# A Randomized, Placebo-Controlled, Multi-site Phase 2 Study Evaluating the Safety and Efficacy of Preemptive Treatment with CMX001 for the Prevention of Adenovirus Disease Following Hematopoietic Stem Cell Transplantation (The ADV HALT Trial)

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# Disclosures

- None

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# Adenovirus (AdV)

- AdV is a serious and often fatal viral infection in immunocompromised patients, especially in hematopoietic cell transplant (HCT) recipients
- Annual incidence of AdV infections in HCT recipients range from 5-50% with reported mortality rates up to 80%
- Incidence of AdV infections in HCT recipients is increasing, likely secondary to increased use of T cell depleted allografts and cord blood as a donor source
- No antiviral drugs are currently approved for treatment of AdV infections

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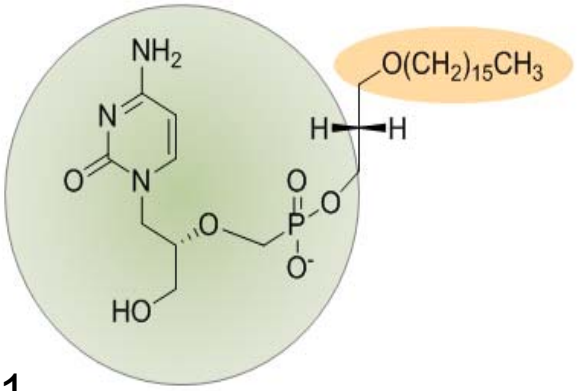
HCT = hematopoietic cell transplant

Sources: Ljungman P, Eur J Clin Microbiol Infect Disease 2004. Nihal G et al, BBMT 2012. Florescu DF et al, BBMT 2012

# CMX001 (Brincidofovir)

- Orally bioavailable lipid-conjugate of the nucleotide analog cidofovir (CDV)
- High intracellular antiviral concentration of the active antiviral cidofovir-diphosphate (CDV-PP) with a long $t_{1/2}$ up to 6.5 days
- Broad spectrum activity against dsDNA viruses
- 65-fold more potent against AdV than CDV *in vitro*
  - $EC_{50}$ < 0.02 uM against AdV
- No evidence of nephrotoxicity
  - Not a substrate of human organic anion transporter 1
  - No renal dysfunction in > 800 patients who have received CMX001 to date
- Announced dosing in the Phase 3 SUPPRESS trial for the prevention of CMV in HCT recipients in September 2013 (ClinicalTrials.gov: NCT01769170)

