Preliminary Results from the AdVise Study Evaluating Brincidofovir (BCV, CMX001) for the Treatment of Disseminated and High-Risk Adenovirus (AdV) Infection

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Disclosure Statement

• Michael Grimley, MD, Associate Professor of Clinical Pediatrics, Bone Marrow Transplant and Immune Deficiency, Cincinnati Children's Hospital Medical Center
  – No disclosures
Adenovirus: Epidemiology and Current Treatment Options

- Wide spectrum of presentation from asymptomatic viremia to severe and often disseminated disease
- Allogeneic hematopoietic cell transplant (allo HCT) recipients at greatest risk
- Mortality reported to be up to 80% for allo HCT recipients with disseminated disease
- 5 to 50% incidence of reported infection in allo HCT appears to be dependent on site-specific risk factors (young age, receipt of T cell-depleted graft, mismatched or unrelated graft, cord blood, acute graft versus host disease, etc.)
- Current standard of care: supportive, reduction of immune suppression, and unproven antivirals (typically IV cidofovir [CDV] despite risk of significant renal injury)

High Short-term Mortality in Patients with Disseminated Disease

Greater than 60% short-term mortality reported in a prospective, single center study in pediatric patients (Lion et al, 2003)

Source: Adapted from Lion T, et al.  Blood 2003;102(3):1114-20
Brincidofovir (BCV, CMX001)

- BCV is a lipid-conjugate of CDV, administered orally twice a week (BIW)
- In Phase 3 clinical development for prevention of cytomegalovirus (CMV) in allo HCT recipients and treatment of AdV
- Also in development as possible medical countermeasure for smallpox (under Animal Rule)
- *In vitro* activity against multiple dsDNA viruses
- Data from pilot part of Phase 3 AdVise (CMX001-304) trial (N = 48) presented at IDSA/ID Week September 2014*

Safety Database of > 1000 Individuals To Date

- Lack of hematologic toxicity allows pre-engraftment dosing
- No nephrotoxicity – Not a substrate of kidney organ anion transporter 1 (OAT 1)
- Drug-related GI events manageable and not dose-limiting
- Non-adverse low-level ALT elevation observed in preclinical testing, without histopathology
- Asymptomatic elevations in serum aminotransferases manageable and not dose-limiting
AdVise: Study Overview

• As of January 8, 2015, data available from 85 subjects enrolled across 20 study centers
  – Median 10 weeks of follow-up (range: 1 to 34)
• Open-label treatment for 12 weeks: 100 mg BIW
  (or 2 mg/kg BIW if < 50 kg)
  – Median treatment duration: 36 days (range: 1 to 167)
Estimated AdV Incidence at AdVise Study Centers

- Pediatric patients: 11.5% (95% CI: 6.9 to 16.1)
- Adults: 4.8% (95% CI: 0.8 to 8.8)

- Estimates based on actual AdVise enrollment and an estimate of the number of allo HCTs performed at AdVise study centers over enrollment period (from BMT Registry)
- True incidences will likely be higher since not all AdV patients at each center are eligible for or agree to participate in AdVise
AdVise: Prospectively Defined Cohorts

**Cohort A:** Allo HCT patients at risk of AdV disease progression (defined as asymptomatic with plasma viral load [VL] ≥ 1000 c/mL or symptomatic in one organ system and plasma VL < 1000 c/mL)

**Cohort B:** Allo HCT patients with disseminated AdV disease (defined as symptomatic in one organ system with plasma VL ≥ 1000 c/mL or symptomatic in two or more organ systems)

**Cohort C:** All other (i.e., non-allo HCT) patients with disseminated AdV disease or at risk of AdV disease progression (as defined for Cohorts A and B)

*Includes 9 solid organ transplant recipients: liver/pancreas/small bowel (2), liver (2), lung (2), heart (1), kidney (1), small bowel (1); 3 chemotherapy patients, and one “other” (patient receiving steroids for fibromyalgia)

