Monitoring Changes in Serum Albumin Concentrations as an Early and Objective Indicator of Potential CMX001-associated Gastrointestinal Adverse Drug Effects

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379

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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: herpes viruses, including cytomegalovirus (CMV), adenoviruses (AdV), polyomaviruses, 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 prevention 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.
- In the CMX001 toxicology program, gastrointestinal (GI) adverse events (AEs), diagnosed as gastropathy and enteropathy, were dose-limiting after daily administration. Dose-related changes in chronic dosing included flattening or loss of epithelial cells lining the small intestine lumen of the small intestine. No GI AEs or gross/microscopic gut changes were observed when dosing frequency was changed to twice-weekly (BIW) for up to 9 months.
- Clinical manifestations of drug-related diarrhea can include secretory and protein-losing components potentially due to leaky mucosal cell junctions.[1] One well-established marker of protein loss is a decrease in serum albumin concentration.[2]
- Serum chemistry data obtained from participants in a Phase 2, dose-escalation study were analyzed to evaluate changes in serum albumin, to assess any potential relationship of serum albumin to diarrhea, and to explore the possibility of using changes in serum albumin concentrations as an early and objective indicator of potential CMX001-associated GI AEs.

Methods

- Study CMX001-201 (ClinicalTrials.gov identifier: NCT00942305) was a Phase 2, dose-escalation study designed to evaluate CMX001 at various doses for the prevention of CMV infection in CMV-seropositive (R+) allogeneic HCT recipients.
- CMX001 was evaluated at doses of 40 mg once-weekly (QW) > 100 mg QW > 200 mg QW > 200 mg 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).
- Serum albumin was monitored at screening, baseline, and during the randomized treatment phase (weekly) through +1 week post-treatment, with all assessments performed at the central laboratory.
- Diarrhea AEs were included in the analysis if a subject reported diarrhea of > 1 day duration.
- Abnormally low serum albumin concentrations were tabulated, using ≤ 3.0 g/dL as the cut-off threshold (lower limit of reference range = 3.3 g/dL) and the lowest albumin value was identified from values obtained through +1 week post treatment.
- To identify new onset changes in subjects entering the study with abnormally low serum albumin values, a clinically meaningful "albumin decrease" was defined as a post-baseline measurement that was ≤ 3.0 g/dL AND ≥ 0.4 g/dL lower than baseline.
- Time to onset of first albumin decrease was analyzed using Kaplan-Meier methods.
- Concomitant proteinuria and liver function were assessed to rule out additional major causes of acute onset hypoalbuminemia.

Results (1)

- Subjects who discontinued treatment for any AE and for GI AEs are listed in **Table 1**.
  - The rate of discontinuation for any AE was highest in the 40 mg QW and 200 mg BIW groups, and the rate of discontinuation for GI AEs overall was highest in the 200 mg BIW dose group. Diarrhea was the most frequent GI AE leading to discontinuation.
- The incidence of GI-related AEs by severity and treatment is summarized in **Table 2**.
  - Subjects who received 200 mg BIW had more severe GI AEs than subjects who received placebo or CMX001 at lower doses, necessitating dose reduction to 200 mg QW.
  - Introduction of a safety monitoring and management plan (SMMP), which included dose interruption in response to significant (Grade 3) diarrhea, was effective in allowing for the completion of subjects managed in this fashion.
  - The increased incidence of Grade 3 GI AEs at 100 mg BIW (20.0% as compared with 11.9% with placebo) was driven by an excess of subjects with Grade 3 diarrhea. This was likely due to a reporting bias and delayed intervention following the introduction of the SMMP during the previous 200 mg BIW/placebo cohort. However, dose interruption was useful in this setting as only 10% of the subjects randomized to receive CMX001 100 mg BIW discontinued treatment due to GI AEs.
- The frequency of new onset albumin decreases (ie, ≤ 3.0 g/dL AND ≥ 0.4 g/dL lower than baseline) and diarrhea are summarized in **Table 3**.
  - There was an increase in the proportion of albumin decreases in the ≥ 200 mg/week treatment groups (30.8%, 43.3%, and 48.0% at 200 mg QW, 200 mg BIW, and 100 mg BIW, respectively) compared with pooled placebo (22.0%).
  - There was also an increase in the proportion of subjects reporting both diarrhea and albumin decreases in the BIW treatment groups (20.0% and 26.0% at 200 mg BIW and 100 mg BIW, respectively), compared with the QW treatment groups (4.0%, 0%, 7.7%) and placebo (5.1%).

