windows are ± 2 days for the weekly assessments through Week 16, ± 7 days for the Week 24 assessment, and + 14 days for the Week 36 follow-up assessment.

A schedule of study assessments/procedures is provided in Table 5.

6.3. Number of Subjects

Approximately 141 pediatric subjects will be randomized between the two treatment arms in a 2:1 ratio to receive either BCV or SoC.

Table 5: Schedule of Study Assessments/Procedures

Assessment/Procedure	Screening[a]	Baseline[b]	Treatment Period[c]																Follow-up[c]	
Study Week	**-3 to -1**	**0**	**1**	**2**	**3**	**4**	**5***	**6**	**7***	**8**	**9***	**10***	**11***	**12**	**13***	**14***	**15***	**16**	**24***	**36***
Planned Study Day	**-21 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**169**	**253**
Written informed consent[d]	X																			
Assess/review entry criteria	X	X																		
Assess/review medical history	X	X																		
Physical examination[e]	X	X				X				X				X				X		
HCT comorbidity[f]		X																		
PELOD score[g]		X	<---------- X ---------->																	
Urine pregnancy test[h]	X	X				X				X				X				X		
HIV, HBV, HCV tests[i]	X																			
Randomization		X																		
BCV[j]			<---------- X ---------->																	
SoC[k]			<---------- X ---------->																	
Height/length		X																		
Body weight[l]	X	X		X																
Plasma for real-time AdV and CMV[m] and storage for other virologic assessments[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine, stool and respiratory secretion sample for AdV assessment[o]		X				X		X		X				X				X		
Stool collection for storage (possible future virologic analyses)[p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Assess clinical signs and symptoms for AdV disease	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessment/Procedure	Screening[a]	Baseline[b]	Treatment Period[c]																Follow-up[c]	
Study Week	**-3 to -1**	**0**	**1**	**2**	**3**	**4**	**5***	**6**	**7***	**8**	**9***	**10***	**11***	**12**	**13***	**14***	**15***	**16**	**24***	**36***
Planned Study Day	**-21 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**169**	**253**
Clinical chemistry and hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lymphocyte (CD4+/CD8+) subsets and other potential immunologic predictors of virologic response		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X				X				X				X				X		
Diarrhea symptoms assessment and review subject e-diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Perform drug accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Clinical AE assessment[q]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review and record all concurrent medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Record hospitalizations/procedures		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PK sample collection[r]		X		X																
Blood for exploratory biomarkers		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Enrollment in BCV Registry[s]																		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 randomization on Day 1.

[b] All Baseline/Day 1 study procedures (other than post-dose PK samples) should be evaluated or obtained prior to randomization.

[c] Visits marked with an asterisk (*) may be performed by a home healthcare provider or at a third party facility (where available) for subjects who are outpatients and who have achieved confirmed undetectable AdV viremia.

[d] Written consent (or assent) must be obtained from the subject and the subject's legal guardian as required by national or local law and institutional practice.

[e] A complete examination will be performed as part of the screening evaluation. An abbreviated (symptom-driven) examination, targeted to new signs and symptoms, will be performed prior to randomization on Day 1 (baseline) and at Weeks 4, 8, 12, and 16.

[f] HCT comorbidities present at baseline will be scored using the HCT comorbidity index assessment; see Appendix 6 for scoring table.

[g] PELOD score will be captured at baseline and as a maximum (aggregate) score over the 16-week treatment period; see Appendix 7 for scoring table.

[h] For females of child-bearing potential only (or as required by local practice). Testing will be performed locally as a urine dipstick (or as required by local practice). A positive result must be confirmed with a local serum test. BCV dosing must not initiate or continue in subjects with a positive pregnancy test.

[i] Tests for HBV, HCV, and/or HIV will be performed at screening if there are no results within prior 6 months evident in patient record.

[j] Subjects randomized to receive BCV will be treated until AdV DNA in plasma is confirmed to be undetectable (two consecutive plasma viral load results of "undetectable" as reported by the designated central virology laboratory), or up to a maximum of 16 weeks post-randomization, whichever occurs first. After a subject's first AdV plasma viral load result is reported as "undetectable" by the designated central virology laboratory, a confirmatory blood sample must be drawn no sooner than 7 days (6 full calendar days and no later than 14 days (13 full calendar days) after the first sample was drawn. Once AdV viremia is confirmed as undetectable, BCV will be discontinued.

[k] Subjects randomized to the SoC arm will be managed according to local or institutional practices and any relevant product labelling. The decisions regarding SoC, including administration of therapy, dose and regimen of therapy, modification of immunosuppression, and monitoring will be the responsibility of the clinical team according to institutional guidelines, local practices, and applicable treatment guidelines for the management of AdV infection.

[l] The lowest weight within 30 days prior to Day 1 will be used to calculate dosing weight for BCV suspension.

[m] Blood will be collected during screening, on Day 1 (before randomization), and at each subsequent assessment during treatment and follow-up and sent to the designated central virology laboratory for real-time analysis of AdV and CMV viremia in plasma. (Note: The plasma collected on Day 1 [baseline] will also be analyzed for BKV viremia.) Subjects will be qualified for the study virologically after recording two consecutive AdV viremia results from the designated central virology laboratory of ≥ 1000 copies/mL and rising, with the second (confirmatory) result drawn at least 48 hours after the first sample and no more than 7 days prior to Day 1. Subjects may have multiple samples sent as screening samples, but will need to have two consecutive samples drawn at least 48 hours apart with AdV viremia ≥ 1000 copies/mL and rising as reported by the central virology laboratory to be eligible for randomization.

[n] Material remaining after processing and viral quantification (i.e., plasma and/or extracted DNA) will be stored for possible future virologic/immunologic analyses (e.g., additional AdV or other dsDNA virus viral load analyses, analyses for other viruses, viral genotypic and/or phenotypic assessments, markers of AdV or other virus-specific immunity).

[o] Additional samples will be collected at (1) the time that AdV viremia is confirmed as undetectable (i.e., when the confirmatory plasma sample is drawn); (2) if BCV is re-initiated after the recurrence of AdV viremia ≥ 1000 copies/mL (with the samples collected prior to re-initiation of BCV), or (3) at any time, on the basis of signs or symptoms suggestive of AdV disease. Based on the clinical status of the subject, in consultation with the Chimerix Medical Monitor (or designee), investigators may request real time analysis of some or all non-plasma specimens for AdV viral load.

[p] While subjects are inpatient and, where practicable, once subjects are outpatient, stool samples will be collected on Day 1 (before randomization) and each subsequent assessment during treatment and follow-up and stored for possible future virologic analyses (e.g., additional AdV or other dsDNA virus viral load analyses, analyses for other viruses, viral genotypic and/or phenotypic assessments).

[q] AEs will be recorded from the time of administration of the first dose of BCV or, for subjects randomized to SoC, from the date of randomization, until the subject has completed the Week 16 assessment or premature discontinuation from the study. In addition, any study procedure-related AE that occurs after study participants have signed the informed consent form and prior to administration of the first dose of BCV (or randomization to SoC) will be recorded as an AE for the purposes of this protocol. After the Week 16 assessment, until completion of the Week 36 assessment, only SAEs will be reported to Chimerix Safety (or designee).

[r] PK samples for analysis of plasma BCV concentrations will be drawn from subjects randomized to the BCV arm and only while they remain on therapy. Samples will be analyzed for both BCV and cyclosporine for subjects receiving concurrent cyclosporine. No PK samples will be drawn from subjects randomized to the SoC arm.

[s] Subjects will be encouraged to additionally participate in the Chimerix CMX001 Registry (Chimerix Study CMX001-333) to assess the longer-term impact of BCV administration on malignancy and survival. While participation in the Registry is encouraged, subjects will not be required to participate in order to participate in the CMX001-999 study.

6.4. Treatment Assignment

Subjects who meet all eligibility criteria will be randomized in a 2:1 ratio to BCV or SoC according to the randomization code through an automated interactive voice or web response system (IV/WRS).

- Arm 1: BCV until plasma AdV viremia is confirmed undetectable, up to a maximum of 16 weeks. BCV suspension will be dosed at 2 mg/kg, up to a maximum of 100 mg, BIW, or, for subjects taking concurrent cyclosporine, at 1.4 mg/kg, up to a maximum of 70 mg. Details of the dosing algorithm are in Section 8.3.
- Arm 2: Local or institutional SoC.

BCV and any SoC regimens will be administered open-label. The first dose of BCV should be administered as soon as possible following randomization and must be administered no more than 24 hours after randomization.

All subjects, regardless of treatment assignment, will be followed for a period of 36 weeks post-randomization.

6.5. End of Study and Study Completion

Study subjects will be considered to have completed the study after completion of the Week 36 assessment.

6.6. Enrollment in Chimerix BCV Registry (Study CMX001-333)

All subjects (both BCV and SoC recipients) will be encouraged to additionally participate in the Chimerix BCV Registry (Chimerix Study CMX001-333) to assess the longer-term impact of BCV administration on malignancy and survival. The BCV Registry assesses vital status and other outcomes over a 10-year period (at 6-month intervals for the first 3 years and annually thereafter). While participation in the BCV Registry is encouraged, subjects will not be required to enroll in the Registry in order to participate in the current study. As allowed by study center practice, subjects will be asked to consider enrollment in the BCV Registry following completion of the Week 16 assessment.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

All screening procedures do not need to be completed on the same day, but all screening procedures must be completed and the results reviewed and approved prior to randomizing a subject.

Subjects who are within 100 days of the qualifying transplant may be eligible to participate in the study. The screening window for this study is 21 days from first detection of AdV in plasma by the local virology laboratory. Subjects will be qualified for the study virologically after recording two consecutive AdV viremia results from the designated central virology laboratory of ≥ 1000 copies/mL and rising, with the second (confirmatory) result drawn at least 48 hours after the first sample and no more than 7 days prior to Day 1. (Day 1 in the study is defined as the day of randomization.) In addition, the sample for serum biochemistry testing by the designated central safety laboratory must be drawn no more than 7 days prior to Day 1. Exclusionary laboratory results may be retested (including repeating AdV viremia until two consecutive qualifying results are obtained); exclusionary serum biochemistry results (ALT, AST, or total bilirubin) may be retested once. Retest results must be available within the relevant screening window to be considered for eligibility, e.g., the second qualifying AdV viremia result must be collected within the maximum 21-day window.

It is the investigator's responsibility to use clinical judgment and consult appropriate treatment guidelines to confirm the suitability of enrolling each subject into a study assessing an orally administered investigational agent with consideration to the likelihood that subjects can complete all study assessments through Week 36.

Subject eligibility must be assessed based on results from the designated central laboratories. Any local laboratory results must be confirmed by the relevant central laboratory prior to randomization.

Eligibility for each potential study subject must be reviewed and approved by the Chimerix Medical Monitor (or designee) prior to randomization. See details for this procedure in the SRM.

7.1. Subject Inclusion Criteria

Subject must meet all of the following criteria, as applicable, to be eligible for participation in this study:

1. Aged at least 2 months and less than 18-years-old on Day 1
2. Have received a T cell-depleted allogeneic (i.e., non-autologous) HCT within the previous 100 days, where "T cell-depleted" describes EITHER:
   - ex vivo T cell depletion via positive selection (e.g., CD34+ cell) or negative selection (e.g., T cell receptor α/β or CD3+ cell removal by column filtration), OR
   - serotherapy with ATG (cumulative dose of ≥ 3 mg/kg rabbit-derived ATG or ≥ 50 mg/kg of equine-derived ATG) administered within 10 days prior to transplant or at any time post-transplant and prior to Day 1 OR
   - serotherapy with alemtuzumab administered within 30 days prior to transplant or at any time post-transplant and prior to Day 1

3. First detectable AdV DNA plasma viremia since the qualifying transplant occurred within 21 days prior to Day 1
4. AdV DNA plasma viremia ≥ 1000 copies/mL and rising, defined as two consecutive results ≥ 1000 copies/mL from the designated central virology laboratory, with the second result being greater than the first. The second sample must be drawn at least 48 hours after the first sample and no more than 7 days prior to Day 1
5. If male of reproductive potential, willing to use an acceptable contraceptive method(s) throughout the duration of his participation in the study and until 90 days following last dose of BCV when engaging in sexual intercourse with a female partner of childbearing potential
6. If female of child-bearing potential (i.e., post menarche and not surgically sterilized), willing to use two acceptable contraceptive methods, one of which must be a barrier method, throughout the duration of her participation in the study and until 90 days following last dose of BCV when engaging in sexual intercourse with a non-sterile male
7. Able to provide written informed consent or assent, with legal guardian consent, as required by applicable local or national law and institutional practice, based on the age of the subject
8. Available to participate in all required study activities for the entire duration of the study (i.e., inclusive of the Week 36 assessment)

7.2. Subject Exclusion Criteria

Subjects who meet *any* of the following criteria, as applicable, are not eligible to participate in this study. Retesting of exclusionary laboratory results (through the designated central laboratory) is permitted.

[Note: The CTCAE grading scales for diarrhea (Table 7) and the NIH staging scales for acute GVHD (Appendix 1) will be used to determine eligibility into this study. Current stool output or volume, as appropriate, should be compared with each subject's pre-transplant stool output or volume (= baseline). Contact the Chimerix Medical Monitor (or designee) for eligibility questions where baseline stool output or volume is unknown or the subject's clinical condition warrants consideration of an alternative baseline measure.]

