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 diphosphate (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 anabolized to CDV-PP (intracellular $t_{1/2}$ ~ 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 CMX001-301) for the prevention of CMV infection in adult HCT recipients, is scheduled to begin enrollment in mid-2013.
- CMX001 is being evaluated as a preemptive therapy for AdV infection in pediatric and adult HCT recipients. A Phase 2 study (Study CMX001-202) has completed enrollment of the planned 48 subjects and data are expected in mid-2013.
- Cidofovir (Vistide®) is currently approved for intravenous administration only, and is limited in its clinical utility by renal toxicity.[1] CDV is concentrated into the epithelial cells of the kidney via the organic anion transporter-1 (hOAT-1). Unlike CDV, CMX001 is not a substrate of hOAT-1, and has not been associated preclinically with nephrotoxicity.
- Infection with BK virus (BKV) in HCT recipients is associated with hemorrhagic cystitis (HC) and renal insufficiency.

Methods

- Study CMX001-201 (ClinicalTrials.gov identifier: NCT00942305) 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 QW -> 200 mg QW -> 200 mg twice weekly (BIW) -> 100 mg BIW
- Subjects post-HCT were enrolled at the time of engraftment, randomized 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, and
  - collection of AEs
- eGFR was calculated using the modified diet in renal disease equation 4 (MDRD4)[2]
- BKV was measured in urine by a qPCR assay (lower limit of detection = 2.7 $\log_{10}$ c/mL)

Results

- Two hundred-thirty (230) subjects were enrolled in the study: 59 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 of ≥ 100 mg per week (QW or BIW dosing) demonstrated anti-CMV activity.[3]
- 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**. The mean change from baseline in GFR is also presented graphically in **Figure 1**.
- Placebo recipients experienced a decline in renal function during the randomized treatment period, while there appeared to be a dose-related improvement in renal function as measured by serum creatinine for the CMX001-treated subjects.
- The comparison between pooled placebo and the 100 mg CMX001 BIW treatment group reached statistical significance ($P < 0.05$, Satterthwaite t-test), denoted by '*' in Tables 1 and 2.
- For the 200 mg BIW group, interpretation was confounded by the discontinuation of subjects due to GI-related AEs and dose reduction to 200 mg QW in the subjects remaining on treatment (see BMT poster/abstract 379).

Table 1:
Mean (n) Change from Baseline in Serum Creatinine (mg/dL) by Treatment and Visit

Visit	40 mg QW (n = 25)	100 mg QW (n = 27)	200 mg QW (n = 39)	200 mg BIW (n = 30)	100 mg BIW (n = 50)	Placebo (n = 59)
Week 2	0.080 (23)	0.178 (26)	0.104 (37)	0.036 (29)	0.036 (49)	0.052 (56)
Week 4	0.053 (19)	0.117 (25)	0.137 (31)	0.043 (21)	0.079 (44)	0.043 (46)
Week 6	-0.030 (13)	0.205 (22)	0.032 (24)	-0.032 (18)	-0.040 (33)	0.048 (35)
Week 8	-0.073 (12)	0.201 (19)	0.049 (18)	0.042 (10)	-0.049 (31)	0.169 (36)
Week 10	0.041 (5)	0.186 (13)	0.070 (14)	0.099 (5)	-0.063 (21)*	0.158 (21)
+1 Week Post	0.027 (19)	0.040 (25)	-0.009 (35)	-0.047 (23)	-0.053 (49)*	0.122 (57)

* P < 0.05 (t-test Satterthwaite) versus placebo

Table 2:
Mean (n) Change from Baseline in GFR (mL/min/1.73 m2) by Treatment and Visit

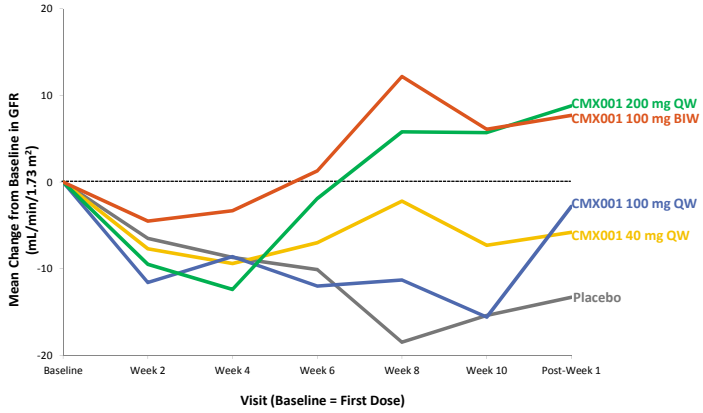
Visit	40 mg QW (n = 25)	100 mg QW (n = 27)	200 mg QW (n = 39)	200 mg BIW (n = 30)	100 mg BIW (n = 50)	Placebo (n = 59)
Week 2	-7.7 (23)	-11.6 (26)	-9.5 (37)	-7.4 (29)	-4.5 (49)	-6.5 (56)
Week 4	-9.4 (19)	-8.6 (25)	-12.4 (31)	-6.5 (21)	-3.3 (44)	-8.7 (46)
Week 6	-7.0 (13)	-12.0 (22)	-1.9 (24)	-1.7 (18)	1.3 (33)	-10.1 (35)
Week 8	-2.2 (12)	-11.3 (19)	5.8 (18)	-7.4 (10)	12.2 (31)*	-18.5 (36)
Week 10	-7.3 (5)	-15.6 (13)	5.7 (14)	-17.1 (5)	6.1 (21)*	-15.4 (21)
+1 Week Post	-5.8 (19)	-2.8 (25)	8.8 (35)	5.2 (23)	7.7 (49)*	-13.3 (57)