Figure 1: Kaplan-Meier Curves Illustrating Decreases in Serum Albumin Concentrations in Subjects Treated with CMX001 (at Doses ≥ 200 mg/week and < 200 mg/week) versus Placebo

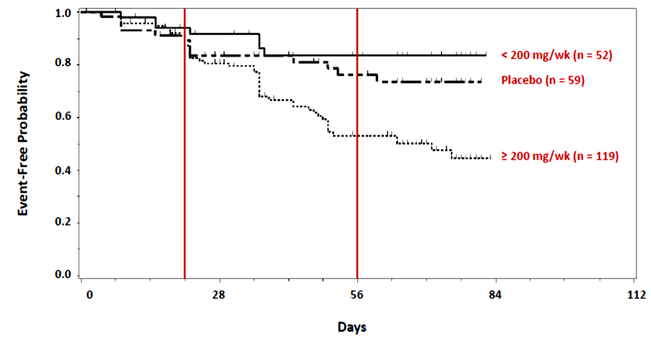


Figure 2: Kaplan-Meier Curves Illustrating the Frequency of Diarrhea of Maximum Grade 2 or 3 Severity Concurrent with Decreases in Serum Albumin Concentrations in Subjects Receiving CMX001 at Doses ≥ 200 mg/Week

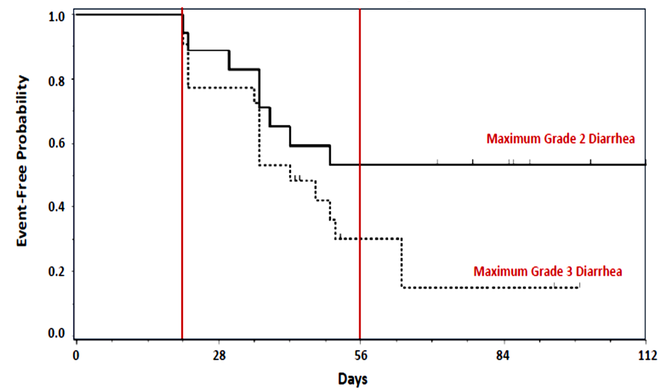


Table 1:
Summary of All AEs, All Gastrointestinal AEs, and All Diarrheal Events Leading to Study Drug Withdrawal

	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 (%)	Pooled Placebo n = 59 (%)
All AEs	15 (60)	9 (33)	15 (39)	18 (60)	18 (36)	27 (46)
GI-associated AEs	0	1 (4)	3 (8)	9 (30)	5 (10)	2 (3)
Diarrhea	0	0	1 (3)	7 (23)	2 (4)	0

Table 2:
Incidence of Gastrointestinal AEs by Severity and Treatment

CTCAE Severity	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 (%)	Pooled Placebo n = 59 (%)
Grade 1	9 (36)	6 (22)	12 (31)	3 (10)	12 (24)	16 (27)
Grade 2	6 (24)	10 (37)	10 (26)	13 (43)	17 (34)	16 (27)
Grade 3	2 (8)	1 (4)	2 (5)	10 (33)	10 (20)	7 (11)
Grade 4	0	0	2 (5)	0	1 (2)	0
Grade 5	0	0	0	1 (3)	0	0

Table 3:
Proportion of Subjects with Abnormal Albumin Levels and Diarrhea by Treatment

