

CMX001 is Not Nephrotoxic or Myelosuppressive in 183 Patients with Life Threatening dsDNA Infections including Cytomegalovirus, Adenovirus, and BK Virus

Late-Breaker Presentation

51st ICAAC

September 18, 2011

G Papanicolaou¹, J Kurtzberg², M Grimley³, GA Storch⁴, R Goyal⁵, M Anderson⁶, H Mommeja-Marín⁶, W Painter⁶

¹MSKCC, New York, NY; ²Duke University Medical Center, Durham, NC; ³Cincinnati Children Hospital's Medical Center, Cincinnati, OH; ⁴Washington University School of Medicine, St. Louis, MO; ⁵University of Pittsburgh School of Medicine, Pittsburgh, PA; ⁶Chimerix, Durham, NC

EIND Program

- ▶ Between March 2009 and June 2011 >200 patients have received CMX001 under EINDs and foreign equivalent
- ▶ Subjects were treated in the US, Canada, France, Switzerland, Spain, the UK, Austria, Israel and Chile
- ▶ In the US, Emergency INDs were granted by the FDA for patients who had life threatening infection and lacked satisfactory treatment alternatives

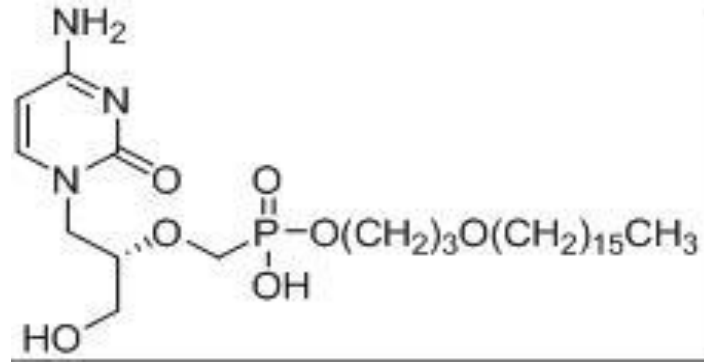
Data Collection

- ▶ Physicians–IND holders shared patient data with Chimerix to help describe the overall experience with the drug
- ▶ Data were abstracted from source documents or entered in a data collection tool
- ▶ Data was entered into a central database to allow for summation of the data
- ▶ Assessment of antiviral activity in this setting is difficult due to lack of controls and concomitant therapeutic intervention
- ▶ Safety data are more objective and informative

Overall Extent of Exposure

- ▶ Patients 1 month–79 years of age were treated under EINDs
- ▶ Duration of exposure ranged from single dose to > 50 doses given over 7 months
- ▶ Median duration/doses of exposure was 35 days/10 doses in children and adolescents and 26 days/8 doses in adults
- ▶ Cut-off date for all entries was 29 April 2011

CMX001



CMX001 is novel, broad spectrum dsDNA antiviral with a unique pharmacokinetic profile based on a proprietary NCE lipid-based structure that is metabolized inside target cells to cidofovir-diphosphate

5-Phospholipid conjugation allows oral bioavailability and passive uptake by cells (rather than inefficient pinocytosis)

Drug is metabolized by the liver and not excreted in urine

CMX001 is not a substrate for the hOAT (human organic anion transporter) and therefore the mechanism related to nephrotoxicity is avoided

To date over 550 patients have received CMX001 in clinical studies

CMX001 has Broad Activity Against dsDNA Viruses

Viral Class	Virus	Cidofovir EC ₅₀ (μM)	CMX001 EC ₅₀ (μM)	Enhanced Activity (<i>in vitro</i>)
Adenovirus	AdV 5	1.3	0.02	65
Herpes	CMV	0.38	0.0009	422
	EBV	>170	0.04	>4250
	HHV 6	0.2	0.004	50
	HSV 1	15	0.06	250
	VZV	0.5	0.0004	1250
Papilloma	HPV 11	716	17	42
Polyoma	BK	115.1	0.13	885
	JC	0.38	0.02	19
Pox	Variola major	27.3	0.1	271
	Vaccinia	46	0.8	57