Ten subjects (77%) had disseminated AdV disease
<table>
<thead>
<tr>
<th>Subject Demographics (N = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age (Range)</strong></td>
</tr>
<tr>
<td><strong>Age &lt; 18 yrs (n [%])</strong></td>
</tr>
<tr>
<td><strong>Male Sex (n [%])</strong></td>
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<tr>
<td><strong>White Race (n [%])</strong></td>
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</tbody>
</table>
### AdVise: Baseline Viral Characteristics

<table>
<thead>
<tr>
<th>AdV Detected by Compartment (n [%]):</th>
<th>Plasma</th>
<th>71 (84%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine</td>
<td>47 (55%)</td>
</tr>
<tr>
<td></td>
<td>Stool</td>
<td>62 (73%)</td>
</tr>
<tr>
<td></td>
<td>Respiratory secretions</td>
<td>39 (46%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline AdV Plasma Viremia ≥ 10^4 c/mL</th>
<th>All Subjects</th>
<th>39 (46%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n [%]):</td>
<td>Cohort A (n = 18)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td></td>
<td>Cohort B (n = 54)</td>
<td>32 (59%)</td>
</tr>
<tr>
<td></td>
<td>Cohort C (n = 13)</td>
<td>5 (38%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior Treatment with IV CDV (n [%]):</th>
<th>Yes</th>
<th>32 (38%)</th>
</tr>
</thead>
</table>

| Co-infection with another dsDNA virus (n [%])* | Yes | 50 (59%) |

*Other dsDNA viruses: 46% BK virus (BKV); 28% CMV, and 6% Epstein-Barr virus (EBV) detected by PCR at baseline
AdVise: A Majority of Subjects Suppressed Plasma AdV DNA to Undetectable Levels

<table>
<thead>
<tr>
<th>Plasma AdV DNA</th>
<th>Undetectable at Any Time On-treatment (n/N [%])</th>
<th>Undetectable at Last On-treatment Assessment (n/N [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects:</td>
<td>42 / 71 (59%)</td>
<td>36 / 71 (51%)</td>
</tr>
<tr>
<td>Cohort A (Asymptomatic or Localized):</td>
<td>8 / 11 (73%)</td>
<td>8 / 11 (73%)</td>
</tr>
<tr>
<td>Cohort B (Disseminated):</td>
<td>29 / 50 (58%)</td>
<td>23 / 50 (46%)</td>
</tr>
<tr>
<td>Cohort C (All Non- allo HCT):</td>
<td>5 / 10 (50%)</td>
<td>5 / 10 (50%)</td>
</tr>
</tbody>
</table>

- **Subjects with detectable AdV in plasma (n = 71):** Median change from baseline to nadir = $-1.4 \log_{10} \text{c/mL}$ (range: -8.0 to 0.6); 65% achieved $\geq 3 \log_{10}$ decrease or to undetectable
- **Disseminated AdV, Cohort B (n = 50):** Median change from baseline to nadir = $-1.9 \log_{10} \text{c/mL}$ (range: -5.4 to 0.6); 66% achieved $\geq 3 \log_{10}$ decrease or to undetectable
## AdVise: Clearance from Respiratory, Gastrointestinal and Genitourinary Compartments

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Respiratory Secretions</th>
<th>Urine</th>
<th>Stool</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Subjects</strong></td>
<td>26 / 39 (67%)</td>
<td>25 / 47 (53%)</td>
<td>34 / 62 (55%)</td>
</tr>
<tr>
<td><strong>Cohort A</strong> (Asymptomatic or Localized)</td>
<td>3 / 4 (75%)</td>
<td>3 / 6 (50%)</td>
<td>7 / 12 (58%)</td>
</tr>
<tr>
<td><strong>Cohort B</strong> (Disseminated)</td>
<td>19 / 27 (70%)</td>
<td>20 / 35 (57%)</td>
<td>21 / 40 (53%)</td>
</tr>
<tr>
<td><strong>Cohort C</strong> (All Non-allo HCT)</td>
<td>4 / 8 (50%)</td>
<td>2 / 6 (33%)</td>
<td>6 / 10 (60%)</td>
</tr>
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</table>
AdVise: Encouraging Short-term Survival in Allo HCT with Disseminated AdV Disease

