Preliminary Safety Results and Antiviral Activity from the Open-label Pilot Portion of a Phase 3 Study to Evaluate Brincidofovir for the Treatment of Adenovirus Infection

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Disclosure Statement: Jo-Anne Young, MD

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Adenovirus: High Unmet Medical Need

- Adenovirus (AdV) causes a wide spectrum of disease ranging from asymptomatic viremia to severe, disseminated disease, particularly in recipients of allogeneic hematopoietic cell transplants (HCT).

- Reported incidence of AdV infection in allo HCT is 5 to 47\%\(^1\).

- Untreated, mortality rates of up to 26\% are reported for HCT patients with symptomatic infection\(^2\) and 60 to 80\% for disseminated disease\(^1-4\).

- Risk factors include young age, receipt of T cell-depleted graft, mismatched or unrelated graft, or cord blood, and presence of acute GvHD\(^5\).

- Current treatment strategies typically involve supportive care with a reduction in immune suppression and/or initiation of antiviral treatment, typically IV CDV despite the risk of significant renal injury.

Brincidofovir (CMX001, BCV)

- BCV is a lipid-conjugate of CDV which allows for oral dosing and high intracellular uptake, delivering high intracellular levels of the active antiviral.

- Broad spectrum *in vitro* activity against dsDNA viruses.
- No evidence of nephrotoxicity; unlike IV CDV, BCV is not concentrated in renal tubules by organic anion transporter 1 (hOAT-1).
- No observed hematologic toxicity, including early after HCT.
- Anti-AdV activity confirmed when BCV used as preemptive therapy for allo HCT patients with asymptomatic AdV viremia in Phase 2 (CMX001-202; NCT01241344).
- In expanded-access study (CMX001-350; NCT01143181):
  - Patients with AdV disease showed improved survival compared to historical data.
  - All-cause mortality was lower when BCV was initiated for AdV viremia vs. disseminated AdV disease.
CMX001-304: Study Overview

• Study CMX001-304 (NCT02087306) is being conducted in two parts: first part ("pilot") in up to 100 patients was initiated to guide final design

• In pilot part, subjects assigned to one of three cohorts:
  o **Cohort A:** allo HCT recipient at risk of AdV disease progression (i.e., asymptomatic viremia \( \geq 1000 \) c/mL or localized disease in one organ system and plasma viremia < 1000 c/mL)
  
  o **Cohort B:** allo HCT recipient with disseminated AdV disease (symptomatic disease in two organ systems, or one organ system with plasma viremia \( \geq 1000 \) c/mL), or
  
  o **Cohort C:** all other patients (inc. auto HCT, SOT, primary immune deficiency, HIV, chemotherapy, etc.) regardless of disease status
CMX001-304: Study Design

- Open label BCV treatment for all cohorts:
  - Adults and children ≥ 50 kg: BCV 100 mg twice a week
  - Children 2 months or older and < 50 kg: BCV 2 mg/kg twice a week

- AdV viral load values in plasma and other body fluids measured by central virology laboratory using the 7500 Adenovirus Quantitative Real-time PCR Test (lower limit of detection = 100 c/mL; lower limit of quantification = 190 c/mL)
CMX001-304: Enrollment

• As of 19-Sep-2014, a total of 48 subjects across 17 centers have enrolled in pilot portion
  o Protocol generally initiated at each site for a symptomatic patient, resulting in delay from identification to first dose for first patient (typically 2 weeks or more)
  o Data include preliminary safety and antiviral activity data from first 26 subjects enrolled through 15-Jul-2014.
    • These subjects have had opportunity for ~2 months of observation
## Subject Demographics (N = 26)

<table>
<thead>
<tr>
<th>Age Category [n (%)]</th>
<th>&lt; 2 yrs</th>
<th>2 to 5 yrs</th>
<th>6 to 11 yrs</th>
<th>12 to 17 yrs</th>
<th>≥ 18 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 (23%)</td>
<td>6 (23%)</td>
<td>3 (12%)</td>
<td>5 (19%)</td>
<td>6 (23%)</td>
</tr>
</tbody>
</table>

| Sex [n (%)]                   | Female  | 9 (35%)    | Male        | 17 (65%)     |            |       |
|                               |         |            |             |              |            |       |

| Race [n (%)]                  | Asian   | 1 (4%)     | Black       | 5 (19%)      | Other      | 3 (12%)|
|                               |         |            |             |              | White      | 17 (65%)|

| Treatment Cohort [n (%)]      | A (Allo HCT, asymptomatic viremia or localized disease) | 4 (15%)    | B (Allo HCT, disseminated disease) | 16 (62%)    | C (Other than allo HCT with or w/out disease) | 6 (23%) |
Patient Subgroups