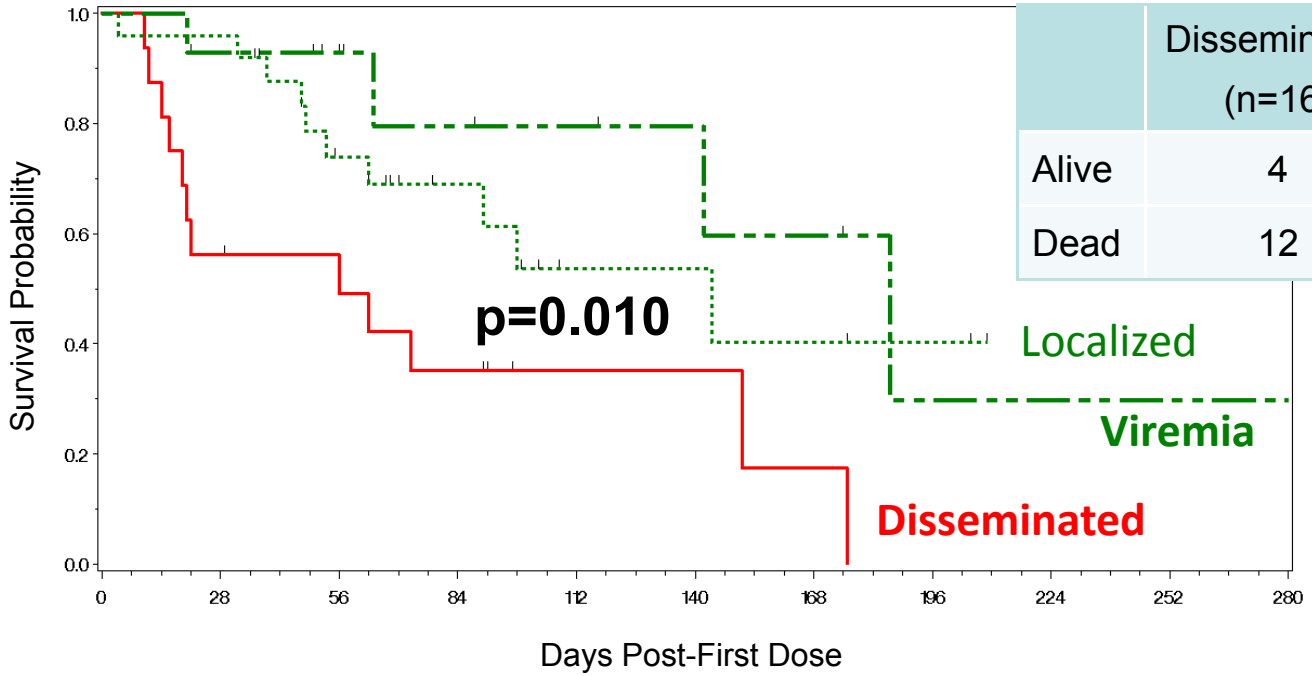



Source: Beadle et al. AAC 2002: 46:2381-6.

# Rationale for Study Design

- Patients who had received CMX001 through EIND or Study 350 had relative improvements in mortality compared to historical controls
- Study was modeled after CMV preemptive treatment protocols

**Expanded Access Study (Study 350):**
**All-Cause Mortality at Study Completion in AdV Subjects by Extent of Disease**




| | Disseminated (n=16) | Localized (n=26) | Viremia (n=15) |
|---|---|---|---|
| Alive | 4 | 16 | 10 |
| Dead | 12 | 10 | 5 |

Source: Grimley et al. EBMT oral presentation, 2013.

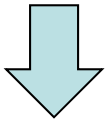
# Study Overview

- Primary objective: To evaluate the safety and efficacy of early intervention with CMX001 versus placebo to prevent the development of AdV disease in HCT recipients
- Randomized, double-blind, placebo-controlled study at 29 US transplant centers (June 2011-December 2012)
- Enrolled 48 pediatric and adult allogeneic HCT recipients who developed asymptomatic AdV viremia (positive serum AdV PCR ≥ 100 copies/mL) but without AdV disease
- Subjects received CMX001 or placebo BIW or QW for 6-12 weeks
- Dosing: 100 mg BIW or 200 mg QW for adults (tablet); 2 mg/kg BIW or 4 mg/kg QW for children (liquid)

BIW = twice weekly, QW = once weekly

# Study Design

735 patients screened for AdV viremia



48 patients with AdV viremia > 100 copies/mL

Stratified by ALC < 300 or ≥ 300 cells/$mm^3$

- CMX001 BIW
- CMX001 QW
- Placebo

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ALC = absolute lymphocyte count

# Outcome Measures

- Safety:  Clinical AEs, changes in laboratory values

- Efficacy:  “Treatment failure” defined as:
  - Progression to probable or definitive AdV disease, or
  - Confirmed increase from Baseline in AdV viremia by ≥ 1 $\log_{10}$ during blinded therapy

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AE = adverse event

# CMX001 Safety Monitoring and Management Plan (SMMP)

- Program-wide plan implemented across all CMX001 clinical studies in July 2011 which describes method for monitoring, characterizing and managing GI and hepatic symptoms or laboratory abnormalities seen with CMX001 dosing

- Implemented during CMX001 Study 201 to address diarrhea and ALT elevations
  - FDA raised no safety concerns since implementation of the plan in 2011 and subsequent updates to the plan

- GI symptoms: Dose level and frequency adjustments of CMX001 based on GI tolerability (Grade 3 or higher GI-related AEs)

- Hepatic enzyme abnormalities: Interruption of CMX001 based on liver enzyme abnormalities (Grade 3 or higher hepatic laboratory abnormalities)