1. Any CTCAE Grade 4 diarrhea (i.e., life-threatening consequences with urgent intervention indicated) within 7 days prior to Day 1
2. Any CTCAE Grade 2 or 3 diarrhea (i.e., increase of ≥ 4 stools per day over baseline), unless attributed to AdV, within 7 days prior to Day 1
3. NIH Stage 4 acute GVHD of the skin (i.e., generalized erythroderma with bullous formation) within 7 days prior to Day 1
4. NIH Stage 2 or higher acute GVHD of the liver (i.e., bilirubin > 3 mg/dL [SI: > 51 μmol/L]) within 7 days prior to Day 1
5. NIH Stage 2 or higher acute GVHD of the gut (i.e., diarrhea > 556 mL/m^2/day, or severe abdominal pain with or without ileus) within 7 days prior to Day 1

6. Active malignancy (with the exception of non-melanoma skin cancer), including relapse or progression of the underlying disease for which qualifying transplant was performed
7. Use of vasopressors within 7 days prior to Day 1
8. PT-INR > 2x upper limit of normal reference range (ULN) in the absence of anticoagulation within 7 days prior to Day 1
9. Requirement for mechanical ventilation within 7 days prior to Day 1, or sustained oxygen delivery for > 24 hours within 7 days prior to Day 1, or any oxygen requirement within 48 hours prior to Day 1
10. Estimated creatinine clearance < 30 mL/min or use of renal replacement therapy (e.g., hemodialysis, continuous renal replacement therapy, peritoneal dialysis) within 7 days prior to Day 1
11. ALT > 5x ULN, AST > 5x ULN, or total bilirubin > 3 mg/dL [SI: > 51 µmol/L] within 7 days prior to Day 1
12. Evidence of active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection within 6 months prior to Day 1, as demonstrated by detectable HBV DNA or HCV ribonucleic acid (RNA) in blood, plasma, or serum. [Note: A negative or undetectable HBV DNA or HCV RNA test is required at screening to confirm the absence of active infection unless testing was performed by the local laboratory within 6 months prior to screening.]
13. Human immunodeficiency virus (HIV) infection as detected through any laboratory method (e.g., enzyme-linked immunosorbent assay, Western Blot, RNA PCR). [Note: Testing to confirm the absence of HIV infection is required at screening unless testing was performed by the local laboratory within 6 months prior to screening.]
14. Females who are pregnant or breastfeeding or planning to become pregnant within 90 days after their last anticipated dose of BCV
15. Receiving or anticipated to receive medications prohibited in this protocol (see Section 8.6.1)
16. Hypersensitivity (not including renal dysfunction or eye disorder) to CDV or to BCV or its formulation excipients
17. Receipt of IV CDV within 48 hours prior to Day 1
18. Previous receipt of BCV at any time
19. Participation in another interventional clinical trial unless prior approval has been received from the Chimerix Medical Monitor (or designee) (see Section 8.6.1.3)
20. Received any cell-based anti-AdV therapy within 6 weeks prior to Day 1 or previously received an anti-AdV vaccine at any time

7.3. Subject Withdrawal Criteria

Subjects randomized to receive BCV must be managed according to the toxicity management criteria described in Section 8.3.2. Subjects randomized to the SoC arm will be managed according to local or institutional practice guidelines and any relevant product labelling.

Subjects randomized to BCV who experience any of the following criteria after initiating treatment in this study will be required to discontinue BCV, but will continue to be followed in the study:

- Subject request to discontinue for any reason
- TEAE that necessitates the discontinuation of BCV as described in Section 8.3.2
- If the investigator or the subject's primary care provider believes that participation in the study is no longer in the best interests of the subject
- Pregnancy in a female subject

  Female subjects who become pregnant will be immediately discontinued from BCV, but will continue to be followed in the study. See Section 11.9.5 for actions to take and reporting requirements for pregnancy. Pregnancies in female subjects randomized to the SoC arm must be reported according to local guidelines and relevant product labelling.
- Discontinuation of the study at the request of Chimerix, a regulatory agency, or the governing institutional review board, research ethics board, or independent ethics committee (collectively referred to as "ethics committee" [EC])

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

- Development of an exclusionary condition, including a decrease in eGFR to < 15 mL/min considered related to BCV, or unrelated to BCV but not being dialyzed; see Section 8.3.2.6
- Treatment with, or requirement for treatment with, a prohibited or excluded medication; see Section 8.6.1.1
- Subject is not compliant with the protocol (i.e., significant protocol deviation)

All subjects who are randomized will be followed in the study through completion of the Week 36 assessment, including subjects who discontinue BCV for any reason and subjects who are randomized but not dosed in either arm. 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 Section 6.2).

Subjects who are randomized and who do not complete the study will not be replaced.

8. TREATMENT OF SUBJECTS

8.1. Administration of Standard of Care

Subjects randomized to the SoC arm in this study will be managed according to local or institutional practice guidelines and any relevant product labelling. The decisions regarding SoC, including administration of therapy, dose and regimen of therapy, modification of immunosuppression, and monitoring will be the responsibility of the clinical team according to institutional guidelines, local practices, and applicable treatment guidelines for the management of AdV infection. Investigators will need to consider the clinical status of the subjects and the local availability of treatment options.

8.2. BCV Administration

Subjects randomized to the BCV treatment arm will receive BCV administered orally as 10 mg/mL suspension.

Subjects will receive a BCV dosage regimen based on their lowest body weight within 30 days prior to Day 1 (to best represent dry weight) and their concurrent cyclosporine use (Table 6).

Table 6: BCV Dosage Regimens for Study CMX001-999

	Initial BCV Dose Regimen	Consolidated BCV Dose Regimen
Cyclosporine	1.4 mg/kg (up to maximum 70 mg) BIW	2.8 mg/kg (up to maximum 140 mg) QW
No cyclosporine	2 mg/kg (up to maximum 100 mg) BIW	4 mg/kg (up to maximum 200 mg) QW

Note: Dosing weight = lowest body weight (in kilograms) within 30 days prior to Day 1.
Abbreviations: BIW = twice weekly; QW = once weekly

As described in Section 8.6, co-administration of BCV and cyclosporine has been shown to increase plasma BCV exposure. Therefore, subjects taking cyclosporine on Day 1 or who initiate cyclosporine at any time while taking BCV will receive a modified dose of BCV of 1.4 mg/kg, up to a maximum of 70 mg, BIW. Subjects who discontinue cyclosporine while taking BCV should increase the BCV dose to 2 mg/kg, up to a maximum of 100 mg, starting with the next scheduled BCV dose following the discontinuation of cyclosporine.

Each BCV dose should be administered using an oral dosing syringe. A 5-mL dosing syringe is recommended for BCV doses ≤ 50 mg, and a 10-mL dosing syringe is recommended for BCV doses > 50 mg. [Note: The study drug kits DO NOT include oral dosing syringes.]

Referring to Section 8.3.2, subjects who resume BCV therapy after a mandated interruption due to a TEAE will resume therapy at a consolidated QW dose of 4 mg/kg (up to a maximum of 200 mg) QW for subjects not receiving concurrent cyclosporine, or 2.8 mg/kg (up to a maximum of 140 mg) QW for subjects receiving concurrent cyclosporine (Table 6).

The dose (volume of BCV oral suspension to be administered) should be determined using the dosing tables provided in Appendix 2 (see Table 14 for BCV dosing of subjects receiving concurrent cyclosporine and Table 15 for BCV dosing of subjects not receiving concurrent cyclosporine).

See Section 9 for detailed description of appropriate storage and management of BCV.

Whenever possible, the BCV doses should be given with food (with or within 30 minutes of finishing a meal) to potentially improve tolerability.

Subjects who are unable to take medicines orally may be dosed through a nasogastric tube, gastrostomy tube, or other feeding tube that allows the dose to be delivered directly into the subject's stomach or duodenum followed by a flush. Intrajejunal delivery is not advised as PK and tolerability data are not available for this route of administration.

Subjects should take BCV doses on the same day(s) each week. BIW dosing will alternate at 3- and 4-day intervals (e.g., each Monday and Thursday, or each Tuesday and Friday). Subjects who have switched to QW dosing for toxicity management should take BCV on the same day each week (e.g., each Monday, or each Tuesday).

8.2.1. Missed Doses of BCV

When a dose of BCV is missed, subjects should take the missed dose as soon as possible, and no later than 2 days prior to the next scheduled dose (i.e., either the next day if the originally scheduled next dose is in 3 days, or within the next 2 days if the originally scheduled next dose is in 4 days).

A subject who normally takes his/her BIW BCV doses on Mondays and Thursdays each week may take a missed Monday dose on Tuesday and a missed Thursday dose on Friday or Saturday.

A subject taking his/her QW BCV doses every Monday should take their missed dose as soon as possible, but may take a missed dose as late as Thursday, which allows 4 days between the late dose and the next scheduled Monday dose.

If the subject cannot take the late dose within these timeframes, it should be omitted and the subject should wait until the next scheduled dosing day to take his/her next dose. The original dosing schedule should be resumed following any missed or omitted doses.

It is important to capture the actual dates and times of all BCV doses and whether each dose was taken with food in the electronic case report form (eCRF), even if the actual dates and times deviate from scheduled. E-dairies will be provided to the subjects to facilitate the collection of this information when outpatient.

8.2.2. Vomiting After Dosing

If a subject vomits within 30 minutes of receiving a dose of BCV, the subject may be re-dosed, as described in the pharmacy manual. If the vomiting occurs more than 30 minutes after dosing, it should be assumed that there was significant absorption of BCV, in which case, the subject should not be re-dosed.

8.3. BCV Dosing Algorithm and Management

In this study, BCV will be dosed using a response-driven approach to the duration of treatment based on both viral response and the emergence of BCV-related toxicity. BCV therapy will be continued until the virus is cleared from the plasma, unless toxicity stopping criteria are met. Investigators will be specifically trained on the management of BCV toxicity.

8.3.1. BCV Dosing Algorithm Based on Virologic Response

The duration of BCV treatment will be determined using results from the designated central virology laboratory only.

In the absence of toxicity requiring dose interruption, BCV will be administered BIW for up to 16 weeks or until plasma AdV viremia is confirmed as undetectable (i.e., two consecutive plasma viral load results of "undetectable" as reported by the designated central virology laboratory). The confirmatory sample must be drawn no sooner than 7 days (6 full calendar days) and no later than 14 days (13 full calendar days) after the last sample was drawn. Once AdV viremia is confirmed as undetectable, BCV will be discontinued. If AdV viremia is subsequently confirmed at ≥ 1000 copies/mL by the designated central virology laboratory, BCV dosing may be re-initiated, unless precluded by the BCV toxicity guidelines (see Section 8.4). See Appendix 3 for a flow chart of the BCV dosing algorithm.

8.3.2. Safety Monitoring, Management, and Criteria for BCV Dose Adjustment

Subjects with signs or symptoms suggestive of BCV-related toxicity must be managed according to the guidelines described in this section. See Appendix 4 for a flow chart for BCV toxicity management.

Investigators should pay particular attention to GI signs and symptoms when questioning subjects about adverse reactions at every study visit. In particular, when a decrease in serum albumin of ≥ 0.4 g/dL (SI: ≥ 4 g/L) to < 3.0 g/dL (SI: < 30 g/L) (suggestive of protein losing enteropathy) is noted, investigators should intensify their questioning of subjects with respect to symptoms of diarrhea (recognizing that albumin loss does not discriminate between GI GVHD and BCV-associated diarrhea) and remind subjects to record daily diarrhea symptoms in the e-diary.

All AEs should be graded in accordance with the protocol-defined scale (CTCAE scale); management of GI-related AEs and hepatobiliary laboratory abnormalities and BCV dosing guidelines are based on CTCAE severity/intensity grading, as described below. The CTCAE severity grading for diarrhea, which is defined as "characterized by frequent and watery bowel movements," is summarized in Table 7.

Table 7: CTCAE Grading Scale for Diarrhea

Grade	Definition:
Grade 1	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline
Grade 3	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADLs[a]
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Results in death

[a] Self-care ADLs (activities of daily living) refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note: Pre-transplant stool output (= baseline).

Educational and risk minimization materials will be used in this study to highlight the potential for BCV-related diarrhea in subjects who are randomized to receive BCV. For example, a reference card summarizing the management of diarrhea may be left in the subject's bedside notes to serve as a reminder to the physicians and nurses caring for the patient to inquire about diarrheal symptoms. Also, the subject or the subject's caregiver may be given a patient alert card describing the potential for BCV-related GI problems and the actions they should take if the subject experiences diarrhea while taking BCV. Examples of the reference and patient alert cards are provided in the SRM.

Please contact the Chimerix Medical Monitor (or designee) for questions related to toxicity management.

8.3.2.1. Treatment-emergent Grade 1 GI-related AEs

Dosing with BCV may continue, while closely monitoring the subject for worsening of the AE(s).

Symptomatic care may be provided as needed (e.g., anti-emetics, anti-diarrheals). Hydration status should be closely monitored, and liquid and electrolyte intake should be encouraged, if appropriate, to avoid dehydration and the downstream consequences of dehydration on renal function.

Additionally:

- Nutritional advice should be given to avoid foods and drinks that affect intestinal water transport (e.g., caffeine, alcohol, carminative spices, and concentrated sugar syrups) as well as lactose- and sucrose-containing drinks because intestinal inflammation may result in down-regulation of intestinal disaccharidases
- Consideration should be given to adjusting medications associated with GI effects (e.g., macrolide antibiotics, magnesium sulfate salts and mycophenolate mofetil [MMF])
- Other causes of new GI symptoms should be investigated promptly and treated as appropriate (e.g., infections)

For treatment-emergent 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). GI biopsy results, if endoscopy and biopsy are performed, may not differentiate GVHD from BCV-related toxicity because GI biopsies from subjects with BCV GI toxicity may show findings (such as crypt apoptotic bodies) that are also observed in biopsies from subjects with GVHD. If the subject is experiencing GVHD symptoms in other organ systems (e.g., skin or liver), biopsy specimens from those sites may be more informative.

In the absence of extra-intestinal involvement, starting or increasing steroids and/or other immunosuppressants for the treatment of GVHD should be delayed if medically feasible for Grade 1 diarrhea.

If steroid treatment of GVHD cannot be delayed (and BCV is continued) in subjects with Grade 1 symptoms, the subject's response to GVHD therapy should be closely monitored.

- If diarrhea persists for > 14 days at Grade 1, the complete subject profile should be reviewed, other etiologies for diarrhea considered, and if deemed appropriate, interruption of BCV should be considered in order to determine whether diarrhea resolves.

If diarrhea worsens to Grade 2 or higher, please see Section 8.3.2.2 below.

8.3.2.2. Treatment-emergent Grade 2 or Higher AEs of Diarrhea in Subjects with ≤ Grade 1 Diarrhea at Baseline

For subjects with CTCAE Grade 1 diarrhea or no diarrhea at baseline, BCV must be interrupted for treatment-emergent CTCAE Grade 2 or higher diarrhea. This includes new-onset Grade 2 or higher diarrhea or progression from Grade 1 to Grade 2 or higher diarrhea, regardless of the cause of the diarrhea.

In general, changing multiple therapies at the same time (e.g., interrupting BCV and starting steroids for new-onset or worsening GI GVHD) is not recommended. In order to assess response to BCV treatment interruption, start of (or increase in) steroid therapy for new-onset or worsening GI GVHD should be delayed, when possible.

- If diarrhea does not improve following ≥ 7 days interruption (at least 6 calendar days off BCV), a trial of steroid therapy for new-onset or worsening GI GVHD (while BCV is still being held) may be considered if deemed clinically appropriate.

If diarrhea does not improve to ≤ CTCAE Grade 1 during interruption, BCV must not be resumed.

If diarrhea improves to ≤ CTCAE Grade 1 in intensity, subjects may resume dosing of BCV, but no sooner than 7 days (i.e., at least 6 full days off drug) following the last BCV dose administration.

- If resumed, BCV must be administered in a consolidated QW dose (total weekly dose administered once weekly, i.e., 4 mg/kg, up to a maximum of 200 mg, QW in the absence of concurrent cyclosporine, or 2.8 mg/kg, up to a maximum of 140 mg, QW for subjects taking concurrent cyclosporine) to potentially improve tolerability, as weekly dosing intervals allow more time for GI mucosal regeneration between doses.

Treatment with the consolidated QW BCV dose will be continued through Week 16 post-randomization or until confirmed undetectable AdV viremia in plasma, whichever occurs first.