Unrelated HCT, 17

Matched related HCT, 1
Haploidentical HCT, 2
Chemotherapy, 2
SOT, 4

Unrelated HCT:
MUD 8
Cord 6
Mismatched 3

SOT:
Lung 2
Kidney 1
Liver 1
### Viral Characteristics (N = 26)

<table>
<thead>
<tr>
<th>AdV Plasma DNA Viral Load [n (%)]</th>
<th>Not detected &lt; LLOQ, detected</th>
<th>1 (4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 10³ c/mL</td>
<td>4 (15%)</td>
</tr>
<tr>
<td></td>
<td>10³ to &lt; 10⁴ c/mL</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>≥ 10⁴ c/mL</td>
<td>14 (54%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (8%)</td>
<td></td>
</tr>
</tbody>
</table>

| AdV Positivity by Site [n (%)]   | Urine                           | 15 (58%)|
|                                  | Stool                           | 15 (58%)|
|                                  | Respiratory secretions          | 12 (46%)|

| AdV Signs and Symptoms [n (%)]   | Pneumonitis                     | 11 (42%)|
|                                  | Hepatitis                       | 4 (15%) |
|                                  | Enterocolitis                   | 6 (23%) |
|                                  | Nephritis                       | 7 (27%) |

| Prior Treatment with IV CDV [n (%)] | Yes | 11 (42%) |

- Other dsDNA viruses: **27% BKV** in urine; **19% CMV** in plasma, and **8% EBV** in plasma detected by PCR at baseline
- AdV serotypes: plasma AdV typed for 18 subjects and included species A31 (n=3), B[11,34,35] (n=4), C[1,2,5,6] (n=10) and one subject with a mix of B11 and C5/6
Subject Disposition / Treatment Duration

• Of first 26 subjects enrolled, as of 12 Sep 2014:
  o 4 subjects have completed treatment
  o 13 subjects discontinued treatment prematurely:
    • death = 4 (15%);
    • AE = 3 (12%);
    • physician decision = 2 (8%);
    • start other AdV therapy = 2 (8%);
    • progression of transplant qualifying disease = 1 (4%)
    • withdrew consent = 1 (4%)
  o In 9 subjects, treatment is ongoing

• Median BCV treatment duration:
  54 days (range 1- 108)
Proportion with AdV DNA clearance from compartments other than plasma

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory secretions</td>
<td>5 / 12</td>
<td>42%</td>
</tr>
<tr>
<td>Urine</td>
<td>5 / 15</td>
<td>33%</td>
</tr>
<tr>
<td>Stool</td>
<td>4 / 15</td>
<td>27%</td>
</tr>
</tbody>
</table>
Subject received prior treatment with CDV, and had baseline T87I mutation, associated with resistance to CDV and BCV \textit{in vitro}.

Prior CDV use may be associated with non-response, yet of the 11 patients with prior IV CDV, 6 reached undetectable levels and one had $> 2\log_{10}$ decline at last on-treatment.
Treatment Interruption

< Prior BCV Treatment >
under EIND protocol

< Enrollment in Study CMX001-304 >

< BCV dosing modified to QW due to moderate diarrhea (assessed as related to BCV)

< BCV >
withheld
due to moderate hyperbilirubinemia (unrelated to BCV)

Log10 AdV Viremia

BCV Dose

Week (Relative to Dosing)
Strong Virologic Responses Observed with BCV

15/23 (65%) had $\geq 3 \log_{10}$ reduction or undetectable levels at nadir

**Median (range) change from baseline to nadir in plasma AdV DNA:**

-1.44 $\log_{10}$ c/mL (- 8.00 to - 0.62 $\log_{10}$)