Overall survival: 59 of 85 subjects (69%)
AdVise: Few Discontinuations due to BCV-related Events

<table>
<thead>
<tr>
<th>Discontinuation Due to:</th>
<th>Any Adverse Event</th>
<th>BCV-related Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects (N = 85)</td>
<td>14 (16%)</td>
<td>3* (4%)</td>
</tr>
<tr>
<td>Pediatrics (n = 59)</td>
<td>9 (15%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Adults (n = 26)</td>
<td>5 (19%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Cohort A (Asymptomatic or Localized; n = 18)</td>
<td>4 (22%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Cohort B (Disseminated; n = 54)</td>
<td>7 (13%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Cohort C (All Non-allo HCT; n = 13)</td>
<td>3 (23%)</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

*Treatment-limiting AEs assessed as related to BCV were: abdominal pain (one adult in Cohort B), worsening diarrhea (one adult in Cohort C), and abdominal pain and diarrhea (in one pediatric subject in Cohort A)
AdVise: Preliminary Conclusions

Among 85 subjects enrolled in AdVise to-date:

• 37% mortality among allo HCT subjects with disseminated disease after median follow-up of 75 days
  – Overall 31% mortality across all three treatment cohorts

• Majority of subjects had ≥ 3 log_{10} c/mL decline or undetectable AdV in plasma, and cleared AdV from respiratory, gastrointestinal, or genitourinary compartments

• Less than 5% of subjects (3 of 85) discontinued therapy due to a BCV-related event

• More than half of subjects enrolled had two or more dsDNA viral infections at study entry
What Next for AdVise?

• Target enrollment in AdVise increased to ~ 200 patients (minimum 100 allo HCT with disseminated AdV disease)

• Survival and other outcomes in allo HCT in AdVise to be compared to historical outcomes in matched controls from the same medical centers

• Epidemiology of AdV and other dsDNA viruses (BKV, CMV, EBV, HHV-6, etc.) will be determined from banked samples at selected centers (Study CMX001-306)
**AdVise Study Centers and Investigators**

- Children’s Hospital of Los Angeles (Dr. Abdel-Azim)
- Stanford University Medical Center (Dr. Agarwal/Dr. Brown)
- Children’s Hospital of Philadelphia (Dr. Bunin)
- MD Anderson Cancer Center (Dr. Chemaly)
- Levine Children’s Hospital (Dr. Eckrich)
- University of Nebraska Medical Center (Dr. Florescu)
- Children’s Hospital of Colorado (Dr. Giller)
- Children’s Hospital of Pittsburgh/University of Pittsburgh Medical Center (Dr. Goyal)
- Cincinnati Children’s Hospital Medical Center (Dr. Grimley)
- Children’s Healthcare of Atlanta (Dr. Haight)
- Intermountain Healthcare (Dr. Hoda)
- Cook Children’s Healthcare System (Dr. Howrey)

- Children’s National Health System Center for Cancer and Blood Disorders (Dr. Jacobsohn)
- Johns Hopkins Hospital (Dr. Loeb/Dr. Boger)
- St. Jude Children’s Research Hospital (Dr. Maron)
- Brigham and Women’s Hospital (Dr. Marty)
- University of Chicago (Dr. Mullane)
- Baylor College of Medicine (Dr. Munoz-Rivas)
- Memorial Sloan Kettering (Dr. Papanicolaou)
- Duke University Medical Center (Dr. Prasad)
- Weill Cornell Medical College (Dr. Soave)
- Medical College of Wisconsin (Dr. Talano)
- Children’s Mercy Hospital (Dr. Yin)
- University of Minnesota (Dr. Young)
- Children’s Hospital of New Orleans (Dr. Yu)