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GI = gastrointestinal, ALT = alanine aminotransferase

# Baseline Characteristics
## ITT Population

| | CMX001 BIW n=14 | CMX001 QW n=16 | Placebo n=18 |
|---|---|---|---|
| **Age, range** | 0-55 | 2-70 | 1-53 |
| **< 12 years** | 9 (64%) | 11 (69%) | 9 (50%) |
| **12-17 years** | 2 (14%) | 1 (6%) | 3 (17%) |
| **> 17 years** | 3 (21%) | 4 (25%) | 6 (33%) |
| **Female, %** | 5 (36%) | 3 (19%) | 7 (39%) |
| **Median weight (range), kg** | 27 (10-98) | 25 (13-84) | 41 (11-95) |
| **Median ALC (range), cells/mm$^3$** | 340 (0-1650) | 420 (50-2230) | 290 (0-1970) |

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ITT = intent to treat

# Transplant Characteristics
## ITT Population

| | CMX001 BIW n=14 | CMX001 QW n=16 | Placebo n=18 |
|---|---|---|---|
| **Time from transplant to first dose, days** | | | |
| **0-100** | 10 (71%) | 13 (81%) | 15 (83%) |
| **100-180** | 3 (21%) | 2 (13%) | 2 (11%) |
| **> 180** | 1 (7%) | 1 (6%) | 1 (6%) |
| **GVHD at first dose, %** | 4 (29%) | 5 (31%) | 4 (22%) |
| **Reason for transplant** | | | |
| **Malignancies** | 4 (29%) | 5 (31%) | 9 (50%) |
| **Non-malignant diseases** | 10 (71%) | 11 (69%) | 9 (50%) |
| **Pre-transplant conditioning** | | | |
| **Myeloablative** | 6 (43%) | 8 (50%) | 10 (56%) |
| **Reduced intensity** | 7 (50%) | 8 (50%) | 7 (39%) |
| **T-cell depletion** | 0 | 0 | 1 (6%) |
| **None** | 1 (7%) | 0 | 0 |
| **Source of graft** | | | |
| **Bone marrow** | 2 (14%) | 10 (63%) | 9 (50%) |
| **Peripheral blood stem cells** | 6 (43%) | 1 (6%) | 4 (22%) |
| **Cord blood** | 6 (43%) | 5 (31%) | 5 (28%) |
| **Type of graft** | | | |
| **Haploidentical** | 3 (21%) | 0 | 1 (6%) |
| **Related donor** | 1 (7%) | 1 (6%) | 4 (22%) |
| **Unrelated donor** | 10 (71%) | 15 (94%) | 13 (72%) |
| **CMV seropositive** | 8 (57%) | 6 (38%) | 12 (67%) |

GVHD = graft versus host disease, CMV = cytomegalovirus

# Adverse Events of Interest (All Grades)

| | CMX001 BIW n=14 | CMX001 QW n=16 | Placebo n=18 |
|---|---|---|---|
| **Renal** | | | |
| **Renal failure** | 2 (14%) | 1 (6%) | 1 (6%) |
| **Hematuria** | 0 | 0 | 2 (11%) |
| **GI** | | | |
| **Diarrhea** | 8 (57%) | 6 (38%) | 5 (28%) |
| **Nausea** | 2 (14%) | 2 (13%) | 4 (22%) |
| **Vomiting** | 1 (7%) | 4 (25%) | 4 (22%) |
| **Abdominal pain** | 2 (14%) | 0 | 2 (11%) |
| **Hematologic** | | | |
| **Neutropenia** | 1 (7%) | 1 (6%) | 2 (11%) |
| **Anemia** | 1 (7%) | 1 (6%) | 0 |
| **Thrombocytopenia** | 2 (14%) | 0 | 0 |