<table>
<thead>
<tr>
<th>Undetectable plasma AdV DNA at Any Time On-Treatment</th>
<th>Baseline AdV Plasma Viremia ($\log_{10}$ c/mL)</th>
<th>Cohort A (n = 3)</th>
<th>Cohort B (n = 16)</th>
<th>Cohort C (n = 4)</th>
<th>All Subjects (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td>2/3 (67%)</td>
<td>10/16 (63%)</td>
<td>2/4 (50%)</td>
<td>14/23 (61%)</td>
</tr>
<tr>
<td>$&lt; 4.0 \log_{10}$ c/mL</td>
<td></td>
<td>1/1 (100%)</td>
<td>6/7 (86%)</td>
<td>1/1 (100%)</td>
<td>8/9 (89%)</td>
</tr>
<tr>
<td>$\geq 4.0 \log_{10}$ c/mL</td>
<td></td>
<td>1/2 (50%)</td>
<td>4/9 (44%)</td>
<td>1/3 (33%)</td>
<td>6/14 (43%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Undetectable plasma AdV DNA at Last On-treatment Assessment</th>
<th>Baseline AdV Plasma Viremia ($\log_{10}$ c/mL)</th>
<th>Cohort A (n = 3)</th>
<th>Cohort B (n = 16)</th>
<th>Cohort C (n = 4)</th>
<th>All Subjects (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td>2/3 (67%)</td>
<td>8/16 (50%)</td>
<td>2/4 (50%)</td>
<td>12/23 (54.2%)</td>
</tr>
<tr>
<td>$&lt; 4.0 \log_{10}$ c/mL</td>
<td></td>
<td>1/1 (100%)</td>
<td>5/7 (71%)</td>
<td>1/1 (100%)</td>
<td>7/9 (78%)</td>
</tr>
<tr>
<td>$\geq 4.0 \log_{10}$ c/mL</td>
<td></td>
<td>1/2 (50%)</td>
<td>3/9 (33%)</td>
<td>1/3 (33%)</td>
<td>5/14 (36%)</td>
</tr>
</tbody>
</table>

- Similar proportion of patients with undetectable AdV viremia at the last timepoint on-treatment across all AdV subtypes (45-60%)
Survival Improved in BCV-treated vs. Previous Reports

**CMX001-350**
AdV : 31/61 (mortality 51%)

**CMX001-304**
Cohorts A/B/C enrolled through 15Jul2014: 12/26 (mortality 46%)
All of Cohort B: Plasma AdV PCR >1000 or 2 or more compartments PCR+, 11/29 (mortality 38%)
All of Cohorts A/B/C: 17/48 (mortality 35%)

Prospective, single center pediatric cohort (N=132)\(^1\)

*Blood and compartment AdV PCR neg*

*Blood neg, compartment PCR +*

*Any blood AdV PCR+ (N=36, 33 with disseminated disease, mortality 82%)*

\(^1\) Lion T, et al. Blood 2003;102(3):1114-20
Survival Improved after BCV Treatment

- Observed mortality in CMX001-304 lower than those with disseminated AdV infection from literature and from study CMX001-350 (BCV expanded access)
  - Historic rate with SoC: 60-80%\textsuperscript{1-4}
  - CMX001-350 all-cause mortality through end of study in subjects with AdV infection was 51% (31 of 61)
    - May reflect delayed initiation of therapy and/or
    - Impact of prior IV CDV

Summary of Safety: Adverse Events

<table>
<thead>
<tr>
<th>Subjects with ≥ 1 SAE</th>
<th>Pediatrics (n = 20)</th>
<th>Adults (n = 6)</th>
<th>All (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14 (70%)</td>
<td>6 (100%)</td>
<td>20 (77%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects with ≥ 1 fatal AE*</th>
<th>Pediatrics (n = 20)</th>
<th>Adults (n = 6)</th>
<th>All (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 (30%)</td>
<td>1 (17%)</td>
<td>7 (27%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects with ≥ 1 AE requiring treatment discontinuation#</th>
<th>Pediatrics (n = 20)</th>
<th>Adults (n = 6)</th>
<th>All (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 (10%)</td>
<td>1 (17%)</td>
<td>3 (12%)</td>
</tr>
</tbody>
</table>

* Respiratory failure (4); AdV infection (2); AdV pneumonia, Klebsiella sepsis, multi-organ failure, septic shock, transplant failure (1 each); none BCV related

# Severe diarrhea in 2 subjects (both assessed as related to BCV); moderate increases in serum ALT, AST, and total bilirubin in one subject (all assessed as unrelated to BCV).
Conclusions

• BCV demonstrated **potent virologic activity** in patients with AdV disease
  o 15 / 23 (65%) had ≥ 3 log_{10} decline in AdV DNA by PCR (or were undetectable)

• Subjects treated with BCV appeared to have **improved survival** vs. historic controls
  o Among allogeneic HCT subjects with disseminated disease, mortality was 38%
    (vs. ~ 60-80% reported in literature)

• **No new safety signals** were identified in this highly complicated patient population

• Data from the pilot portion of CMX001-304 clearly **support progression** to pivotal Phase 3 study of BCV for AdV