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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Ethical review	Approved WMO
Status	Will not start
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON46433

Source
ToetsingOnline

Brief title
AdAPT: Adenovirus after Allogeneic Pediatric Transplantation

Condition

- Viral infectious disorders

Synonym
Adenovirus Infections in High-risk Pediatric Allogeneic Hematopoietic Cell Transplant Recipients

Research involving
Human

Sponsors and support

Primary sponsor: Chimerix, Inc.
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Adenovirus Infections, Allogeneic Hematopoietic Cell Transplant, Brincidofovir, pediatrics

Outcome measures

Primary outcome

The primary objective of this study is to compare the safety, overall

tolerability, and virologic response of BCV vs. SoC (i.e.,

investigator-assigned therapy) 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 (log10 copies/mL) from randomization

through Week 16 post-randomization.

Secondary outcome

* 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

For Exploratory Objectives refer to protocol section 5.2.2.

Study description

Background summary

In immunocompetent individuals, adenovirus (AdV) infections and resulting illnesses are generally mild, typically self-limited and resolve without sequelae. 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. Children are at higher risk of infection and manifestations can be severe among pediatric patients. 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 and renal damage, such as nephritis and obstructive nephropathy. The incidence of AdV infection and risk of serious disease is generally higher among children as well as recipients of T cell depleted grafts and patients with acute graft versus host disease (GVHD); risk is also high among recipients of unrelated or human leukocyte antigen-mismatched transplants due to profound and persistent immunodeficiency. Earlier detection of AdV viremia after HCT and higher viral loads have also been correlated with increased risk of fatal outcome. Severe and persistent lymphopenia is also associated with increased incidence of AdV infection, as well as progression to disseminated and often fatal AdV disease. 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.
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. However, IV CDV is associated with dose-limiting nephrotoxicity which can result in renal failure or death with a single administration. 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. 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.

Study objective

The primary objective of this study is to compare the safety, overall tolerability, and virologic response of BCV vs. SoC (i.e., investigator-assigned therapy) 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 (log10 copies/mL) from randomization through Week 16 post-randomization.

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 (i.e., investigator-assigned therapy), 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, or until Week 16 post randomization, whichever occurs first. During randomization, subjects will be stratified based on the following variables: last AdV viremia (* 10,000 copies/mL vs. < 10,000 copies/mL) measurement available from the designated central virology laboratory prior to randomization, 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.

Intervention

Subjects who meet all eligibility criteria will be randomized in a 2:1 ratio to BCV or Standard of Care (SoC) according to the randomization code through an automated interactive voice or web response system (IV/WRS).
* Arm 1: BCV until 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, twice weekly (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.
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.
In the absence of toxicity requiring dose interruption, BCV will be administered BIW through Week 16 post-randomization, or until AdV viremia is confirmed as undetectable (i.e., two consecutive plasma viral load results of *undetectable* as reported by the designated central virology laboratory), whichever occurs first. 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 Protocol Appendix 3 for a flow chart of the BCV dosing algorithm).

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 and their concurrent cyclosporine use.
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

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.
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).
Subjects randomized to the SoC arm in this study (i.e., investigator-assigned therapy) will be managed according to local or institutional practice guidelines, and which are in the best interests of the subject. 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.

Study burden and risks

The primary clinical risks associated with BCV therapy are GI in nature, particularly diarrhea, and elevations in serum aminotransferases. 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 protocol 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.
In addition to the side effects of BCV, patients may also experience other possible discomforts as part of the different study procedures.
Risks associated with drawing blood include pain and/or bruising, redness, infection, nerve damage excess bleeding, clotting or fainting are possible.

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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

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 */* 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 viremia since the qualifying transplant occurred within 21 days prior to Day 1
4. EITHER:
* AdV DNA 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 OR
* AdV DNA viremia * 10,000 copies/mL from the designated central virology laboratory
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)

Exclusion criteria

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 *mol/L]) within 7 days prior to Day 1
5. NIH Stage 2 or higher acute GVHD of the gut (i.e., diarrhea > 556 mL/m2 /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 *mol/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 anti-AdV specific cell-based therapy within 6 weeks prior to Day 1 or previously received an anti-AdV vaccine at any time

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	brincidofovir
Generic name:	brincidofovir

Ethics review

Approved WMO

Date:	13-04-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

	metc-ldd@lumc.nl
Approved WMO Date:	21-12-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-001735-39-NL
ClinicalTrials.gov	NCT03339401
CCMO	NL63567.058.18