# Summary of Adverse Events
## ITT Population

| | CMX001 BIW n=14 | CMX001 QW n=16 | Placebo n=18 |
|---|---|---|---|
| **Grade 3, 4, or 5 AE** | 10 (71%) | 9 (56%) | 11 (61%) |
| **Drug-related Grade 3, 4, or 5** | 2 (14%) | 4 (25%) | 2 (11%) |
| **SAE** | 6 (43%) | 7 (44%) | 6 (33%) |
| **AE leading to dose change or interruption** | 5 (36%) | 1 (6%) | 1 (6%) |
| **AE leading to study drug discontinuation** | 2 (14%) | 2 (13%) | 1 (6%) |
| **Abdominal pain** | 1 (7%) | 0 | 0 |
| **Diarrhea** | 0 | 1 (6%) | 0 |
| **Lower GI hemorrhage** | 1 (7%) | 0 | 0 |
| **Toxic epidermal necrosis** | 0 | 0 | 1 (6%) |
| **Neutrophil decrease, anorexia, fatigue** | 0 | 1 (6%) | 0 |

AE = adverse event, WBC = white blood cell

# Treatment Failure (Primary Endpoint)
## ITT Population

| | CMX001 BIW n=14 | CMX001 QW n=16 | Placebo n=18 |
|---|---|---|---|
| **Subjects with treatment failure** | 3 (21%) | 6 (38%) | 6 (33%) |
| **Increase in viremia only** | 1 | 1 | 1 |
| **Evidence of end-organ disease +/- increasing viremia** | 2 | 5 | 5 |
| **p-value (versus placebo)[a]** | 0.450 | 0.779 | N/A |

- Treatment failure defined as:
  - Progression to probable or definitive AdV disease, or
  - Confirmed increase from Baseline in AdV viremia by ≥ 1 $\log_{10}$ during blinded therapy

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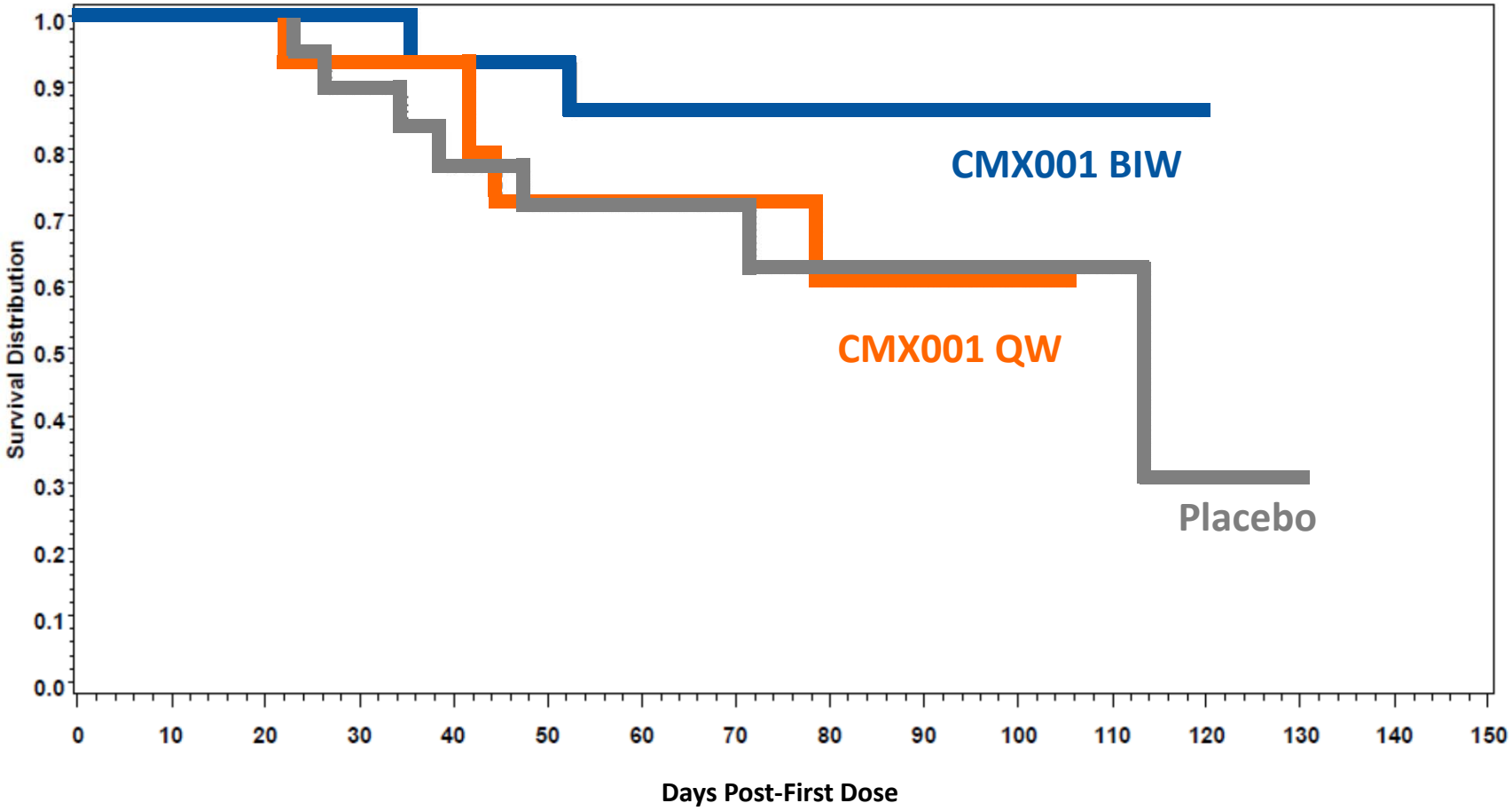
[a] Based on a logistic regression model adjusted for randomization stratum (absolute lymphocyte < 300 vs. ≥ 300 cells/$mm^3$).

