Demographic/Baseline Characteristics of Patients Treated with CMX001 for Serious or Life-threatening Double-stranded DNA (dsDNA) Virus Infections: Predictors of Multiple dsDNA virus Infection

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Hervé Mommeja-Marin, Thomas Brundage, Gregory Chittick
Chimerix, Inc., Durham, North Carolina, USA

Hervé Mommeja-Marin, MD
Chimerix, Inc.
2505 Meridian Parkway, Suite 340
Durham, NC 27713, USA
Tel: (00) 1 919-972-7119
Email: hmommeja-marin@chimerix.com

Abstract

Background: CMX001 is an orally bioavailable, lipid acyclic nucleotide converted intracellularly to the active antiviral, cidofovir diphosphate. CMX001 has demonstrated broad-spectrum *in vitro* activity against dsDNA human pathogenic viruses, including adenoviruses (AdV), herpesviruses [such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV)], orthopoxviruses, papillomaviruses and polyomaviruses, such as BK virus (BKV). CMX001 has successfully completed Phase 2 clinical development for the prevention of CMV infection and is in Phase 2 clinical development for preemption/ treatment of AdV infection. CMX001 has been administered to patients (pts) with serious/life-threatening disease caused by dsDNA viruses through an open-label, expanded access trial (CMX001-350; ClinicalTrials.gov ID: NCT01143181) or under US Emergency IND (EIND) regulations. **Methods:** Preliminary demographic/baseline characteristics (D/B) data from 210 expanded access pts and 110 evaluable EIND pts were analyzed using a logistic regression model. The model assessed the association of D/B factors (study, sex, age, race, transplant type) in pts with evidence of infection with one or more dsDNA viral infections. **Results:** In 320 pts, median (range) age was 31 (0-78) yrs, with 38% < 18 years old (YO), 55% 18-65 YO and 8% > 65 YO. Most were white (67%), male (58%) and had received a prior hematopoietic cell transplant (HCT, 71%) or solid organ transplant (SOT, 16%). The most common dsDNA virus infections (whether single or multiple) were CMV (54%), AdV (31%), BKV (23%) and EBV (7%). By transplant type (HCT vs SOT), the most common infections (single or multiple) were CMV (56% vs 68%), AdV (36% vs 20%) and BKV (28% vs 10%). Approx. 30% (95/320) of pts had evidence of multiple (2-5) dsDNA virus infections; the most common co-incident infections in the same pt were CMV + BKV at 34/95 (36%), AdV + BKV at 28/95 (29%) and AdV + CMV 22/95 (23%). Younger age (p=0.0004), black race (p=0.047) and HCT (p=0.039) were significantly associated with multiple dsDNA virus infections. **Conclusions:** A significant proportion of expanded-access and EIND pts qualifying for CMX001 therapy had evidence of multiple dsDNA infections. Pts enrolled post-HCT, particularly children, appear to have an increased likelihood of multiple dsDNA virus infections. The potential for broad-spectrum clinical benefit with CMX001 is being evaluated in these pts and will be further explored in future clinical studies.

Background

- CMX001 is a novel, orally bioavailable, broad spectrum, lipid acyclic nucleotide that is converted intracellularly to the active antiviral, CDV-PP.
- CMX001 has *in vitro* antiviral activity against all five families of dsDNA viruses pathogenic for humans, including herpesviruses, such as CMV and EBV, adenoviruses, polyomaviruses, such as 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 CDV, which is anabolized to CDV-PP (intracellular half-life = ~ 6.5 days).
- Cidofovir (Vistide® for Injection) is currently approved for IV administration only, and is limited in its clinical utility by renal toxicity, caused by concentration of CDV 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.
- CMX001 successfully completed Phase 2 clinical development for prevention of CMV infection in adult HCT recipients. The Phase 3 SUPPRESS trial (Study CMX001-301) for the prevention of CMV infection in adult HCT recipients, is scheduled to begin enrollment in mid-2013.
- CMX001 is also being evaluated as 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.
- Study CMX001-350 (ClinicalTrials.gov ID: NCT01143181) was an open-label, expanded-access study to provide access to CMX001 for patients with immediately life-threatening conditions caused by dsDNA viruses, who had no other treatment options, and who were ineligible to participate in controlled clinical studies of CMX001.
- Prior to the initiation of Study CMX001-350, to meet the unmet medical need for treatment of dsDNA virus infections in patients with no other treatment options, more than 180 patients received CMX001 under EIND regulations in the USA and equivalent regulations outside of the USA (including Canada, France, Israel, and Switzerland).
- With a significant proportion of the patients enrolled in Study CMX001-350 and treated under EINDs infected by more than one pathogenic dsDNA virus, the demographic and baseline characteristics of the patients were analyzed for predictors of infection with multiple dsDNA viruses.