Recurrence of CTCAE Grade 2 or higher diarrhea after restarting BCV requires permanent discontinuation of BCV.

8.3.2.3. Treatment-emergent Diarrhea AEs in Subjects with Grade 2 or 3 Diarrhea Attributed to AdV at Baseline

For subjects with CTCAE Grade 2 or 3 diarrhea at baseline that is attributed to AdV**,** BCV dosing must be interrupted if:

- the diarrhea has not improved to ≤ CTCAE Grade 1 after 21 days of therapy, or

- the subject experiences on-treatment worsening of one CTCAE grade or more at any time following initiation of BCV (i.e., Grade 2 worsens to ≥ Grade 3, or Grade 3 worsens to ≥ Grade 4), regardless of the cause of the diarrhea

If the diarrhea does not improve during interruption, BCV must not be resumed.

If diarrhea improves to ≤ Grade 1 in intensity during interruption, subjects may resume dosing, but no sooner than 7 days (i.e., at least 6 full days off drug) following the last BCV dose administration.

- If resumed, BCV must be administered in a consolidated QW dose (total weekly dose administered once weekly, i.e., 4 mg/kg, up to a maximum of 200 mg, QW in the absence of concurrent cyclosporine, or 2.8 mg/kg, up to a maximum of 140 mg, QW for subjects taking concurrent cyclosporine) to potentially improve tolerability, as weekly dosing intervals allow more time for GI mucosal regeneration between doses.

Recurrence of CTCAE Grade 2 or higher diarrhea after restarting BCV requires permanent discontinuation of BCV.

See Table 8 and Table 9 for tabular summaries of the interruption and discontinuation thresholds for managing BCV in the setting of treatment-emergent diarrhea and recommendations for the management/evaluation of treatment-emergent GI AEs during BCV therapy.

Table 8: BCV Interruption and Discontinuation Thresholds for Treatment-emergent Diarrhea

Action Taken with BCV	≤ Grade 1 Diarrhea at Baseline	AdV-related Grade 2 Diarrhea at Baseline	AdV-related Grade 3 Diarrhea at Baseline
Temporary interruption	• Interrupt if diarrhea worsens to ≥ Grade 2 • Consider interruption for Grade 1 diarrhea if persists for > 14 days, and starting treatment for acute GVHD	• Interrupt if diarrhea not ≤ Grade 1 within 21 days of first dose of BCV • Interrupt if diarrhea worsens to ≥ Grade 3 at any time	• Interrupt if diarrhea not ≤ Grade 1 within 21 days of first dose of BCV • Interrupt if diarrhea worsens to ≥ Grade 4 at any time
Resumption	• May resume if diarrhea improves to ≤ Grade 1, and after a minimum 7-day interruption (i.e., at least 6 full days off BCV) • Must resume at 4 mg/kg (max 200 mg) QW or 2.8 mg/kg (max 140 mg) QW with concurrent cyclosporine administration		
Permanent discontinuation	• Permanently discontinue BCV if, following resumption of dosing, diarrhea ≥ Grade 2 returns		

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 (ADLs)
Grade 4: Life-threatening consequences; urgent intervention indicated
Note: Action taken with BCV is regardless of the etiology of diarrhea.
Note: Pre-transplant stool output (= baseline).

Table 9: Recommended Management/Evaluation of Treatment-emergent GI Adverse Events during BCV Therapy

	Grade 1 Events	Grade 2 or Higher Events
Action with BCV	See Table 8 and Section 8.3.2	
Other interventions	• Avoid food/drinks that affect water transport (e.g., caffeine, alcohol, carminative spices, concentrated sugar syrups) • Avoid lactose- and sucrose-containing products • Adjust other medications associated with GI effects (e.g., macrolides, magnesium, MMF) • Symptomatic treatment dosed as needed (e.g., anti-emetics, anti-diarrheals) • Avoid starting steroid/immunosuppressants for GVHD (while dosing BCV) unless Grade 1 diarrhea persists for > 14 days	• Same as for Grade 1 events • Interrupt other medications that may cause GI events (e.g., magnesium supplements, MMF) • Measure levels of immunosuppressants • Consider symptomatic treatment (e.g., anti-emetics, anti-diarrheals) dosed at regular intervals, if clinically appropriate • Fluid supplementation to maintain hydration
Other diagnostic evaluations	• Monitor hydration status, and supplement as needed • Evaluate for other infection • Evaluate for acute GVHD in other organ systems; consider non-GI biopsy	• Same as for Grade 1 events

NOTE: When considering new-onset or worsening GI GVHD as the cause of GI symptoms:

- **Co-administration of BCV and steroids for GI GVHD is not recommended**
- In order to assess response to BCV treatment interruption, start of (or increase in) **steroid therapy for GI GVHD should be delayed, when possible**

If diarrhea does not improve following ≥ 7 days interruption (i.e., at least 6 full days off BCV), a trial of steroid therapy for new or worsening GI GVHD (while BCV is still being held) may be considered, if deemed clinically appropriate.

8.3.2.4. Grade 2 or Higher Non-diarrheal GI AEs

For CTCAE Grade 2 or higher non-diarrheal GI AEs (e.g., nausea, vomiting, abdominal pain) measures described in Section 8.3.2.1 for Grade 1 events should be considered, including anti-emetic medications for nausea and vomiting, if clinically appropriate. In addition, investigators should remain vigilant to worsening of symptoms over time and interrupt BCV if non-diarrheal GI AEs reach Grade 3 in intensity.

For one or more Grade 3 or higher non-diarrheal GI events, BCV dosing must be interrupted.

If non-diarrheal GI AE(s) improve to ≤ Grade 2 in intensity, subjects who have interrupted BCV may resume dosing, but no sooner than 7 days (i.e., at least 6 full days off drug) following the last BCV dose administration.

- If resumed, BCV must be administered in a consolidated QW dose (total weekly dose administered once weekly, i.e., 4 mg/kg QW up to a maximum of 200 mg QW in the absence of concurrent cyclosporine or 2.8 mg/kg up to a maximum of 140 mg QW for

subjects taking concurrent cyclosporine) to potentially improve tolerability, as weekly dosing intervals allow more time for GI mucosal regeneration between doses.

If non-diarrheal GI AE(s) do not improve during interruption, BCV must not be resumed.

In the event of recurrence of CTCAE Grade 3 or higher non-diarrheal GI AEs after restarting BCV, BCV may be allowed to continue only after discussion and agreement with the Chimerix Medical Monitor (or designee).

8.3.2.5. Elevations in Serum Aminotransferases

Treatment with BCV must be interrupted for at least 7 days (i.e., at least 6 full days off drug) if any of the following confirmed abnormalities occur:

1. ALT or AST > 8x ULN and ≥ 2x baseline value
2. ALT or AST > 5x ULN and ≥ 2x baseline value for more than 2 weeks
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%)
5. Total bilirubin > 3 mg/dL and ≥ 2x baseline value

Abnormal laboratory values should be confirmed at the central laboratory as soon as feasible. Both initial and confirmatory values should be central laboratory values, however, if waiting for central laboratory confirmation is not deemed clinically appropriate, a sample can be drawn in parallel for local laboratory analysis, and if necessary, BCV may be interrupted pending further investigation of the laboratory abnormalities.

If confirmed, increases in serum aminotransferases, as described above, should result in immediate interruption of BCV dosing. The investigations to be undertaken should include, but are not limited to: imaging, testing for hepatotropic infections, evaluations for GVHD, review of other concomitant medication, and possibly liver biopsy, as appropriate. Potential lactic acidosis should also be ruled out. For subjects on azoles, interruption of dosing with azoles should be considered if criterion 2 above is the only one met (i.e., there is no bilirubin elevation).

If an alternate reason for the laboratory abnormalities is identified and after the abnormalities decrease by ≥ 1 CTCAE grade below the grade that triggered BCV interruption listed above, dosing with BCV may resume, however, BCV should be administered as a consolidated weekly dose (i.e., 4 mg/kg, up to a maximum of 200 mg, QW in the absence of concurrent cyclosporine, or 2.8 mg/kg, up to a maximum of 140 mg, QW for subjects taking concurrent cyclosporine).

Generally, subjects with persistent and significant ALT or AST elevations (> 5x ULN) should not resume administration of BCV unless there is clear evidence of a causal association with a viral disease being treated. In these cases, continued treatment with BCV may be allowed after discussion and agreement with the Chimerix Medical Monitor (or designee).

Recurrence of the liver abnormalities after reintroduction of BCV requires permanent discontinuation of BCV.

8.3.2.6. Decrease in Estimated Glomerular Filtration Rate to < 15 mL/min

To be eligible for this study, subjects must have an estimated creatinine clearance of ≥ 30 mL/min and must not have received renal replacement therapy (e.g., hemodialysis, continuous renal replacement therapy, or peritoneal dialysis) within 7 days prior to Day 1. In cases where the eGFR of a subject receiving BCV therapy decreases to < 15 mL/min, the benefit:risk proposition of continuing treatment with BCV must be re-evaluated for the subject, because even with dialysis there remains a risk of increased CDV exposure. Given the lack of alternative therapy for treatment of AdV in the setting of end-stage renal disease, continuation of BCV in a subject receiving dialysis may be considered after consultation with the Chimerix Medical Monitor and/or designee.

8.4. Re-initiation of BCV Dosing for AdV Viremia

Subjects who stop BCV therapy due to confirmed undetectable AdV viremia may re-initiate treatment with BCV if AdV viremia is subsequently confirmed at ≥ 1000 copies/mL by the designated central virology laboratory. For the purposes of re-initiating BCV therapy, "confirmed viremia ≥ 1000 copies/mL" is defined as two consecutive results ≥ 1000 copies/mL from the designated central laboratory, with the second sample drawn at least 48 hours after the first sample. BCV dosing will be resumed at the same dose and dose frequency the subject was receiving when BCV therapy was stopped (e.g., if BCV dosing had been consolidated to QW administration for toxicity management purposes, the subject would resume at the QW dose). Subjects should be managed as per the toxicity monitoring and management criteria as outlined in Section 8.3.2.

Subjects who permanently discontinue BCV for toxicity reasons are not eligible to re-initiate BCV dosing.

8.5. Access to BCV after Week 16

Subjects randomized to the BCV arm may receive up to 16 weeks of therapy with BCV (through Week 16 post-randomization). Treatment with BCV may not be extended past Week 16 under this protocol. Therefore, investigators wishing to extend or re-initiate treatment with BCV for a subject after Week 16 will need to request access to the drug through the local NPP (or other expanded access program), where available. If applicable, approval for access to BCV through the NPP should be secured prior to the subject completing the Week 16 assessment to ensure continuity of care.

Subjects randomized to the SoC arm are not allowed to receive BCV during the 16-week treatment period, whether under this protocol or through an expanded access mechanism. After completion of the Week 16 assessment, investigators may request access to BCV through the local NPP (or other expanded access program), where available.

8.6. Concomitant Medications

All concomitant medication use (with the exception of IV fluids, vitamins, and nutritional or electrolyte supplements other than oral magnesium) will be captured through Week 16.

BCV was a direct in vitro inhibitor of cytochrome (CYP)3A, 2B6 and 2C8 (IC_{50} 5 to 17 μM); and CYP1A2, 2C9, 2C19, and 2D6 (IC_{50} 22 to 28 μM) in human liver microsomes.

No significant induction of CYP enzymes 1A2, 2B6, and 3A by BCV was observed after incubation with freshly isolated and cultured human hepatocytes. Inhibition of the drug transporters P-glycoprotein (P-gp, IC_{50} 20 μM), breast cancer resistance protein (IC_{50} 11 μM), and OATP1B1 (IC_{50} 21 μM) by BCV was observed in vitro.

BCV is not an inhibitor of either CYP3A or P-gp in vivo. Co-administration of oral BCV 200 mg with IV and oral midazolam, a sensitive CYP3A substrate, did not alter plasma midazolam PK. Co-administration of oral BCV 200 mg with oral dabigatran etexilate 150 mg, a sensitive P-gp substrate, did not increase plasma total dabigatran exposure. Therefore, BCV is not expected to alter concentrations of other compounds metabolized by CYP enzymes or other compounds transported by P-gp.

BCV was not a substrate for P-gp or breast cancer resistance protein; however, BCV was a substrate for OATP1B1 and OATP1B3.

Cyclosporine

Co-administration of cyclosporine (a potent OATP inhibitor) increased plasma BCV exposure. Based on population PK analysis, plasma BCV exposure (AUC_{ss}) is increased by approximately 43% when cyclosporine is co-administered. The magnitude of PK interaction identified in a drug-drug interaction study (CMX001-120) conducted in healthy volunteers (average 4.74-fold increase in plasma BCV AUC_{inf}) was greater than estimated in virally-infected patients enrolled in BCV clinical studies based on a Population PK analysis. To adjust for the PK interaction observed in patients, subjects receiving concurrent cyclosporine in this study will receive a lower BCV dose (Table 6).

Analyses conducted with data from subjects enrolled in five clinical studies showed that the co-administration of cyclosporine and unadjusted BCV increased the odds of elevations of total bilirubin ≥ Grade 2 and of moving to a higher hepatobiliary AE level (levels were "no AE," "non-serious/< Grade 3," and "serious/≥ Grade 3"). BCV and cyclosporine had independent, not synergistic, effects on total bilirubin and hepatobiliary AEs in a safety exposure-response analysis.

Due to the overlap of BCV and cyclosporine safety profiles, subjects receiving BCV and cyclosporine should be closely monitored for hepatobiliary AEs and laboratory abnormalities, as specified in Section 8.3.2. Other immunosuppressant therapies (e.g., tacrolimus) should be considered, if clinically appropriate.

8.6.1. Prohibited Medications

8.6.1.1. Prohibited Medications for Subjects Randomized to Receive BCV

The following medications are prohibited while subjects are receiving treatment with BCV.

Cidofovir (Vistide)

As CDV and BCV deliver the same active antiviral (CDV-PP), these two medications must not be administered concurrently. Subjects who are receiving IV CDV at randomization and who are randomized to the BCV arm should wait at least 48 hours after administration of the last CDV dose (dose-to-dose) before initiating treatment with BCV.

Ketoconazole (non-topical formulations) and Sesamin-containing Products

In vitro experiments have shown that BCV is a substrate of CYP4F2. No clinical drug-drug interaction studies have been completed with CYP4F2 inhibitors to-date; however, given the in vitro data, co-administration of BCV with the potent CYP4F2 inhibitor ketoconazole (non-topical formulations) and sesamin-containing products is contraindicated.

No interaction is expected with other azole antifungals, including voriconazole, fluconazole, or posaconazole, based on in vitro data demonstrating that these drugs do not inhibit CYP4F2 at relevant physiologic concentrations, providing therapeutic alternatives to treatment with ketoconazole.

8.6.1.2. Prohibited Medications for Subjects Randomized to Receive SoC

As described in Section 8.5, subjects randomized to SoC will not be allowed to receive treatment with BCV until after completion of the Week 16 assessment.

