Renal Safety of the Broad-spectrum Antiviral, CMX001, in the Prevention of Cytomegalovirus Infection Post-Allogeneic Hematopoietic Cell Transplantation

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Background

- CMX001 is a novel, orally bioavailable, broad spectrum, lipid acyclic nucleoside phosphonate converted intracellularly into the active antiviral, cidofovir diprophosphate (CDV-PP).
- CMX001 has in vitro antiviral activity against all five families of double-stranded deoxyribonucleic acid (dsDNA) viruses pathogenic for humans: herpesviruses, including cytomegalovirus (CMV), adenoviruses (AdV), polyomaviruses, including BK virus (BKV), papillomaviruses, and orthopoxviruses.
- CMX001 is absorbed in the small intestine, circulates in the periphery, and is delivered to cells throughout the body. Inside cells, CMX001 is cleaved to release cidofovir (CDV), which is phosphorylated to CDV-PP (intracellular t1/2 ~6.5 days).
- CMX001 has completed Phase 2 clinical development for prevention of CMV infection in adult allogeneic hematopoietic cell transplant (HCT) recipients. The Phase 3 SUPPRESS study (Study CMX001-101) for the prevention of CMV infection in adult HCT recipients, is scheduled to begin enrollment in mid-2013.
- Cidofovir (Vistide®) is currently approved for intravenous administration only, and is limited in its clinical utility by renal toxicity. CMV is concentrated into the epithelial cells of the kidney via the organic anion transport-1 (OAT-1). Unlike CDV, CMX001 is not a substrate of OAT-1, and has not been associated practicably with nephrotoxicity.
- Infection with BK virus (BKV) in HCT recipients is associated with hemorrhagic cysts (HC) and renal insufficiency.

Methods

- Study CMX001-201 (ClinicalTrials.gov identifier: NCT00943205) was a placebo-controlled Phase 2 dose-escalation study designed to evaluate CMX001 for the prevention of CMV infection in CMV-seropositive (R) allogeneic HCT recipients.
- CMX001 was orally administered at the following doses: 40 mg once weekly (QW) = 100 mg BIW (200 mg QW) = 100 mg BIW (200 mg QW) (n=32) to placebo recipients (n=31) by randomization to CMX001 or placebo (3:1 ratio), and received blinded therapy until approximately Day 100 post-transplant (9 to 11 weeks of treatment).
- Renal function was assessed throughout the treatment phase until one week post-treatment based on:
  - Measurement of serum creatinine concentrations,
  - Calculation of estimated glomerular filtration rate (eGFR),
  - Urinalysis,
  - Collection of AEs
- eGFR was calculated using the modified diet in renal disease equation 4 (MDRD4). *BKV was measured in urine by qPCR assay (lower limit of detection = 2.7 log10 c/mL)*

Results

- Two hundred thirty (230) subjects were enrolled in the study; 97 subjects received placebo and 171 subjects received CMX001 at various doses.
- The primary endpoint of the trial was prevention of CMV reactivation.
- CMX001 at doses ≥ 100 mg per week (QW or BIW dosing) demonstrated anti-CMV activity.
- Gastrointestinal (GI) adverse events (AEs) were dose limiting at 200 mg BIW, while lower doses (≤ 200 mg/week) were generally well tolerated.
- No subject discontinued the study due to a renal AE, with the exception of one subject discontinued at 40 mg QW due to acute renal failure (reported as acute kidney injury and assessed by the investigator as unrelated to CMX001 administration).
- Mean changes from baseline in serum creatinine (mg/dL) are summarized in Table 1 and the corresponding mean changes from baseline eGFR (mL/min/1.73 m2) are summarized in Table 2.
- Abnormal renal function, new onset 2.4 or more (serum creatinine > 1.36 mg/dL, last value)
- Abnormal renal function, new onset grade 2-4 (serum creatinine > 1.36 mg/dL, last value and ≥ 25% from baseline)

Conclusions

- CMX001 demonstrated no evidence of nephrotoxicity at doses up to 200 mg BIW.
- The decline in renal function in placebo subjects is consistent with historical data in HCT. Subjects randomized to CMX001 demonstrated a dose-dependent improvement in eGFR and a dose-related decrease in new hematrua.
- Improved eGFR and decrease in new hematrua were more apparent in BKV+ subjects on CMX001 than in BKV− subjects on placebo.
- CMX001 will be explored as a prevention for BKV-related renal dysfunction and hemorrhagic cysts in the Phase 3 SUPPRESS study.

References