Methods

Study CMX001-350:

- To participate, prospective subjects had to:
  - Have an immediately life-threatening or serious disease or condition caused by infection with a dsDNA virus.
  - Have a life expectancy of ≥ 2 weeks and a commitment to the continuation of supportive care for ≥ 4 weeks.
  - Have no comparable or satisfactory therapeutic alternative available (in the judgment of the treating physician).
  - Be able to ingest and absorb oral medicine.
- A total of 210 patients were enrolled with no restrictions on age or renal impairment.
- Subjects were treated for an initial period of up to 3 months until clinical disease had resolved or stabilized and/or viral DNA measurements by polymerase chain reaction (PCR) testing were negative for 4 consecutive weeks, whichever was longer.
- Treatment could be extended for up to 3 additional months in subjects with ongoing disease or who were at risk of disease recurrence (total treatment duration of 6 months) after a satisfactory review of safety parameters.

EIND Patients:

- In total, more than 220 patients have been treated under EIND regulations in the USA or under equivalent regulations outside the USA. Treatment was for 3 months initially, and extendable at 3-month intervals thereafter with FDA or other relevant regulatory authority approval.
- In USA, the EIND program involves independent investigators using CMX001 under a specific investigator-sponsored IND granted by FDA for each individual patient. EIND investigator-sponsors were asked to share data with Chimerix, but were under no legal obligation to do so; therefore, data contained in the EIND database were not obtained or monitored through typical procedures applied to clinical trials.
- Data are available in a subset of 110 evaluable US EIND patients that satisfied the following criteria:
  - Chimerix received confirmation that a written consent form was signed by or on behalf of the patient that included language that Chimerix could use the patient's de-identified data.
  - The patient was treated for ≥ 10 days (from date of first to last CMX001 dose administration).
  - The investigator-sponsor reported ≥ 1 adverse event, and ≥ 2 weeks of clinical laboratory results for key hematologic, hepatic, and renal parameters following CMX001 dosing.

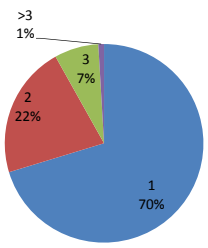
Results

Demographic and baseline characteristics are summarized in Table 1. The number of dsDNA virus infections in each subject and the overall incidence of primary or secondary dsDNA virus infections in HCT, SOT, pediatric (≤ 12 YO), and adult/adolescent subjects is presented graphically in Figures 1 to 5, respectively.

Table 1: Summary of Demographic and Baseline Characteristics

Characteristic	All Subjects (N =320)
Age (years):	
N	320
Mean (SD)	32.5 (23.3)
Median	31
Range	0, 78
Age Range [n (%)]:	
0-5 years	51 (15.9%)
6-12 years	48 (15.0%)
13-17 years	21 (6.6%)
18-64 years	175 (54.7%)
65+ years	25 (7.8%)
Sex [n (%)]:	
Male	184 (57.5%)
Female	136 (42.5%)
Race [n (%)]:	
Asian	17 (5.3%)
Black or African-American	37 (11.6%)
White	214 (66.9%)
Other or Unknown Race	52 (16.3%)
Transplant Type [n (%)]:	
HCT	224 (70.0%)
SOT	50 (15.6%)
HCT + SOT	2 (0.6%)
None	44 (13.8%)

Figure 1: Number of dsDNA Virus Infections



Results (cont.)

Figure 2: Viral Infections in HCT Subjects

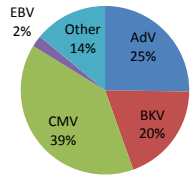


Figure 3: Viral Infections in SOT Subjects

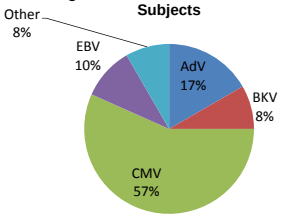


Figure 4: Viral Infections in Pediatric Subjects

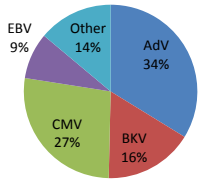
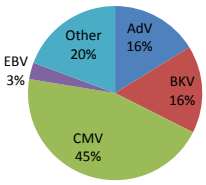


Figure 5: Viral Infections in Adult/ Adolescent Subjects



Logistic Regression Analysis of Demographic/ Baseline Characteristics:

- Data were analyzed as follows:
  - Dependent variable: infection with > 1 dsDNA virus
  - Independent variables: Full model: study, sex, age, race, transplant type; Selected model: age (linear), race, transplant type
- Results:
  - Age was strongly associated with infection with multiple dsDNA viruses (p=0.0004) with older patients having a lower probability of multiple infection and younger patients a higher probability of multiple infection.
  - Black/African-American race (p=0.047) and prior HCT transplant (p=0.039) were also associated with multiple infection.

Conclusions

1. A significant proportion of expanded-access and EIND patients qualifying for CMX001 therapy had evidence of multiple dsDNA infections.
2. Patients enrolled post-HCT, particularly children, appear to have an increased likelihood of multiple dsDNA virus infections, which is not unexpected given the use of conditioning regimens in BMT combined with the use of immunosuppressant medications to prevent or treat graft versus host disease.
3. The potential for broad-spectrum clinical benefit with CMX001 therapy is being evaluated in HCT patients and will be further explored in future clinical studies, including the Phase 3 SUPPRESS trial.

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