8.6.1.3. Co-enrollment in Other Studies

Co-enrollment of subjects in other interventional clinical studies involving the administration of an investigational drug(s) (i.e., a drug or drugs not approved by the appropriate regulatory authority for any indication) is not permitted while enrolled in the current study (including the post-treatment follow-up period).

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

Generally, co-enrollment in other studies involving conditioning regimens or graft manipulation in HCT recipients will be allowed as long as the study intervention and endpoint exclude impact on AdV infection. In particular, for pediatric subjects, enrollment in multiple studies should take into consideration the blood volumes required for participation in the studies.

8.7. Treatment Compliance

While subjects are inpatients, BCV should be administered under the supervision of site personnel. Once subjects are scheduled to be discharged from the hospital, the subjects and/or their caregivers must receive careful instructions on continued BCV dosing prior to discharge. Subjects and their caregivers 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. If preferred, investigators may require some or all outpatient doses to be administered under supervision. Subjects and their caregivers will be required to bring the bottles of BCV (even if empty) back to the clinic at each assessment during the treatment period, so site personnel can complete drug accountability.

8.7.1. Subject Electronic Diary

All subjects will be provided with software and/or devices equipped with an e-diary for collection of study information. Subjects or caregivers will record daily diarrhea symptoms and may record the dates and times of doses of BCV and whether each dose was taken with food (for

subjects randomized to the BCV treatment arm) in the e-diary through Week 16 (see Section 11.6). While subjects are inpatients, the information may be entered in the e-diary by study staff.

8.8. Randomization and Blinding

All treatments will be administered under open-label conditions.

Subjects who meet all applicable eligibility criteria will be randomized to one of two treatment arms (BCV or SoC) in a 2:1 ratio using an automated IV/WRS. During randomization, subjects will be stratified based on the following variables:

- last (non-baseline) screening AdV viremia (≥ 10,000 copies/mL vs. < 10,000 copies/mL)
- time from transplant to randomization (≥ 28 days vs. < 28 days), and
- T cell-depletion methodology (receipt of alemtuzumab or ex vivo depletion vs. receipt of ATG)

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

BCV will be administered orally as 10 mg/mL oral suspension (Table 10).

Table 10: Investigational Product

Product Name:	Brincidofovir Oral Suspension 10 mg/mL
Product Code:	CMX001-P-SUS-HPI-001
Dosage Form:	Oral suspension
Unit Dose:	10 mg/mL
Route of Administration:	Per os (oral)
Physical Description:	An opaque-white to yellowish suspension in a round, amber bottle
Manufacturer:	Halo Pharma, Inc. 30 North Jefferson Road Whippany, New Jersey 07981, USA
Clinical Labelling and Shipment to Clinical Sites:	PCI Pharma Services Biotec House, Central Park Western Avenue Bridgend CF31 3RT, UK
	Xerimis, Inc. 102 Executive Drive, Suite 8 Moorestown, New Jersey 08057, USA

Standard of care, including CDV and other anti-AdV medications, will be administered according to local institutional practice.

9.2. Study Drug Packaging and Labelling

BCV 10 mg/mL oral suspension formulation is supplied as an amber polyethylene terephthalate bottle with a child-resistant closure with press-in bottle adaptor insert. The suspension formulation is supplied in a kit containing one bottle with a 55 mL-fill volume.

At the start of treatment, each subject randomized to BCV will be dispensed one kit according to the randomization number assigned to that subject by the IV/WRS. Additional kits will be dispensed by the IV/WRS at future visits as additional study drug is needed.

The kits of BCV 10 mg/mL oral suspension will be shipped to the study centers from a depot using a traceable courier service. Each kit of BCV suspension will be labelled in accordance with applicable regulatory requirements and will include the following minimum information:

- Chimerix protocol number (CMX001-999)
- Sponsor name and address
- Name of study drug and strength
- Contents

- Lot number
- Subject number line
- Kit identification number
- Storage conditions
- Expiry date (if applicable)
- Route of administration
- Applicable caution statement according to in-country requirements

Label information will be translated into approved in-country languages, as applicable.

9.3. 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°C to 25°C (59°F to 77°F), with excursions permitted to 30°C (86°F), and protected from freezing.

9.4. 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), 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 bottle (even if empty) and e-diary to each study visit so site personnel can conduct drug accountability. Subjects will be instructed not to dispose of the bottle once empty. All study drug records must be maintained at the site and copies must be submitted to Chimerix at the end of the study.

9.5. 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 pharmacy manual and/or any applicable site-specific standard operating procedures. If necessary, unused study drug supplies may also be returned to the appropriate depot with prior approval from Chimerix (or its 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.

10. ASSESSMENT OF EFFICACY

It is recognized that the volume of blood required for all protocol assessments may be constrained due to clinical or ethical considerations, e.g., taking into account subject age, weight, and overall clinical condition. Consult the SRM for guidance on managing and prioritizing samples. Consult the Chimerix Medical Monitor (or designee) with any questions or to discuss specific issues for a subject.

10.1. Virologic Evaluations and Sample Collection

Blood (plasma), urine, stool, and respiratory secretions, and other samples/specimens for virologic evaluations will be collected at screening, on Day 1 (before randomization), and at periodic intervals throughout the treatment and post-treatment periods of the study as follows:

- Blood will be collected during screening, on Day 1 (before randomization), and at each subsequent assessment for real-time analysis of AdV viremia in plasma at the designated central virology laboratory. These samples will also be analyzed in real time for CMV viremia. The Day 1 (baseline) samples will also be analyzed for BKV viremia. The testing for BKV viremia will not be performed in real-time and the results will not be reported to the sites.
- Urine, stool (where available), and respiratory secretions (nasopharyngeal swab and bronchoalveolar lavage, if appropriate, based on symptoms) will be collected from all subjects on Day 1 (before randomization) and at Weeks 4, 6, 8, 12, and 16. Samples will also be collected from subjects: (1) at the same time that AdV viremia is confirmed as undetectable (i.e., at the time the confirmatory plasma sample is drawn), or (2) if BCV is re-initiated after the recurrence of AdV viremia ≥ 1000 copies/mL (with the samples collected prior to re-initiation of BCV), as applicable. Samples may also be collected at any time on the basis of signs or symptoms suggestive of AdV disease. Based on the clinical status of the subject, in consultation with the Chimerix Medical Monitor (or designee), investigators may request real time analysis of some or all non-plasma specimens for AdV viral load.
- While subjects are inpatient and, where practicable, once subjects are outpatient, stool samples will be collected on Day 1 (before randomization) and each subsequent assessment during treatment and follow-up and stored for possible virologic analyses (e.g., additional AdV or other dsDNA virus viral load analyses, analyses for other viruses, viral genotypic and/or phenotypic assessments).
- Collected samples (blood/plasma, urine, respiratory secretions, and stool) and/or remaining extracted DNA will be stored for possible future virologic/immunologic analyses (e.g., additional AdV or other dsDNA viral load analyses, viral typing, retrospective analyses for other viruses, longitudinal viral genotypic and/or phenotypic assessments, markers of AdV- and other virus specific immunity). See Section 10.1.3 for details of AdV-specific resistance testing.

Detailed instructions for the collection, processing, storage, and shipping of samples for virologic analysis to the designated central virology laboratory are provided in the laboratory manual.

Samples and viral DNA extracted may be stored for a period of up to 10 years after study completion. Stored samples will not be used for any other purposes than virologic/immunologic testing for AdV and/or other viruses of interest, and/or additional testing to measure concentrations of BCV and its metabolites. 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 review and approval by a central EC, as applicable.

10.1.1. Quantitative Assessment of AdV and Other dsDNA Viremia

Currently, there is no FDA-approved assay for quantitative determination of AdV viremia in plasma. For this study, AdV viremia in plasma and other samples, as applicable, will be determined by the designated central virology laboratories using the 7500 Adenovirus Quantitative Real-time (PCR) Test (Viracor Eurofins Clinical Diagnostics). The stated range of quantitation in human plasma is 190 to 1 x 10^{10} copies/mL. The lower limit of detection (LLOD) is 127 copies/mL. Thus, AdV titers from 127 to 189 copies/mL are defined as detectable, but below the lower limit of quantification (LLOQ).

CMV viremia in plasma will be determined by the designated central laboratories using the FDA-approved and Conformité Européene-marked COBAS® AmpliPrep/COBAS® TaqMan® CMV Test (Roche Molecular Systems, Inc.). The stated range of quantitation in human plasma is 137 to 9.1 x 10^6 IU/mL (or 150.7 to 1.0 x 10^7 copies/mL) and the LLOD is 91 IU/mL (or 100 copies/mL). Thus, CMV DNA titers from 100 to 150 copies/mL are defined as detectable, but below the LLOQ (i.e., < 151 copies/mL after rounding).

BKV viremia in plasma will be determined by the designated central laboratory using the 2500 BK Virus Quantitative Real time PCR Test (Viracor Eurofins Clinical Diagnostics). The stated range of quantitation in human plasma is 39 to 1 x 10^{10} copies/mL and the LLOD is 26 copies/mL. Thus, BKV titers from 26 to 39 copies/mL are defined as detectable, but below the LLOQ.

10.1.2. Virologic Assessment at Local Laboratories

If and when samples are collected for AdV DNA testing in a local virology laboratory, including any unscheduled AdV assessments performed per local SoC, samples should be collected and sent to the designated central virology laboratory for analysis in parallel. Results from local laboratories may not be used to determine subject eligibility nor to make protocol-defined treatment decisions. Results from local laboratories will not be used for data analysis.

If local practice allows, samples should be sent to the designated central virology laboratory as priority over local laboratories to keep the blood draw volume for study participants as low as possible.

10.1.3. Adenovirus Hexon Sequencing (Typing) and Resistance Analysis

Currently, there is no approved assay for AdV typing, resistance phenotyping, or genotyping of AdV DNA polymerase. AdV viral typing and resistance analyses will be performed by the Chimerix Virology Laboratory (Durham, North Carolina) using assays developed in-house. Historically, the Adenoviridae family has been subdivided into seven serotypes (A to G) based on antibody neutralization assays. However, virus neutralization assays are suboptimal because of the lack of a full panel of hyper immune sera against every known serotype and the

requirement for the successful propagation of virus in cell culture. Chimerix has adopted a method to determine AdV type using DNA sequencing of the hexon gene. Because the hexon gene encodes the dominant epitopes recognized by neutralizing antibodies it is recognized as the preferred major identifier of AdV type and has the advantage of being amenable to standard amplification and sequencing methods (Aoki 2011).

Stored blood (plasma) samples, or extracted DNA, will be used for AdV typing by PCR amplification and sequencing of the variable region of the hexon gene. Determination of baseline genotype will be carried out by PCR amplification and sequencing of the AdV DNA polymerase gene. The emergence of potential antiviral resistance in subjects who are virologic failures will be determined by genotyping the AdV polymerase gene from subjects where: (1) confirmed recurrence of AdV viremia ≥ 1000 copies/mL is noted subsequent to viral clearance; (2) confirmed increase in plasma AdV DNA by ≥ 1 $\log_{10}$ copies/mL after experiencing a ≥ 1 $\log_{10}$ copies/mL decrease from baseline, and (3) non-responders and/or subjects with detectable plasma AdV DNA at the last on-treatment measurement. Stored samples may also be used for AdV viremia/viral load assessments; additional resistance analyses based on newly available assays, including phenotyping for resistance and deep sequencing; and for retrospective analyses of other dsDNA virus viremia/viral loads.

10.2. Assessment of Clinical Efficacy

Subjects will be monitored for clinical signs and symptoms of AdV disease at every visit throughout the study. Investigators will be prompted to enter symptom information into the eCRF at each visit. Definitions and criteria for assessing probable and definitive AdV disease are summarized below and in Appendix 5.

AdV Infection:

- AdV infection defined as positive AdV test, regardless of the biological specimen analyzed
- Systemic AdV infection or viremia is defined as positive AdV PCR, virus isolation, or antigen detection in peripheral blood

AdV Disease:

- Probable AdV disease is defined as AdV infection plus symptoms and signs attributed to AdV without histological confirmation
- Definitive AdV disease is defined as AdV infection plus symptoms and signs attributed to AdV with histological confirmation

Disseminated AdV Disease defined as:

- AdV disease (probable or definitive) in one or more organ systems with AdV viremia
- AdV disease (probable or definitive) in two or more organ systems without AdV viremia

10.3. Healthcare Resource Utilization

The clinical impact of treatment with BCV, as compared with SoC, on healthcare resource utilization will be assessed by number of and reasons for emergency room (A&E) visits; number of, duration, and reasons for hospital admissions (i.e., initial and subsequent hospitalizations); number of days spent in ICU; number of days spent in isolation; number of days confined to bed; other infections; receipt of and duration of relevant concomitant medications and therapies (e.g., transfusions, receipt of hematopoietic growth factors, anti-infective medications, and calcineurin inhibitors and other immunosuppressive medications of interest); type and number of certain diagnostic or therapeutic procedures (e.g., invasive GI procedures, such as endoscopies, biopsies, renal dialysis, mechanical ventilation, bladder irrigations); and provision of home healthcare (other than home healthcare services provided through this protocol to facilitate sample collection for subjects who are outpatients) through Week 16.

10.4. Pharmacokinetic Assessments

Blood samples for analysis of plasma concentrations of BCV will be drawn from all subjects randomized to BCV (i.e., PK samples will not be drawn from subjects randomized to the SoC arm).

10.4.1. Blood PK Sample Collection and Analysis

Blood samples for plasma BCV PK analysis will be collected from all subjects randomized to BCV on Day 1 and Week 2 (where blood volume loss limits allow). The Week 2 PK samples will only be collected if the subject receives a BCV dose in Week 2, i.e., subjects who have permanently discontinued BCV by Week 2 or have their therapy interrupted due to toxicity during Week 2 will not have PK samples drawn. In addition, the blood samples collected from BCV subjects who are receiving concurrent cyclosporine will be analyzed for both BCV and cyclosporine concentrations.

10.4.1.1. Day 1 and Week 2 PK Sampling

A blood sample will be collected within each of the following time windows (for a total of 5 PK samples) beginning on Day 1 and during Week 2.

- First sample: Pre-dose (within 2 hours prior to BCV dose)
- Second sample: From 1 to 2 hours after BCV dose
- Third sample: From 3 to 5 hours after BCV dose
- Fourth sample: From 8 to 12 hours after BCV dose
- Fifth sample: From 24 to 48 hours after BCV dose

If PK samples cannot be collected over the 24 to 48 hours following administration of the first BCV dose on Day 1, e.g., due to significant scheduling or resource issues, then the PK samples may be collected following administration of the second dose of BCV on Day 4.