* P < 0.05 (t-test Satterthwaite) versus placebo.

Table 3: Incidence of Hematuria and Abnormal Renal Function by BKV Status and Treatment: Pooled CMX001 versus Pooled Placebo

	BK Viruria Positive		BK Viruria Negative	
	CMX001 (n = 94)	Placebo (n = 32)	CMX001 (n = 77)	Placebo (n = 27)
New onset microscopic hematuria (≥ 1+ blood in urine, confirmed)	6 **(6.4%)**	8 **(25.0%)**	6 (7.8%)	1 (3.7%)
Abnormal renal function (Grade 2 or more) (serum creatinine > 1.36 mg/dL, last value)	14 **(14.9%)**	11 **(34.4%)**	10 (13.0%)	3 (11.1%)
Abnormal renal function, new onset Grade 2-4 (serum creatinine > 1.36 mg/dL, last value and ≥ 25% from baseline)	7 **(7.4%)**	6 **(18.8%)**	6 (7.8%)	2 (7.4%)

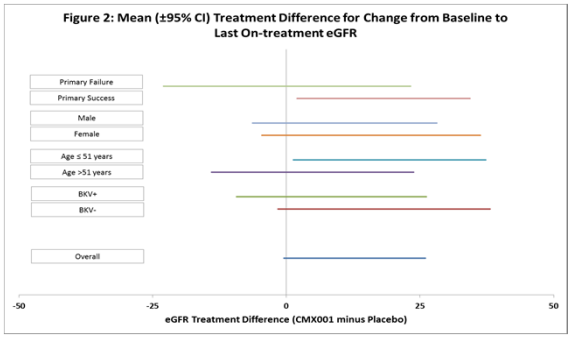
Figure 1: Mean Change from Baseline in GFR (mL/min/1.73 m²) by Visit and Dose



Results (cont.)

- Subjects who had BKV detected in urine (BK viruria) and who received placebo had a 4-fold higher incidence of microscopic hematuria (i.e., confirmed ≥ 1+ blood in urine) than BKV+ CMX001-treated subjects (placebo: 25% versus CMX001: 6.4%). The incidence of microscopic hematuria in subjects without BK viruria was low independent of cohort (7.8% of CMX001-treated subjects vs. 3.7% of placebo recipients). **(See Table 3)**
- BK viruria appeared associated with evidence of renal dysfunction. For placebo-recipients, 34.4% of BK viruria positive subjects had Grade 2 serum creatinine concentrations > 1.36 mg/dL at last value, compared to 11.1% of BK viruria negative subjects; new onset renal dysfunction (serum creatinine concentration > 1.36 mg/dL AND ≥ 25% from baseline) also appeared to be related to the BK viruria positive status of placebo-recipients (18.8% of BK viruria positive subjects versus 7.4% of BK viruria negative subjects).
- A multivariate analysis of change from baseline to last on-treatment GFR was performed. Factors included in ANCOVA fixed effects model were: CMV disease or progressive CMV infection at end of treatment (primary CMV response), BK viruria positive (BKV+) at any time during study, treatment group, baseline eGFR, gender, and age.
- Results:
  - No evidence of association between GFR change and primary CMV response, BKV+, or age ($p > 0.2$); removed from model
  - Gender marginally associated with GFR change ($p = 0.097$); with a greater improvement in GFR in males vs. females
  - 100 mg BIW vs. placebo marginally associated with GFR change ($p = 0.051$); with a greater improvement in GFR in subjects who received CMX001 at 100 mg BIW vs. placebo
  - In BKV+ subjects, 100 mg BIW vs. placebo was not associated with GFR change (p=0.33, 95% CI for treatment difference -9.0 to 26.2)
- **Figure 2** is a Forest Plot illustrating the relative impact of CMX001 vs. Placebo in improving eGFR in various subgroups as well as overall.

Figure 2: Mean (±95% CI) Treatment Difference for Change from Baseline to Last On-treatment eGFR



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 decrease in new hematuria.
- Improved eGFR and decrease in new hematuria 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 cystitis in the Phase 3 SUPPRESS study.

References

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