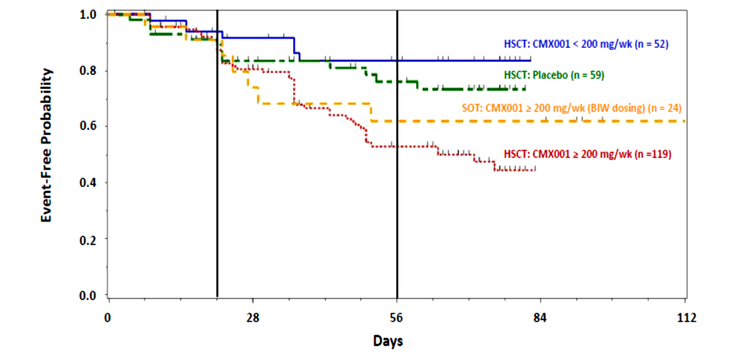
	CMX001 40 mg QW n = 25 (%)	CMX001 100 mg QW n = 27 (%)	CMX001 200 mg QW n = 39 (%)	CMX001 200 mg BIW n = 30 (%)	CMX001 100 mg BIW n = 50 (%)	Pooled Placebo n = 59 (%)
Albumin Decrease[1]	4 (10)	2 (7)	12 (31)	13 (43)	24 (48)	13 (22)
Diarrhea, any grade, > 1 day	2 (8)	5 (19)	10 (26)	21 (70)	25 (50)	16 (27)
Diarrhea and Albumin Decrease	1 (4)	0	3 (8)	6 (20)	13 (26)	3 (5)

[1] Albumin Decrease = post-baseline measurement that was ≤ 3.0 g/dL AND ≥ 0.4 g/dL lower than baseline.

Results (2)

- **Figure 1:** Kaplan-Meier curves demonstrate dose-related serum albumin decreases, with CMX001 total weekly doses of ≥ 200 mg separating from CMX001 doses of < 200 mg/week and placebo around Week 3.
- **Figure 2:** Time to first albumin decrease for subjects reporting diarrhea of maximum Grade 2 or 3 severity. While time of first onset ~Week 3 is similar in subjects who had decreases in serum albumin and Grade 2 diarrhea, only 6% of subjects with Grade 2 diarrhea had decreasing serum albumin, versus 12% of subjects reporting Grade 3 diarrhea. This association between proportion of subjects with low serum albumin values and severity of reported diarrhea provides a rationale to consider changes in serum albumin as a potential early indicator of clinically relevant enteropathy during CMX001 treatment.
- As there could be other reasons for GI enteropathy in HCT recipients, including GI-GVHD[3], the data from solid organ transplant (SOTs) patients treated with CMX001 in an open-label, expanded access study (Study CMX001-350; ClinicalTrials.gov ID: NCT01143181) for serious or life-threatening dsDNA viral infections were also evaluated. In these SOT recipients (n = 24), who are highly unlikely to have GVHD, similar decreases in serum albumin concentrations were also observed over time. Urinalysis data and serum transaminase levels from subjects with hypoalbuminemia were examined and did not indicate proteinuria or hepatic impairment as the etiology of these finding (data not shown). The overlay of the Kaplan-Meier curve for the SOT recipients with the HCT recipients from Study CMX001-201 is shown in **Figure 3**. All subjects are shown in this figure; however, there is an almost complete overlap between individuals with ≥ Grade 2 diarrhea and concomitant decreases in serum albumin concentrations, indicating that initiating dose interruption for persistent Grade 2 diarrhea is an appropriate course of action to mitigate progression of drug-related diarrhea in future CMX001 studies.

Figure 3: Kaplan-Meier Curves Illustrating Decreases in Serum Albumin Concentrations in HCT and SOT Recipients Treated with CMX001 or Placebo (Studies CMX001-201 and CMX001-350)



Discussion/Conclusions

- Our clinical experience in the HCT population in CMX001-201 is consistent with preclinical findings. On chronic dosing, CMX001 likely accumulates in the gut mucosa in some patients and causes diarrhea that may be more pronounced in individuals with other causes of diarrhea, e.g., incipient graft versus host disease of the gut. Dose interruption gives the gut mucosa time to recover, allowing subjects the opportunity to resume therapy.
- Increased grade and/or duration of diarrhea correlates with a decrease in serum albumin concentrations over time.
- Given the dose-response relationships seen with diarrheal frequency, diarrheal severity, and concomitant decreases in serum albumin in both the HCT recipients in Study CMX001-201 and SOT recipients in Study CMX001-350, routine monitoring of serum albumin may serve as an early signal for clinicians to identify subjects potentially at risk for progression of GI symptoms, allowing early intervention through dose interruption and adjustment.
- The SMMP introduced during CMX001-201 has been revised to recommend interruption of study drug upon occurrence of Grade 2 diarrhea that persists for ≥ 3 days, especially if the diarrhea is associated with decreases in serum albumin. Persistent Grade 3 diarrhea calls for mandatory dose interruption. The revised SMMP will be implemented in the Phase 3 SUPPRESS study.

References

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