The following information will be captured in the eCRF:

- Actual date and time of the last dose of BCV administered prior to collection of the pre-dose PK sample on Week 2 (and Day 4 if samples are not collected on Day 1)

- The actual date and time of the BCV dose administered on Day 1 and Week 2 after collection of the pre-dose PK sample
- Actual date and time that each PK sample on Day 1 and Week 2 was collected

Note: It is important to capture the actual dates and times for BCV dosing and each PK sampling, even if the actual dates and times deviate from scheduled times.

Cyclosporine: The blood samples collected on Day 1 and Week 2 from BCV subjects who are receiving concurrent cyclosporine will be analyzed for both plasma BCV and whole blood cyclosporine concentrations. The following additional information will need to be captured in the eCRF:

- Actual date and time and the actual dose of the last dose of cyclosporine administered prior to collection of the pre-dose PK sample on Day 1 (or Day 4 if samples are not collected on Day 1) and Week 2
- The actual date and time and the actual dose of each cyclosporine dose administered to the subject through Week 3

10.4.2. PK Sample Analysis

Concentrations of BCV in plasma and, where applicable, cyclosporine in whole blood will be determined using validated bioanalytical assays. Concentrations of BCV metabolites may also be determined. The PK samples will be shipped to a bioanalytical laboratory(ies) designated by Chimerix for analysis.

Detailed instructions for the collection, processing, storage and shipping of the PK samples for BCV (and, where applicable, cyclosporine analysis) will be provided in a separate document.

11. ASSESSMENT OF SAFETY

Safety monitoring procedures, including complete/targeted physical examination, vital sign measurements, the collection of blood and urine for clinical laboratory testing, and the recording of AEs, concomitant medication intake, and interventions with non-drug therapies or procedures, will be performed at screening, on Day 1 prior to randomization (to establish baseline), and at periodic intervals throughout the treatment and post-treatment periods of the study.

11.1. Demographic/Medical History

Subject demographic and baseline characteristics, including birth month and year (where allowed by local regulations), sex, race, ethnicity, medical history, and qualifying transplant information will be obtained from each subject as part of the screening evaluation.

Medication history will include:

- Pre-transplant induction/conditioning regimen
- All systemic antivirals (including CDV) and immunosuppressants (including steroids) taken from the time of HCT to Day 1
- All other medications taken within 30 days prior to Day 1

The date of first positive laboratory AdV result post-HCT (by any laboratory, in any biological matrix) will be documented for each subject as the date of diagnosis for the current episode being treated (i.e., disregarding any episodes of AdV infection prior to HCT).

Medical and medication 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/medication history, then medical records may be requested from the subject's primary care physician, if appropriate. Any conditions in the subject's medical history that are still ongoing on Day 1 should be noted.

Qualifying transplant information will include transplant date, underlying condition(s) responsible for qualifying transplant, graft source (cord blood, bone marrow, peripheral blood stem cell), type of graft received (cord blood, matched related donor, matched unrelated donor, mismatched, or haploidentical), T cell depletion method (ex vivo T cell depletion via positive or negative selection or serotherapy [ATG or alemtuzumab]), and pre-transplant induction/conditioning regimen (myeloablative or reduced intensity) with the relevant drugs/interventions specified (e.g., ATG, alemtuzumab, total body irradiation, etc.).

Methods of contraception, as applicable, should be documented in the source documentation. [Note: For the purposes of this study, acceptable forms of contraception include barrier methods of contraception (e.g., male or female condom, diaphragm), an intra-uterine device, or hormonal contraception (e.g., oral pill, implant, injection, ring, or transdermal patch).]

11.2. Height and Weight

Height (or length, as applicable) will be collected and recorded on Day 1. Body weight will be collected and recorded at the screening evaluation and on Day 1 and at Week 2 to support analysis of PK data. In addition, dosing weight (= lowest body weight measurement in the 30 days prior to Day 1) will be recorded.

11.3. Physical Examination

A complete examination will be performed as part of the screening evaluation and will include all body organ systems. (Note: A full pelvic examination for females may be omitted unless medically indicated.) An abbreviated (symptom-driven) examination, targeted to new signs and symptoms, will be performed prior to randomization on Day 1 (baseline) and at Weeks 4, 8, 12, and 16, to assess for any changes from previous status and review of those organ systems. Clinically significant abnormalities or findings that meet the definition of an AE (see Section 11.9.1) will be recorded on the AE eCRF module, and abnormalities present at screening or prior to randomization on Day 1 will be recorded as medical history. Findings that meet the definition of SAE will be recorded and reported as directed in Section 11.9.

11.4. HCT Comorbidities Assessment

HCT comorbidities present at baseline will be scored using the HCT comorbidity index assessment (Sorror 2005) (see Appendix 6 for scoring table).

11.5. PELOD Score

Each subject's PELOD score will be captured at baseline and as a maximum (aggregate) score over the 16-week treatment period; see Appendix 7 for scoring table. For each organ system, the maximum (i.e., worst-case) score over the 16-week treatment period will be used to calculate an aggregate score for the subject.

11.6. Daily Diarrhea Symptoms Assessment

Subjects or their caregivers will use an e-diary to record daily diarrhea symptoms, capturing the number and consistency of stools based on the Bristol Stool Form Scale (see Appendix 8). The e-diary will be reviewed with the subject and caregiver at each visit.

11.7. Concomitant Medications

All medications taken by subjects will be assessed and recorded in the eCRF at each study visit through Week 16, as described in Section 8.6.

11.8. Laboratory Assessments

The minimum test parameters to be evaluated are presented in Table 11.

11.8.1. Hematology and Serum Biochemistry

Blood for hematology, coagulation panel, and serum biochemistry testing will be collected as part of the screening evaluation, prior to randomization on Day 1 (baseline), and at each study visit.

Lymphocyte subset (percent and total [absolute] CD4+ and CD8+ counts) will be performed prior to randomization on Day 1 (baseline) and at each study visit. Other potential immunologic predictors of virologic response (e.g., AdV-specific CTLs) may be analyzed.

Estimated GFR will be calculated and reported by the central safety laboratory based on serum creatinine results.

11.8.2. Urinalysis

Samples for standard urinalysis will be collected as part of the screening evaluation, prior to randomization on Day 1 (baseline), and at Weeks 4, 8, 12, and 16.

Table 11: Study CMX001-999: Clinical Laboratory Evaluations

BIOCHEMISTRY PANEL Alanine aminotransferase (ALT [SGPT]) Albumin Alkaline phosphatase Aspartate aminotransferase (AST [SGOT]) Bilirubin (total and direct [conjugated]) Blood urea nitrogen (BUN) Calcium Creatine phosphokinase (CPK) Creatinine Electrolyte Panel (Na^+, K^+, Cl^-, and HCO_3 [or CO_2]) Gamma-glutamyltransferase (GGT) Globulin, total Glucose Lactate dehydrogenase (LDH) Lipase Phosphate Protein (total) Uric acid **URINALYSIS PANEL** Albumin (microalbumin) Blood* Glucose Leukocytes (leukocyte esterase)* Protein *Reflex to microscopic analysis if blood or leukocytes are present	**HAEMATOLOGY PANEL** 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+) **MISCELLANEOUS TESTS** Prothrombin time-international normalized ratio (PT-INR) Pregnancy Test HBV DNA, HCV RNA, HIV RNA[a] Samples for exploratory biomarker analysis for BCV-related toxicity (e.g., citrulline, ST2, TIM3, and CRP) Immunologic predictors of virologic response (e.g., AdV-specific CTLs)

[a] If documented results within 6 months prior to Day 1 are not available

11.8.3. Pregnancy Screen

Urine screens for pregnancy in female subjects of childbearing potential will be performed as part of the screening evaluation, prior to randomization on Day 1 (baseline), and at Weeks 4, 8, 12, and 16 (or as required by standard site practice). The central safety laboratory will provide urine pregnancy test kits for use at each site, although, if preferred, the site may use testing protocols specified by standard site practice.

11.8.4. Biomarker Analysis

Blood will be collected for exploratory biomarker analysis (e.g., citrulline, ST2, TIM3, and CRP) prior to randomization on Day 1 (baseline) and at each study visit through Week 16. Samples will be stored for future analyses.

11.9. Adverse and Serious Adverse Events

11.9.1. Definition of Adverse Event

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.

AEs will be recorded from the time of administration of the first dose of BCV or, for subjects randomized to SoC, from the date of randomization, until the subject has completed the Week 16 assessment or premature discontinuation from the study. In addition, any study procedure-related AE that occurs after study participants have signed the informed consent form (ICF) and prior to administration of the first dose of BCV (or randomization to SoC) will be recorded as an AE for the purposes of this protocol. After the Week 16 assessment, and until completion of the Week 36 assessment, only SAEs, regardless of treatment arm or relatedness, will be recorded and reported to Chimerix Safety (or designee).

Disease-specific signs and symptoms (including clinical laboratory abnormalities) that were ongoing before administration of the first dose of BCV (or randomization to SoC) should not be considered AEs unless they worsen (i.e., increase in frequency or severity by at least one CTCAE grade) after administration of the first BCV dose (or randomization to SoC). In addition, unless fatal, AEs related to AdV infection (including viremia or viral load in other body fluids/compartments) or AdV disease do not need to be reported as AEs or SAEs for the purposes of this study; these events will be captured as part of the endpoints for the study.

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

1. Medical or surgical procedures (e.g., surgery, endoscopy, transfusion); the condition that requires the procedure is the AE
2. Situations where an untoward medical occurrence had not occurred (e.g., hospitalization for elective surgery or social and/or convenience admissions)
3. Overdose of BCV or concomitant medication without any signs or symptoms, unless the subject was hospitalized for observation
4. Uncomplicated pregnancy
5. 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, whichever is later. Additionally, clinically significant abnormal laboratory values should be monitored periodically using central

laboratory results until the abnormality resolves, returns to baseline levels, or is otherwise explained.

11.9.2. Definition of Serious Adverse Event

An SAE is any AE that results in any of the following outcomes:

- Death
- Life-threatening (subject at immediate risk of death)
- Requires inpatient 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 an 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. Unless fatal, SAEs related to AdV infection or AdV disease do not need to be reported as SAEs for the purposes of this study; these events will be captured as part of the endpoints for the study.

11.9.3. 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 BCV or other anti-AdV drug, as applicable), action taken (with BCV or other anti-AdV drug as well as other action taken), seriousness, outcome (if applicable), and whether it caused the subject to discontinue BCV or other anti-AdV 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 grading scales. The CTCAE scales provide unique clinical descriptions of severity for each AE based on the following general guideline:

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

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL (see below)

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

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., electrocardiogram, 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 Section 11.9.1 or Section 11.9.2, respectively. The 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 AE, not the laboratory result (e.g., record anemia, not decreased hemoglobin as the 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 numeric 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.

11.9.4. Relationship to BCV or Other Anti-AdV Medication

An investigator who is qualified in medicine must make the determination of relationship to BCV or other anti-AdV medication for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by BCV or other anti-AdV medication. If no valid reason exists for suggesting a relationship, then the AE should be classified as "not related." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between BCV or the other anti-AdV medication and the occurrence of the AE, then the AE should be considered "related."

The relationship to BCV or other anti-AdV medication should be assessed using clinical judgment and the following definitions:

"Related": A temporal relationship exists between the AE onset and administration of BCV or other anti-AdV medication 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 BCV or other anti-AdV medication. In case of cessation or reduction of the dose, the AE may abate or resolve and reappear upon re-challenge.

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

Any medication(s), including those administered in the SoC arm, that are considered to have caused or contributed to a SAE must be recorded as suspect medication(s) on the SAE form. Additional instructions for completing the SAE form are provided in the SRM.

11.9.5. Occurrence of Pregnancy and Reporting

If a subject suspects that she is pregnant, a urine test will be performed at the site. If the urine test is positive, BCV 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 BCV, but should remain in the study and complete all remaining study assessments (with the exception of drug dosing and PK assessments), 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 BCV.

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) in female subjects and female partners of male subjects must be followed up and documented to the extent possible, even if the subject was discontinued from the study, provided appropriate consent is obtained from the pregnant subject or female partner. 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.

Additional details regarding the reporting of pregnancies is provided in the SRM.

11.9.6. Reporting Serious Adverse Events

All SAEs must be recorded from the time of administration of the first dose of BCV (or the date of randomization for subjects randomized to SoC) until completion of the Week 36 assessment. In addition, any SAE that is considered to be related to BCV and discovered by the investigator at any time after the subject has completed the study should also be reported. Study procedure-related SAE that occurs after a study participant has signed the ICF and prior to administration of the first dose of BCV (or randomization) should also be recorded as an SAE for the purposes of this protocol.

All SAEs should be reported to Chimerix Safety (or designee). The investigator should complete and forward the study-specific SAE Report Form to Chimerix Safety (or designee) according to the specific instructions provided in the SRM. **SAEs must be reported <u>within 24 hours</u> of learning of the event.** Additional follow-up information, if required or available, should be detailed on a follow-up SAE Report Form to Chimerix Safety (or designee) within 1 business day of receipt of the information, or as instructed by Chimerix Safety (or designee). Responses to SAE queries should be provided to Chimerix Safety (or designee) 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 reporting SAEs to Chimerix Safety (or designee) (including contact information) is provided in the SRM.

Chimerix (or its designee) is responsible for notifying the relevant regulatory authority(ies) of certain events. It is the investigator's responsibility to notify the relevant EC of all SAEs that occur at his or her site. Investigators and the DSMB Chair will also be notified of all unexpected, serious, drug-related events (i.e., 7- or 15-day expedited safety reports) that occur during the study. Each site is responsible for notifying its EC of these expedited safety reports, in accordance with applicable site practices.

12. 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 initially finalized as soon as possible during study enrollment with subsequent amendments clearly documenting changes to the plan throughout the study. No amendments to the SAP will be made after the database lock for the primary analysis and subsequent changes will be presented as post hoc analyses. All statistical analyses will be conducted using SAS® software, unless otherwise specified in the SAP.

12.1. Determination of Sample Size

A total of approximately 141 subjects will be enrolled into this study. Sample size calculations were based on the primary endpoint, i.e., AAUC through Week 16. Assuming the observed standard deviation of 1.03 $\log_{10}$ copies/mL in AAUC at Week 16 from a comparable subset of SoC subjects, the study has > 90% power with the currently planned sample size to demonstrate superiority of BCV vs. SoC, given that the true difference in means is > 0.6 $\log_{10}$ copies/mL (i.e., an effect size of ~ 0.58). In addition, the overall mortality at Week 16 non-inferiority comparison will have > 80% power in the event that the expected mortality for SoC is 20% to 30% and there is a true mortality advantage of 6% to 9% in favor of BCV (Feghoul 2015, Hiwarkar 2017, Mynarek 2014).