# All-Cause Mortality Through End of Study

## ITT Population

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# Cause of Death

| | CMX001 BIW n=14 | CMX001 QW n=16 | Placebo n=18 |
|---|---|---|---|
| **Cause of death** | 2 (14%) | 5 (31%) | 7 (39%) |
| **Cardiopulmonary failure** | 0 | 0 | 1 (6%) |
| **Chronic GVHD** | 0 | 1 (6%) | 0 |
| **Intracranial hemorrhage** | 1 (7%) | 1 (6%) | 0 |
| **Leukemia relapse** | 0 | 1 (6%) | 1 (6%) |
| **Multi-organ failure** | 0 | 0 | 2 (11%) |
| **Pneumonia aspiration** | 0 | 0 | 1 (6%) |
| **Respiratory failure** | 1 (7%) | 2 (13%) | 2 (11%) |

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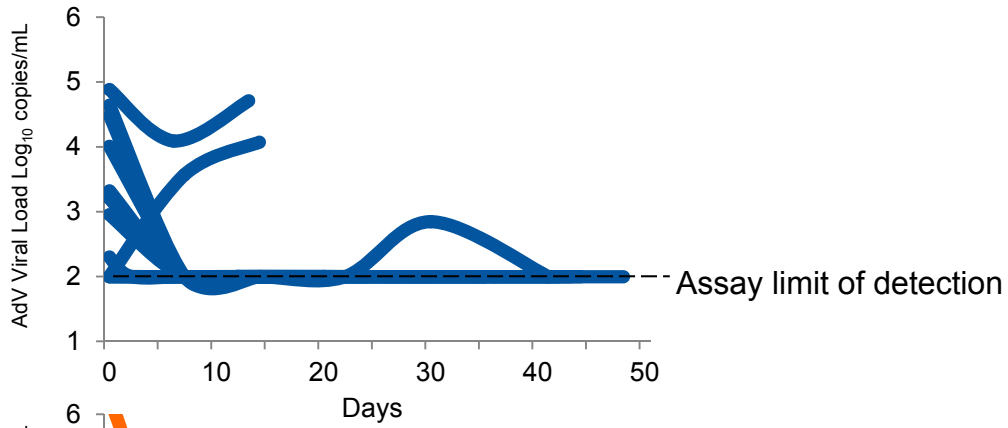
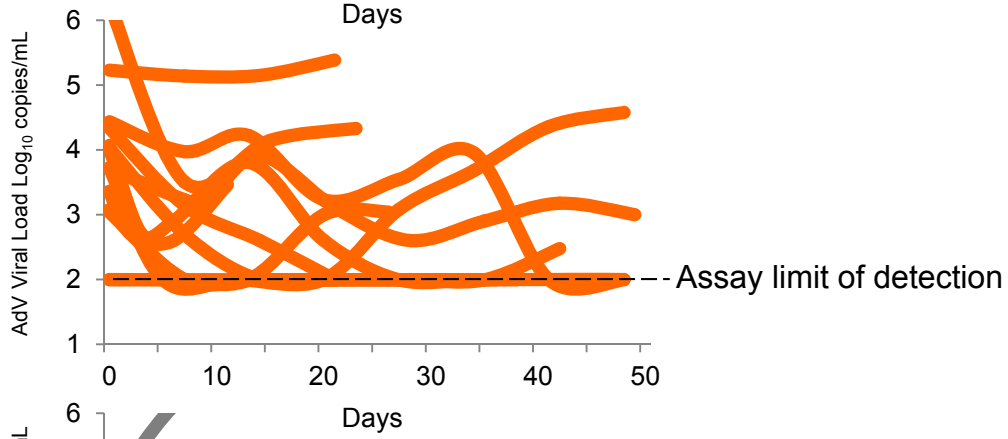
# Adenovirus Viremia During Blinded Treatment Period
## ITT Population