12.2. Analysis Sets

All subjects will be classified into Intent-to-Treat (ITT), modified Intent-to-Treat (mITT), Per Protocol (PP), Safety, and PK analysis sets. The following definitions will be used:

- **ITT:** The ITT analysis set will include all subjects who are randomized.
- **mITT:** The mITT analysis set will include all subjects in the ITT analysis set with AdV viremia ≥ 1000 copies/mL measured by the designated central virology laboratory in the last sample on or prior to randomization. Subjects randomized to BCV and not treated will be excluded from the mITT analysis set.
- **PP:** The PP analysis set will include all subjects in the mITT analysis set who complete the study through Week 16 (or die prior to Week 16) and do not have any major protocol deviations (defined as significant inclusion/exclusion criteria violation or noncompliance that would be expected to impact the analysis of efficacy).
- **Safety:** The safety analysis set will include all subjects who are randomized to and receive at least one dose of BCV, and all subjects who are randomized to SoC.
- **PK:** The PK analysis set will include all subjects who are randomized to and receive at least one dose of BCV, and have at least one blood sample collected for analysis of plasma BCV concentrations.
- **Safety Exposure-Response:** The safety exposure-response analysis set will include subjects who are in both the safety analysis set and the PK analysis set.
- **Efficacy Exposure-Response:** The efficacy exposure-response analysis set will include subjects who are in both the mITT analysis set and the PK analysis set.

The ITT analysis set will be used to summarize all efficacy endpoints, including the primary endpoint/analysis. The mITT and PP analysis sets will be determined prior to database lock for the primary analysis, and will be used for supportive primary efficacy analyses and possibly other selected endpoints to be defined in the SAP. All efficacy analyses will use the randomized treatment assignment. The safety analysis set will be used for all safety analyses and the PK analysis set will be used for all PK analyses.

12.3. Interim Analyses

No formal interim analyses are planned. At least two safety reviews will be conducted by the DSMB. The first safety review will be performed after the first 30 subjects enrolled have completed through Week 16 (or have died or are lost to follow-up). The second safety review will be performed after the first 60 subjects enrolled have completed through Week 16 (or have died or are lost to follow-up). In addition, safety and safety-exposure response will be monitored by the DSMB periodically, as described in Section 4.5. There are no plans to stop the study for efficacy or futility; hence, no alpha-adjustment for DSMB monitoring is made.

12.4. Efficacy Analyses

12.4.1. Primary Efficacy Endpoint

The primary AAUC analysis will utilize all randomized subjects (ITT) in an analysis of covariance (ANCOVA) with all stratification factors included in the model: T cell-depletion method (alemtuzumab or ex vivo cell selection vs. ATG), time from HCT to randomization (< 28 days vs. ≥ 28 days), and baseline AdV viremia (continuous $\log_{10}$ copies/mL). These stratification factors have been selected as those that are clearly related to time to immune reconstitution (time from HCT to confirmed AdV viremia > 1000 copies/mL and thus randomization, procedural differences in depth and duration of immune suppression by T cell-depletion method) with resulting expected differences in clearance of viremia, and/or association with mortality (peak viral load). Regarding baseline AdV viremia, subjects will be stratified at the time of randomization according to $\geq 10{,}000$ vs. $< 10{,}000$ copies/mL; however, this factor will be included in the analysis as a continuous covariate in order to improve power in determining a treatment effect. In the ANCOVA, AdV viremia values that are undetectable will be imputed at 99 copies/mL (i.e., one less than the lower limit of detection of 100 copies/mL) and values that are detected, but not quantifiable (BLQ) will be imputed at 189 copies/mL (i.e., one less than the lower limit of quantification of 190 copies/mL).

Subjects who die or are lost to follow-up (i.e., drop-outs) prior to Week 16 are accounted for inherently in the AAUC approach by truncating their follow-up period, thereby normalizing AUC over time of follow-up (Li 2012). It should be noted that subjects lost to follow-up are anticipated to be zero or negligible, and approximately 16% to 24% of subjects are expected to die by Week 16. Regardless, the primary analysis will be supplemented by a number of planned sensitivity analyses to assess the impact of subjects who die prior to Week 16 and other potential influential elements on the primary inference and to allow for a more comprehensive assessment of efficacy.

The first three approaches are proposed to account for these subjects in a typical missing data framework:

- Jump to reference imputation, where the missing part of the trajectory is imputed from the control group average (Kenward 2015).
- Multiple imputation, where the missing part of the trajectory is imputed based on a model (Rubin 1978). This imputation is repeated to create multiple simulated data sets (e.g., 5-times the number of deaths plus drop-outs). Each of these simulated data sets is analyzed independently and the results from these analyses are pooled to yield a final inference.
- Undetectable imputation, where the missing part of the trajectory is imputed as undetectable.

In addition to the above, three other supportive analyses are proposed to directly account for subjects who die prior to Week 16:

- Baseline imputation, where the missing part of the trajectory for deaths only is imputed at the baseline value for the subject.
- Analysis of time below the detection limit, whereby subjects who die are considered to be above the detection limit after death. This approach will be repeated using time below 1000 copies/mL, which is a clinically-meaningful level of viremia often signaling viral control vs. need to address in clinical practice.
- Generalized pairwise comparisons of prioritized outcomes (Buyse 2010). In this approach, all BCV subjects are compared with all SoC subjects in the same stratum. Comparisons will be made based on the following hierarchy:
  - Alive or dead at Week 16
  - If both die before Week 16, compare time to death
  - If both are alive at Week 16, compare AAUC

  Each comparison yields a favorable, unfavorable, or neutral result. The "proportion in favor of treatment" (Δ) is the net difference between the number of favorable pairs and the number of unfavorable pairs divided by the total number of pairs. The null hypothesis H_0: $\Delta=0$ is tested using a randomization test.

Another important factor that may influence the primary inference is the imputation of undetectable and BLQ AdV viremia values, with additional sensitivity analyses conducted in order to assess the potential impact of this imputation:

- Impute all undetectable/BLQ values at 1 copy/mL (i.e., 0 $\log_{10}$ c/mL)
- Impute all undetectable/BLQ values at 189 copies/mL
- Impute all values < 1000 copies/mL at 1 copy/mL

In addition, a supportive analysis of overall mortality (adjusting for advanced baseline disease, Matthes-Martin 2008) will examine the non-inferiority of BCV treatment to SoC. No negative impact on mortality will be concluded if the upper bound of the one-sided 95% confidence

interval (CI) for the absolute difference between BCV mortality and SoC mortality is < 10%. The proposed sample size will have > 80% power to demonstrate this conclusion, assuming SoC mortality in the expected range of 20% to 30% and a risk difference of 6% to 9% in favor of BCV (Feghoul 2015, Hiwarkar 2017, Mynarek 2014). In the event this supportive analysis concludes non-inferiority and the primary endpoint is met, superiority for overall mortality at Week 16 will be tested at alpha 0.05. Non-relapse mortality will be assessed in a similar fashion.

12.4.2. Secondary Efficacy Endpoints

Continuous secondary efficacy analyses will use the same method used for the primary analysis.

Dichotomous secondary efficacy analyses will be analyzed using a Cochran-Mantel-Haenszel test stratified by each of the stratification factors. Number of failures and failure rates will be presented for each treatment arm. Cochran-Mantel-Haenszel p-values, estimated common odds ratios, and corresponding approximate 95% CIs will be presented for each comparison. The Breslow-Day test will be used to test the homogeneity of the odds ratios. Missing data will be imputed as failure.

Most time-to-event analyses will be performed using Kaplan-Meier methods/plots and Cox models. P-values and hazard ratios along with their 95% CIs will be presented for each treatment comparison. Missing data will be censored, generally at the earlier of the end of study for each subject or the time point for the specific analysis.

Non-relapse mortality will be analyzed with relapse as a competing risk adjusted for baseline strata, with corresponding cumulative incidence plots, Fine-Gray models, and cause-specific and sub-distribution hazard ratios with corresponding 95% CIs.

12.5. Virology Analyses

Only data analyzed by the designated central virology laboratories will be used for any viral load analyses.

12.6. Safety Analyses

All safety analyses will be presented by randomized treatment arm using the safety analysis set. Inferential analyses will generally not be performed for safety endpoints; exceptions are defined herein or will be defined in the SAP.

12.6.1. Adverse Events

On-study AEs are those events that occur from Day 1 through Week 16. Only on-study AEs are summarized unless otherwise specified.

For the BCV arm, TEAEs are those events 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. For the SoC arm, TEAEs are those that begin on or after Day 1 and on or before 7 days after the date of the last dose of anti-AdV therapy (or Week 16 if no anti-AdV therapy was used in SoC arm.

Follow-up AEs are those that begin beyond 7 days after the last dose of study drug through Week 16.

Summaries (number and percent of subjects) of AEs by system organ class and preferred term will be provided as follows:

- TEAEs
- ≥ CTCAE Grade 3 TEAEs
- Treatment-emergent SAEs
- Treatment-related AEs
- ≥ CTCAE Grade 3 treatment-related AEs
- Treatment-related SAEs
- AEs resulting in permanent BCV or other anti-AdV drug discontinuation
- AEs requiring BCV or other anti-AdV drug interruption
- AEs requiring dose modification or consolidation of BCV or other anti-AdV drug
- On-study AEs
- ≥ CTCAE Grade 3 on-study AEs
- On-study SAEs
- Follow-up AEs
- ≥ CTCAE Grade 3 follow-up AEs
- Follow-up SAEs
- SAEs starting after Week 16
- AEs beginning after Week 16 and leading to death

12.6.2. Laboratory Results

Descriptive statistics (N, mean, standard deviation [SD], median, first and third quartiles [Q1, Q3], minimum, and maximum) will be provided for each continuous laboratory test by treatment arm. Values will be summarized at baseline, at each on-treatment time point, for the minimum and maximum on-treatment values, for the last on-treatment value, and for the last on-study value. These results will also be presented as boxplots.

Dichotomous laboratory endpoints will be descriptively analyzed using counts and percentages.

12.7. Pharmacokinetic and Exposure-Response Analyses

Plasma BCV concentrations will be listed and summarized using descriptive statistics (including N, mean, SD, percent coefficient of variation [%CV], median, minimum, and maximum). Concentrations that are BLQ will be treated as zero (0) for the purposes of descriptive statistics.

The plasma BCV concentration-time data will be included in a population PK analysis to characterize plasma BCV PK, evaluate the impact of covariates of interest, and derive individual post hoc PK exposure parameters (plasma BCV AUC and C_{max}). An existing population PK model developed with data from six previous BCV studies (CMX001-115, CMX001-201,

CMX001-301, CMX001-202, CMX001-304, and CMX001-350) will be applied. If necessary, additional modelling may be completed with data from only this study or by combining data from this study with data from previous studies. Population PK analyses will be completed in NONMEM®. A Population PK analysis plan will be written separately from the study SAP.

The post hoc plasma BCV AUC and C_{max} estimates from the population PK model will be used to characterize the potential impact of plasma BCV exposure on clinical safety, virologic, and mortality endpoints, and to evaluate the modifying influence of various covariates of interest on these relationships and endpoints. Data from this study may be analyzed alone or in combination with data from previous studies for exposure-response analyses. Exposure-response analysis may include time-to-event, logistic regression, linear regression, and/or nonlinear regression models, and analyses will be completed in R, S-plus, and/or SAS. An exposure-response analysis plan will be written separately from the study SAP.

12.8. Other Analyses

12.8.1. Subject Enrollment and Analysis Sets

The number and percent of subjects randomized in each country and by each investigator will be summarized overall and by treatment arm. 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 arm.

12.8.2. 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, AdV viral load, disease for which HCT was conducted, pre-transplant conditioning regimen, source of graft, type of graft) will be summarized by treatment arm 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 in years at the date of randomization. Summaries of demographic data and baseline characteristics will be provided for the ITT, mITT, PP, and safety analysis sets.

12.8.3. Prior and Concomitant Medications

Medications started prior to Day 1 and those taken on or after Day 1 will be summarized separately (number and percentage of subjects) by treatment arm, Anatomical Therapeutic Chemical classification second-level category, and World Health Organization generic name, using the safety analysis set.

12.8.4. Study Drug Exposure/Compliance

Duration of exposure to BCV 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 BCV 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 BIW durations

(decreasing cumulative) for the safety analysis set. Other measures of exposure/compliance may be presented as defined in the SAP.

12.8.5. Subject Disposition

A summary of subject disposition will be provided by treatment arm using the ITT analysis set. This summary will present the number and percent of subjects who:

- complete the study through Week 16
- do not complete the study through Week 16 (with summary of reasons)

12.9. Subgroup Analyses

The primary and all-cause mortality endpoints will be analyzed by various subgroups, including, but not limited to, each of the stratification factors, sex, age, race, transplant characteristics, underlying disease (malignant, non-malignant), advanced disease status, and investigator's intended SoC selected at the time of randomization. Multivariate modelling will be considered and defined in the SAP.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Quality Controls and Study Monitoring

Quality controls are incorporated into project management activities conducted by Chimerix (or its designee), including the monitoring and verification of clinical and safety data.

Each investigational site will be subject to an assessment of the adequacy of site facilities, including responsibilities as related to the study and protocol requirements.

The progress of the study will be monitored by periodic onsite visits and frequent communications between Chimerix (or designee) and the investigator. A monitor assigned to the investigational site is responsible for assessment of the progress of the study, review and verification of study data collected, and identifying and assisting in resolution of issues. The objectives of monitoring procedures are to verify that study data are accurate, authentic and complete; that the safety and rights of subjects are being protected; and, that the study is conducted in accordance with the approved protocol (including any amendments), International Conference on Harmonisation (ICH) GCP and applicable regulatory requirements.

The investigator and study staff will allocate time to the monitor as required during on-site monitoring visits. The monitor will continue to support the investigational site between monitoring visits.

13.2. Quality Assurance Audits and Regulatory Inspections

Authorized representatives of Chimerix (or its designee), a regulatory authority, or the applicable EC 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, GCP, and 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 notify Chimerix immediately if contacted by a regulatory agency intending to conduct an inspection.

14. ETHICS

14.1. Ethics Review

This protocol, the informed consent document, relevant supporting information, and all types of subject recruitment or advertisement information must be approved by the appropriate EC before the study is initiated. Any amendments to the protocol must also be approved, where necessary, by the EC prior to implementing changes in the study. Documentation of these approvals must be provided to Chimerix (or designee) prior to the initiation of the amendment.

The investigator's responsibilities regarding the EC are as follows:

- Obtain EC approval of the protocol, informed consent document, and any advertisements for subject recruitment prior to their use. Maintaining this documentation in the site's study file.
- Obtain EC approval for any protocol amendments and revisions to the informed consent document before implementing the changes. Maintaining this documentation in the study file.
- Provide the EC with any required information before or during the study.
- Submit progress reports to the EC, as required, during the conduct of the study; request re-review and approval of the study, as needed; provide copies of all EC re-approvals and relevant communication to Chimerix (or designee).
- Notify the EC within the required timeframe of all serious and unexpected AEs related to the study drug that are reported to you by Chimerix (or designee). The investigator is responsible for updating the EC on the progress of the study and of any changes made to the protocol at least once a year or at regular intervals as required. The investigator must also keep the EC informed of any AEs at the site, according to the EC policy.
- Notify the EC of protocol deviations according to the EC's policy. Maintaining this documentation in the site's study file.

14.2. 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 in the respective territory where the study is conducted.

14.3. Written Informed Consent/Assent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation in layman's terms regarding the nature of the study, along with the purpose, methods, objectives, and any potential risks or benefits.

Written assent should be obtained from minor subjects in accordance with institution practice using an assent form that summarizes the study in age-appropriate language, as approved by the EC.

The informed consent document shall also contain the subject's authorization for the use and disclosure of his/her protected health information (PHI) in connection with the study. The authorization shall include at a minimum a clear description of the following: the duration of the authorization, the subject's right of access to the PHI (or any suspension thereof during the course of the study), type of information to be used/disclosed in the study, the names or classes of parties that may use or disclose the PHI, the purpose of the use/disclosure of PHI, the extent of the subject's right to revoke the authorization, the extent to which participation in the study is conditioned on signing the authorization, and the potential for re-disclosure of PHI.

The informed consent/assent document must be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining the consent (if required by the EC) prior to conducting/obtaining any study-related assessments including the discontinuation of any medications prohibited for the study.

If the informed consent/assent document(s) is amended during the study (e.g., new safety information), the investigator must follow all applicable regulatory requirements pertaining to approval of the amended informed consent/assent document(s) by the EC prior to use. All new subjects enrolling in the study should be consented with the amended, approved informed consent/assent document(s), including ongoing subjects in treatment as directed by the EC.

The investigator must maintain the original and any amended signed and dated informed consent document(s) and/or assent form(s) as applicable. A copy of the signed informed consent document(s) or assent form(s) must be given to the subject or the subject's legally authorized representative.

15. DATA HANDLING AND RECORD-KEEPING

15.1. 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 guidelines. 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.

15.2. Inspection of Records

Chimerix (or its 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.

15.3. Retention of Records

Essential documents maintained in conduct of the study should be retained for one of the following time periods:

- At least 2 years after approval of the last marketing application,

  OR

- At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents should be retained for a longer period (e.g., 15 years or more), however, if required by applicable local or country-specific regulatory requirements or by an agreement with Chimerix. It is the responsibility of Chimerix to inform the investigator/institution as to when these documents no longer need to be retained. If it becomes necessary for Chimerix or any regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

15.4. Confidentiality

Subject names will remain confidential and will not be supplied to Chimerix 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 or its designee. All study findings will be stored in electronic databases. Subjects will give explicit permission for representatives of Chimerix or its designee, regulatory authorities, and the relevant EC 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 Health Insurance Portability and Accountability Act (HIPAA; in USA) or national data protection/privacy laws (outside of the 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.

16. PUBLICATION POLICY

It is the intention of Chimerix to publish the results of this study in their entirety within a reasonable period of time following the completion of the study. Chimerix will determine when and where data will be first disclosed.

Details of this study protocol will be posted to a publically accessible register(s) to the extent required by applicable laws and regulations prior to the first subject enrolling into the study, or as regional applicable.

All information generated from this study is the proprietary property of Chimerix. Chimerix 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 to seek patent protection of any invention contained therein.

Please refer to the separate agreement for this research for further specifics on publication.

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APPENDIX 1. ACUTE GRAFT VERSUS HOST DISEASE NIH STAGING SCALE

The following table, adapted from the Center for International Blood & Marrow Transplant Research (CIBMTR): 2100 Post-HCT Follow-up Form, Question 169 (https://www.cibmtr.org/manuals/fim/1/en/topic/f2100-q131-233), should be used for staging acute GVHD.

Table 12: NIH Staging of Acute GVHD by Extent of Organ Involvement

Stage	Extent of Organ Involvement		
	Skin[a]	**Liver (Total Bilirubin)**[b]	**Gut (Stool Output)**[c]
0	No GVHD rash	< 2 mg/dL [SI: < 34 µmol/L]	< 280 mL/m^2/day or < 10 mL/kg/day
1	Rash on < 25% BSA	2 to 3 mg/dL [SI: 34 to 51 µmol/L]	280 to 555 mL/m^2/day or 10 to 19.9 mL/kg/day or persistent nausea[d]
2	Rash on 25 to 50% BSA	> 3 to 6 mg/dL [SI: > 51 to 103 µmol/L]	556 to 833 mL/m^2/day or 20 to 30 mL/kg/day
3	Rash on > 50% BSA	> 6 to 15 mg/dL [SI: > 103 to 257 µmol/L]	> 833 mL/m^2/day or > 30 mL/kg/day
4	Generalized erythroderma with bullous formation	> 15 mg/dL [SI: > 257 µmol/L]	Severe abdominal pain with or without ileus, and/or grossly blood stool

[a] Use "Rule of Nines" (see Table 13 below) or burn chart to determine extent of rash.
[b] Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.
[c] Range given as volume of diarrhea based on body surface area (BSA) or body weight in kilograms. Downgrade one stage if an additional cause of diarrhea has been documented
[d] Persistent nausea with histologic evidence of GVHD of the stomach or duodenum.

Table 13: Percent Body Surfaces

Body Area	Percent	Total Percentage
Each arm	9%	18%
Each leg	18%	36%
Chest & Abdomen	18%	18%
Back	18%	18%
Head	9%	9%
Pubis	1%	1%

APPENDIX 2. BCV DOSING TABLES

Separate dosing tables are provided for subjects receiving BCV with concurrent cyclosporine (Table 14) and for subjects receiving BCV without concurrent cyclosporine (Table 15).

Please verify that you are using the correct table for each individual subject.

Both tables present the volume of BCV oral suspension (in mL) to be administered for BIW administration (second columns) and QW administration (fourth column) in the event that the BCV dose is consolidated in response to a treatment-emergent toxicity.

Look down the table for the appropriate weight range for your subject based on his or her lowest recorded body weight measurement (in kilograms) in the 30-day period prior to Day 1.

Note: A 5-mL dosing syringe is recommended for BCV doses ≤ 50 mg (i.e., ≤ 5 mL), and a 10-mL dosing syringe is recommended for BCV doses > 50 mg (i.e., > 5 mL).

Table 14 BCV Suspension Volume by Dosing Weight for Subjects Receiving Concurrent Cyclosporine

BCV BIW: 1.4 mg/kg dose		BCV QW: 2.8 mg/kg dose (Dose Consolidation)	
Dosing weight (kg)[a]	**BCV Suspension Volume**	**Dosing weight (kg)[a]**	**BCV Suspension Volume**
5 to 5.3	0.7 mL	5 to 5.3	1.4 mL
5.4 to 6.1	0.8 mL	5.4 to 6.1	1.6 mL
6.2 to 6.8	0.9 mL	6.2 to 6.8	1.8 mL
6.9 to 7.5	1 mL	6.9 to 7.5	2 mL
7.6 to 8.2	1.1 mL	7.6 to 8.2	2.2 mL
8.3 to 8.9	1.2 mL	8.3 to 8.9	2.4 mL
9 to 9.6	1.3 mL	9 to 9.6	2.6 mL
9.7 to 10.3	1.4 mL	9.7 to 10.3	2.8 mL
10.4 to 11.1	1.5 mL	10.4 to 11.1	3 mL
11.2 to 11.8	1.6 mL	11.2 to 11.8	3.2 mL
11.9 to 12.5	1.7 mL	11.9 to 12.5	3.4 mL
12.6 to 13.6	1.8 mL	12.6 to 13.6	3.6 mL
13.7 to 15	2 mL	13.7 to 15	4 mL
15.1 to 16.4	2.2 mL	15.1 to 16.4	4.4 mL
16.5 to 17.8	2.4 mL	16.5 to 17.8	4.8 mL
17.9 to 19.3	2.6 mL	17.9 to 19.3	5.2 mL
19.4 to 20.7	2.8 mL	19.4 to 20.7	5.6 mL
20.8 to 22.2	3 mL	20.8 to 22.2	6 mL
22.3 to 23.6	3.2 mL	22.3 to 23.6	6.4 mL
23.7 to 25	3.4 mL	23.7 to 25	6.8 mL
25.1 to 26.4	3.6 mL	25.1 to 26.4	7.2 mL
26.5 to 27.8	3.8 mL	26.5 to 27.8	7.6 mL
27.9 to 29.3	4 mL	27.9 to 29.3	8 mL
29.4 to 30.7	4.2 mL	29.4 to 30.7	8.4 mL
30.8 to 33.9	4.5 mL	30.8 to 33.9	9 mL
34 to 37.5	5 mL	34 to 37.5	10 mL
37.6 to 41.1	5.5 mL	37.6 to 41.1	11 mL
41.2 to 44.6	6 mL	41.2 to 44.6	12 mL
44.7 to 47.9	6.5 mL	44.7 to 47.9	13 mL
≥ 48	7 mL	≥ 48	14 mL

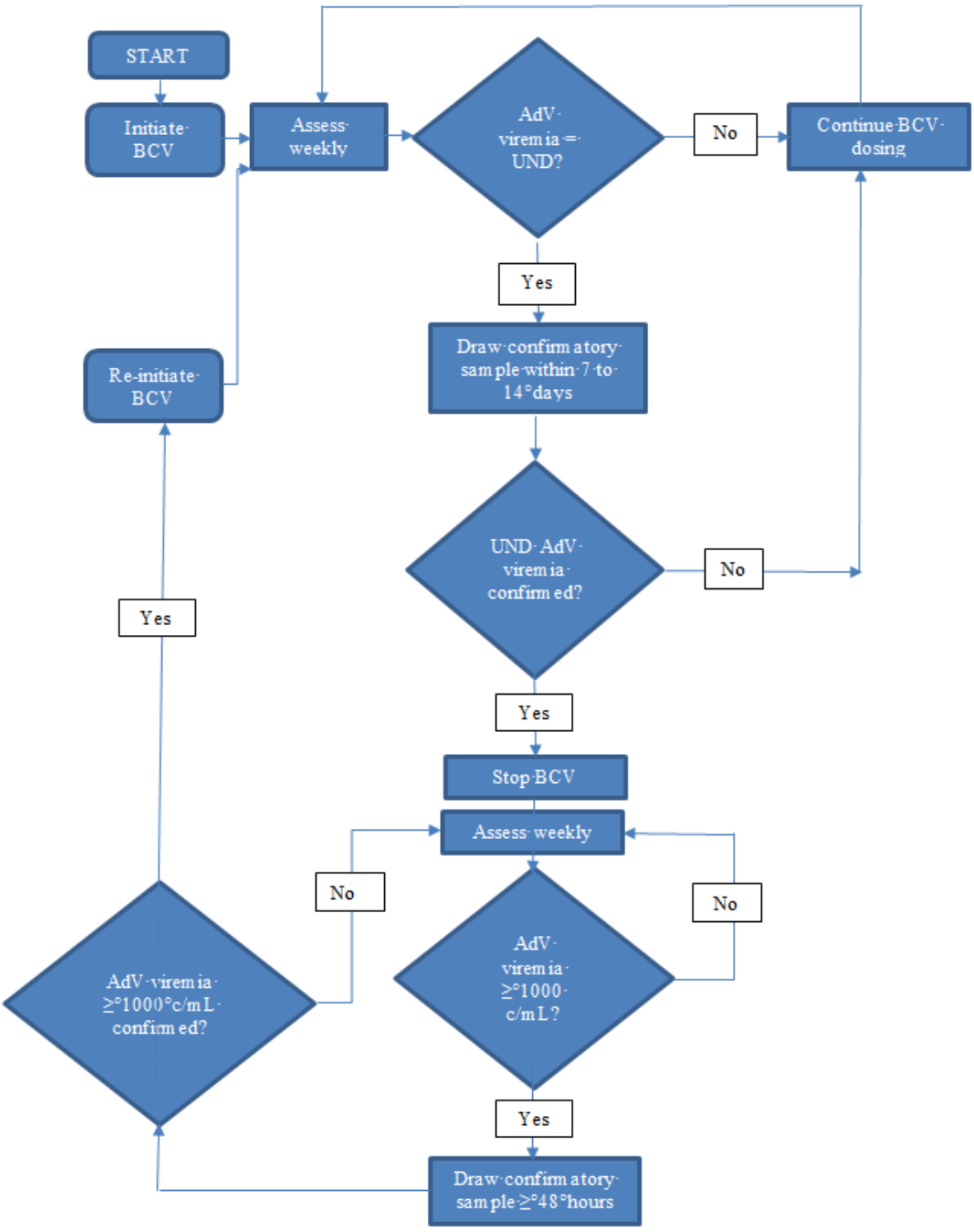
[a] Dosing weight = lowest body weight (in kilograms) within 30 days prior to Day 1.
Abbreviations: BCV = brincidofovir; BIW = twice weekly; QW = once weekly

Table 15 BCV Suspension Volume by Dosing Weight for Subjects NOT Receiving Concurrent Cyclosporine

BCV BIW: 2 mg/kg dose		BCV QW: 4 mg/kg dose (Dose Consolidation)	
Dosing weight (kg)[a]	BCV Suspension Volume	Dosing weight (kg)[a]	BCV Suspension Volume
5 to 5.2	1 mL	5 to 5.2	2 mL
5.3 to 5.7	1.1 mL	5.3 to 5.7	2.2 mL
5.8 to 6.2	1.2 mL	5.8 to 6.2	2.4 mL
6.3 to 6.7	1.3 mL	6.3 to 6.7	2.6 mL
6.8 to 7.2	1.4 mL	6.8 to 7.2	2.8 mL
7.3 to 7.7	1.5 mL	7.3 to 7.7	3 mL
7.8 to 8.2	1.6 mL	7.8 to 8.2	3.2 mL
8.3 to 8.7	1.7 mL	8.3 to 8.7	3.4 mL
8.8 to 9.5	1.8 mL	8.8 to 9.5	3.6 mL
9.6 to 10.5	2 mL	9.6 to 10.5	4 mL
10.6 to 11.5	2.2 mL	10.6 to 11.5	4.4 mL
11.6 to 12.5	2.4 mL	11.6 to 12.5	4.8 mL
12.6 to 13.5	2.6 mL	12.6 to 13.5	5.2 mL
13.6 to 14.5	2.8 mL	13.6 to 14.5	5.6 mL
14.6 to 15.5	3 mL	14.6 to 15.5	6 mL
15.6 to 16.5	3.2 mL	15.6 to 16.5	6.4 mL
16.6 to 17.5	3.4 mL	16.6 to 17.5	6.8 mL
17.6 to 18.5	3.6 mL	17.6 to 18.5	7.2 mL
18.6 to 19.5	3.8 mL	18.6 to 19.5	7.6 mL
19.6 to 20.5	4 mL	19.6 to 20.5	8 mL
20.6 to 21.5	4.2 mL	20.6 to 21.5	8.4 mL
21.6 to 23.7	4.5 mL	21.6 to 23.7	9 mL
23.8 to 26.2	5 mL	23.8 to 26.2	10 mL
26.3 to 28.7	5.5 mL	26.3 to 28.7	11 mL
28.8 to 31.2	6 mL	28.8 to 31.2	12 mL
31.3 to 33.7	6.5 mL	31.3 to 33.7	13 mL
33.8 to 36.2	7 mL	33.8 to 36.2	14 mL
36.3 to 38.7	7.5 mL	36.3 to 38.7	15 mL
38.8 to 41.2	8 mL	38.8 to 41.2	16 mL
41.3 to 43.7	8.5 mL	41.3 to 43.7	17 mL
43.8 to 46.2	9 mL	43.8 to 46.2	18 mL
46.3 to 47.9	9.5 mL	46.3 to 47.9	19 mL
≥ 48	10 mL	≥ 48	20 mL