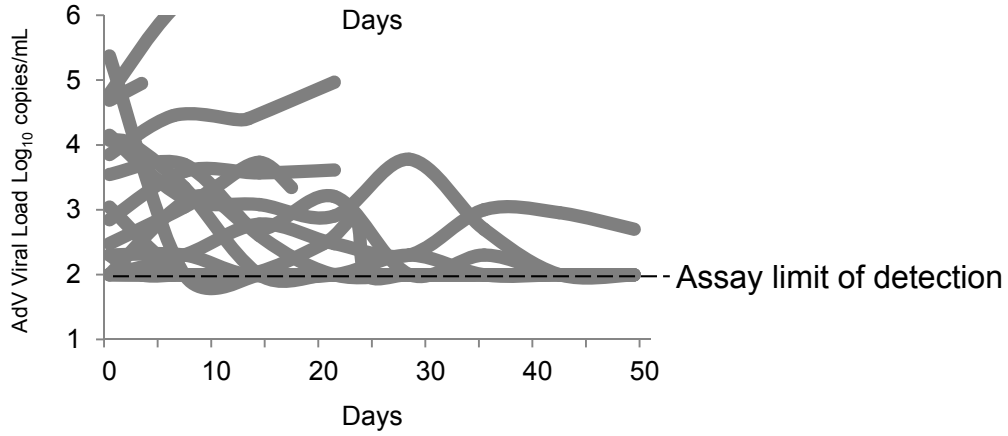
**CMX001 BIW**
**n=14**



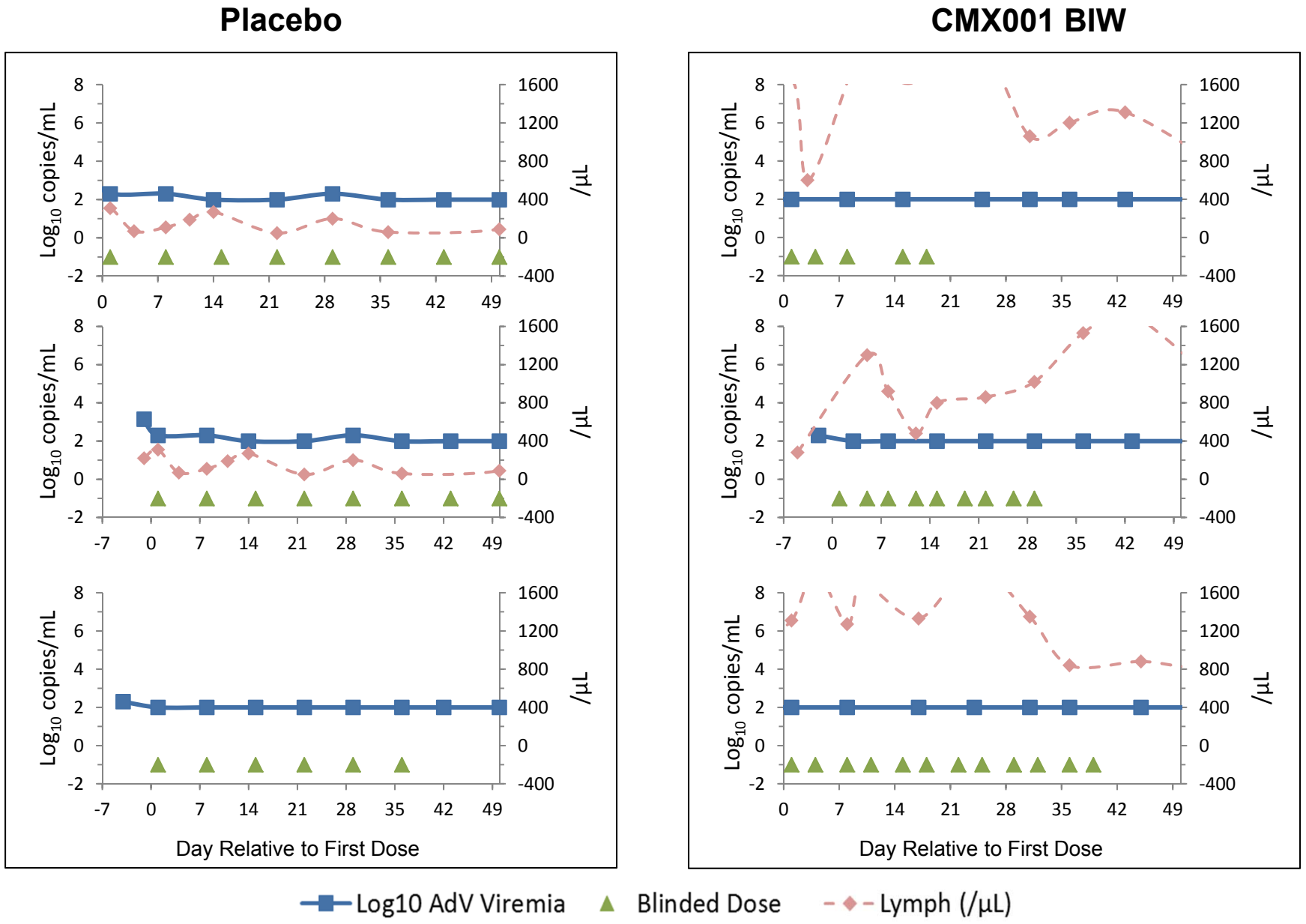

**CMX001 QW**
**n=16**



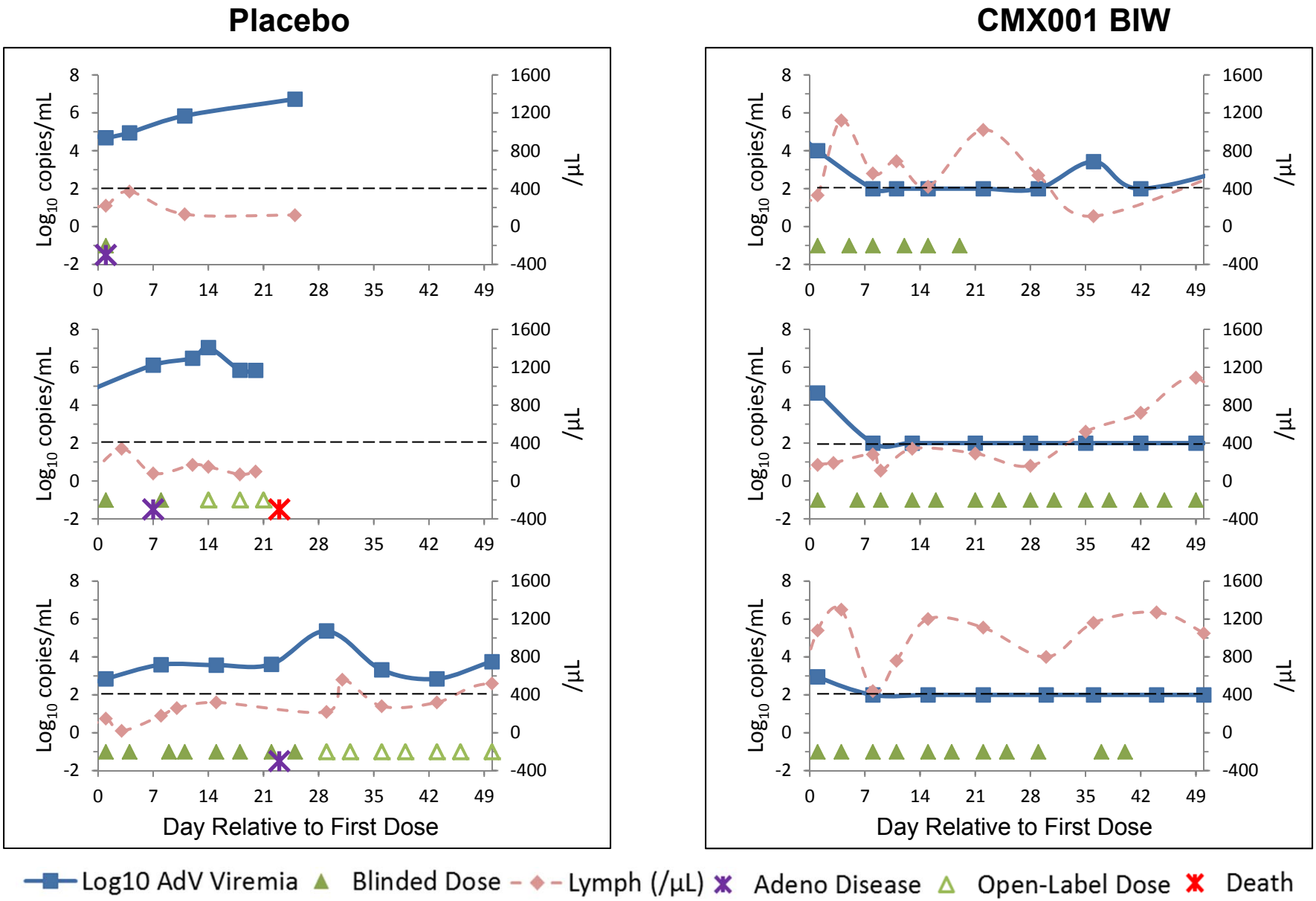

**Pooled Placebo**
**n=18**



# Low Level AdV Viremia
## (100 to < 1,000 copies/mL at Baseline)



# High Level AdV Viremia
## (≥ 1,000 copies/mL at Baseline)



# Conclusions

- In this exploratory study for AdV infection, CMX001 BIW showed greater antiviral activity and lower all-cause mortality compared with the placebo and CMX001 QW cohorts
- Safety: No evidence of renal or hematologic toxicity
  - Higher rates of diarrhea reported in subjects receiving CMX001 BIW but successful implementation of the SMMP allowed the majority of patients to continue dosing on study drug
- AdV viremia does not appear to be an appropriate indication of "early" AdV disease
  - Low level AdV viremia spontaneously cleared
  - Emergence of AdV viremia was sometimes concomitant with end organ disease
- These data support continued development of CMX001 as prevention of dsDNA viruses in at-risk transplant recipients

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dsDNA = double-stranded DNA

# Centers That Enrolled Patients in Study 202

- Children's Hospital (New Orleans)
- Children's Hospital of Los Angeles
- Children's Hospital of Orange County
- Children's Hospital of Pittsburgh of UPMC
- Cincinnati Children's Hospital Medical Center
- City of Hope National Medical Center
- Cleveland Clinic
- Duke University Medical Center
- Hackensack University Medical Center
- Lucile Packard Children's Hospital at Stanford
- Memorial Sloan-Kettering Cancer Center
- New York Medical College
- Phoenix Children's Hospital
- Seattle Children's Hospital
- University of Minnesota Medical Center
- University of Texas, MD Anderson Cancer Center

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