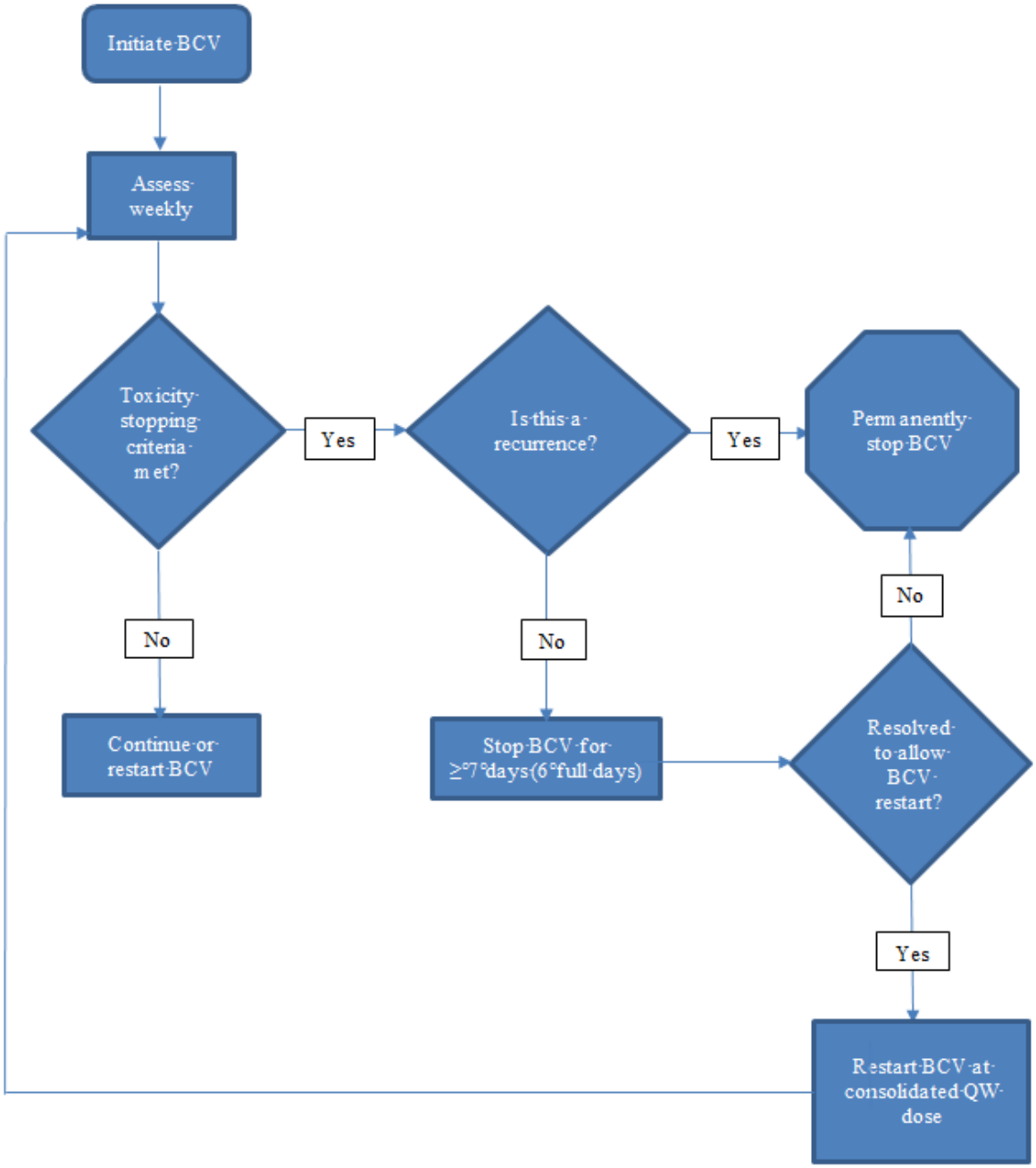
[a] Dosing weight = lowest body weight (in kilograms) within 30 days prior to Day 1.
Abbreviations: BCV = brincidofovir; BIW = twice weekly; QW = once weekly

APPENDIX 3. FLOW CHART FOR BRINCIDOFOVIR DOSING ALGORITHM



Abbreviations: AdV = adenovirus; BCV = brincidofovir; c/mL = copies per milliliter; UND = undetectable

APPENDIX 4. FLOW CHART FOR BRINCIDOFOVIR TOXICITY MANAGEMENT



Abbreviations: BCV = brincidofovir; QW = once weekly

APPENDIX 5. DEFINITIONS FOR PROBABLE OR DEFINITIVE ADENOVIRUS INFECTION OR DISEASE

Table 16: Definitions and Criteria for Probable or Definitive Adenovirus Disease

Probable	Definitive
Cardiac AdV Infection or Disease	
• AdV detected by viral blood culture, or by a positive or detectable AdV DNA PCR value in blood or plasma • AND other causes (e.g., HIV, bacterial infection) ruled out • AND at least **one** of the following suggestive signs/symptoms: – dyspnea – chest pain – peripheral edema • AND confirmation of heart enlargement or pericardial effusion by imaging	• AdV detected on cardiac or pericardium biopsy via antigen/IHC, culture, or PCR • AND at least **one** of the following suggestive signs/symptoms: – dyspnea – chest pain – peripheral edema • AND confirmation of heart enlargement or pericardial effusion by imaging
Gastrointestinal AdV Infection or Disease	
• AdV isolated from intestinal biopsy by PCR OR • AdV detected by viral culture, or by AdV DNA PCR (positive or detectable value) in both stool and blood (with plasma ≥ 1000 copies/mL) • AND other causative agents (e.g., bacterial, viral, amoebic) ruled out • AND endoscopic evidence of lesions (macroscopic or microscopic) not attributed to GVHD (i.e., biopsy-proven) • AND suggestive signs or symptoms (e.g., diarrhea, abdominal pain, ileus, vomiting, GI hemorrhage)	• AdV detected on intestinal biopsy via antigen/IHC, culture or PCR • AND EITHER: – Suggestive signs or symptoms (e.g., diarrhea, abdominal pain, ileus, vomiting, GI hemorrhage) and – Endoscopic evidence of lesions (macroscopic or microscopic) not attributed to GVHD OR • Cytopathic adenoviral aspect identified on biopsy

Table 16: Definitions and Criteria for Probable or Definitive Adenovirus Disease (Continued)

Probable	Definitive
Hepatic AdV Infection or Disease	
• AdV detected by viral blood culture, or by a plasma AdV DNA PCR ≥ 1000 copies/mL • AND other causative agents (e.g., hepatitis viruses) and causes (e.g., drug-induced, GVHD) ruled out • AND at least **one** of the following confirmed laboratory abnormalities: – ALT > 5x ULN – AST > 5x ULN – serum total bilirubin > 5x ULN	• AdV identified via hepatic biopsy via antigen/IHC or culture • AND at least **one** of the following confirmed laboratory abnormalities: – ALT > 5x ULN – AST > 5x ULN – serum total bilirubin > 5x ULN
Central Nervous System AdV Infection or Disease	
• AdV detected by viral blood culture, or by a positive or detectable AdV DNA PCR value in blood or plasma • AND other causes (e.g., bacterial, amoebic and stroke/infarct/CSF leak) ruled out • AND at least **two** of the following: – Abnormal CSF – Focal deficit – Cognitive impairment – Visual symptoms – Seizure – Evidence of lesions by CT scan or MRI	• AdV identified in CSF via antigen/IHC, culture or PCR • AND at least **one** of the following signs/symptoms of encephalitis: – Abnormal CSF – Focal deficit – Cognitive impairment – Visual symptoms – Seizure – Evidence of lesions by CT scan or MRI

Table 16: Definitions and Criteria for Probable or Definitive Adenovirus Disease (Continued)

Probable	Definitive
Renal AdV Infection or Disease	
• AdV detected by viral culture, or by AdV DNA PCR (positive or detectable value) in both urine and blood (with plasma ≥ 1000 copies/mL) • AND other causes (e.g., bacterial, drug-induced) ruled out • AND at least **one** of the following: – Suggestive signs or symptoms (impaired renal function, proteinuria, microscopic hematuria, dysuria) – Enlarged kidney on imaging – Renal/bladder obstruction	• AdV identified via renal or bladder biopsy via antigen/IHC or culture • AND at least **one** of the following: – Suggestive signs or symptoms (impaired renal function, proteinuria, microscopic hematuria, dysuria) – Enlarged kidney on imaging – Renal/bladder obstruction
Respiratory AdV Infection or Disease	
• AdV identified in nasopharyngeal secretions, sputum, BAL, or endotracheal aspirate (culture, antigen or by PCR) • AND plasma AdV DNA PCR ≥ 1000 copies/mL • AND no bacterial, fungal or other probable causative agent identified/cultured • AND **both** of the following: – Suggestive signs or symptoms (cough, tachypnea, desaturation) – CT scan or x-ray with infiltrates	• AdV identified in lung biopsy via PCR, culture, or via antigen/IHC methods • AND no bacterial, fungal or other probable causative agent identified/cultured • AND **both** of the following: – Suggestive signs or symptoms (cough, tachypnea, desaturation) – CT scan or x-ray with infiltrates

Abbreviations: AdV = adenovirus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAL = bronchoalveolar lavage; CSF = cerebrospinal fluid; CT = computed tomography; DNA = deoxyribonucleic acid; GI = gastrointestinal; GVHD = graft versus host disease; HIV = human immunodeficiency virus; IHC = immunohistochemistry; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; ULN = upper limit of normal

APPENDIX 6. HCT COMORBIDITY INDEX SCALE

The following table, adapted from Sorror et al (Sorror 2005), should be used for assessing HCT comorbidities.

Table 17: Definitions of HCT Comorbidities

HCT Comorbidity	Definition	Score
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmia	1
Cardiac	Coronary artery disease[a], congestive heart failure, myocardial infarction, or EF ≤ 50%	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemic medication, but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5x ULN, ALT > ULN to 2.5x ULN, or AST > ULN to 2.5x ULN	1
Obesity	Body mass index ≥ 35 kg/m^2	1
Infection	Requiring continuation of antimicrobial treatment after Day 0 (Day 0 = day of transplant)	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Renal, moderate to severe	Serum creatinine > 2 mg/dL (SI: 177 µmol/L), on dialysis, or prior renal transplantation	2
Pulmonary, moderate	DLco and/or FEV_1 66% to 80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's past history, excluding non-melanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Pulmonary, severe	DLco and FEV1 ≤ 65% or dyspnea at rest or requiring oxygen	3
Hepatic, moderate or severe	Liver cirrhosis, bilirubin > 1.5x ULN, ALT > 2.5x ULN, or AST > 2.5x ULN	3

[a] One or more vessel-coronary artery stenosis requiring medical treatment, stent or bypass graft.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTD = connective tissue disorder; DLco = diffusion capacity of carbon monoxide; EF = ejection fraction; FEV_1 = forced expiratory volume in the first second; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; ULN = upper limit of normal reference range.

APPENDIX 7. PELOD SCORE

The following table, reproduced from Leteurtre et al (Leteurtre 2003), should be used for calculating the PELOD score.

Table 18: PELOD Scoring System

Organ Dysfunction	Variable	Scoring System			
		0	**1**	**10**	**20**
Neurological[a]	Glasgow coma score	12 to 15	7 to 11	4 to 6	3
		AND		**OR**	
	Pupillary reactions	both reactive	NA	both fixed	NA
Cardiovascular[b]	Heart rate (beats/min)				
	< 12 years of age	≤ 195	NA	> 195	NA
	≥ 12 years	≤ 150	NA	> 150	NA
		AND		**OR**	
	Systolic blood pressure (mm Hg)				
	< 1 month of age	> 65	NA	35 to 65	< 35
	1 month to < 1 year	> 75	NA	35 to 75	< 35
	1 to < 12 years	> 85	NA	45 to 85	< 45
	≥ 12 years	> 95	NA	55 to 95	< 55
Renal	Creatinine (µmol/L)				
	< 7 days of age	< 140	NA	≥ 140	NA
	7 days to < 1 year	< 55	NA	≥ 55	NA
	1 to < 12 years	< 100	NA	≥ 100	NA
	≥ 12 years	< 140	NA	≥ 140	NA
Respiratory[c]	PaO_2 (kPa)/FIO_2 ratio	> 9.3	NA	≤ 9.3	NA
		AND		**OR**	
	$PaCO_2$ (kPa)	≤ 11.7	NA	> 11.7	NA
		AND			
	Mechanical ventilation	No	Yes	NA	NA
Hematological	White blood cell count ($x10^9$/L)	≥ 4.5	1.5 to 4.4.	< 1.5	NA
		AND	**OR**		
	Platelets ($x10^9$/L)	≥ 35	< 35	NA	NA
Hepatic	Aspartate aminotransferase (IU/L)	< 950	≥ 950	NA	NA
		AND	**OR**		
	Prothrombin time[d] (or INR)	> 60 (< 1.40)	≤ 60 (≥ 1.40)	NA	NA

[a] Glasgow coma score: use lowest value. If patient is sedated, record estimated Glasgow coma score before sedation. Assess patient only with known or suspected acute central nervous system disease. Pupillary reactions: non-reactive pupils must be > 3 mm. Do not assess after iatrogenic pupillary dilatation.

[b] Heart rate and systolic blood pressure: do not assess during crying or iatrogenic agitation.

[c] PaO_2: use arterial measurement only. PaO_2/FIO_2 ratio, which cannot be assessed in patients with intracardiac shunts, is considered as normal in children with cyanotic heart disease. $PaCO_2$ may be measured from arterial, capillary, or venous samples. Mechanical ventilation: the use of mask ventilation is not counted as mechanical ventilation.

[d] Percentage of activity.

Abbreviations: FIO_2 = fraction of inspired oxygen; INR = international normalized ratio; NA = not applicable; $PaCO_2$ = arterial carbon dioxide pressure; PaO_2 = arterial oxygen pressure.

APPENDIX 8. BRISTOL STOOL FORM SCALE

Bristol stool form scale created by Heaton and Lewis at the University of Bristol, UK. Originally published in Scan J Gastroenterol. 1997;32(9):920-4.

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces, **Entirely liquid**