EINDs and Foreign Equivalents: Baseline Characteristics

	Adults n=108	Pediatrics n=75
Gender Number(%) Male/ Female	63 (58%)/ 44 (41%)	36 (48%)/ 39 (52%)
Age (years) Median/ Mean	n=107 50.4/ 48.4	n=75 8.5/ 8.3
Weight (kg) Median/ Mean	N=106 70/ 71	N=75 27/ 31.9
Race n=(%)		
Caucasian	50 (46%)	22 (29%)
Black	9 (8%)	9 (12%)
Asian	5 (5%)	1 (1%)
Native American	0	0
Pacific Islander	0	0
Other/ Unknown	3 (3%)/ 41 (38%)	3 (4%)/ 40 (53%)

Baseline Characteristics (Contd)

	Adults n=108	Pediatrics N=75
VIRAL INFECTION(S)*		
ADENOVIRUS	15 (14%)	47 (63%)
CMV	54 (50%)	22 (29%)
HSV	7 (7%)	14 (19%)
EBV	5 (5%)	11 (15%)
HHV-6	6 (6%)	4 (5%)
JCV	15 (14%)	1 (1%)
BKV	26 (24%)	17 (23%)
Other	7 (6%)	3 (4%)
Transplant Recipient ? (YES)	72 (67%)	56 (75%)
Respiratory failure at the time of CMX001	11 (10%) 6 (6%)	21 (28%) 6 (8%)
Renal failure requiring dialysis		
Prior <u>IV</u> Cidofovir Tx n (%)		
Yes	24 (22%)	41 (55%)
No	77 (71%)	24 (32%)
Unknown	7 (6%)	10 (13%)

*Subjects may have more than one viral infection

EINDs: Subject Disposition

	Adults N=108	Pediatrics N=75
Total number of subjects dosed	108	75
Subjects with dosing ongoing ^{a)}	27 (25%)	36 (48%)
Subjects discontinued from study	81 (75%)	39 (52%)
Reason for Discontinuation:		
Infection resolved	15 (19%)	8 (21%)
Adverse event	20 (25%)	1 (3%)
Death	26 (32%)	22 (56%)
Futility of care decision	13 (16%)	3 (8%)
Lack of efficacy	1 (1%)	1 (3%)
OTHER	6 (7%)	4 (10%)

^{a)} Ongoing or unverified dosing status

Median Change from Baseline in LFTs in Recipients of CMX001

Parameter	Duration of CMX001 dosing	Adults		Pediatrics	
		Patient #	Median change from Baseline	Patient #	Median change from Baseline
ALT	< 4 weeks	62	17 U/L	37	11 U/L
	Week 4	40	20 U/L	26	12 U/L
AST	< 4 weeks	67	5 U/L	37	7 U/L
	Week 4	43	1 U/L	26	5 U/L
Total Bilirubin	< 4 weeks	68	0.1 mg/dL	39	0.2 mg/dL
	Week 4	43	0.3 mg/dL	29	0.2 mg/dL

Effect of CMX001 on Liver Function Tests

- ▶ Increases in ALT (typically 2x baseline) were noted early after CMX001 treatment was initiated (i.e., @ 4 weeks of therapy) without further increases if drug was continued
- ▶ There was no parallel increase in bilirubin

Change from Baseline in Creatinine and Hematological Parameters

Parameter	Duration of CMX001 dosing	Adults		Pediatrics	
		N=	Median change from Baseline	N=	Median change from Baseline
Creatinine (mg/dL)	< 4 weeks	75	0	43	0
	Week 4	45	-0.03	29	-0.10
	Week 8	10	-0.23	17	-0.10
	Week 12	8	-0.40	10	-0.07
WBC (x10 ³ /uL)	< 4 weeks	75	0.82	42	0.07
	Week 4	43	1.60	27	0.20
	Week 8	10	1.20	17	-0.40
	Week 12	7	1.80	10	0.94
ANC (x10 ³ /uL)	< 4 weeks	62	0.08	36	0
	Week 4	34	1.45	22	0.22
	Week 8	7	0.20	12	0.45
	Week 12	6	-0.15	8	1.90
Platelets (x10 ³ /uL)	< 4 weeks	75	1	42	3
	Week 4	45	-7	28	12
	Week 8	10	-9	17	24
	Week 12	7	-10	10	7

No Indication of Nephrotoxicity and Myelotoxicity

- ▶ In this very compromised patient population there was no significant effect on renal function as opposed to the intravenous form of cidofovir
- ▶ Hematologic parameters were not adversely affected by CMX001 administration

Summary

- ▶ Based on a large dataset of uncontrolled data CMX001 appears to differ markedly from IV cidofovir :
 - No signal of nephrotoxicity
 - No signal of myelotoxicity
- ▶ Gastro-intestinal toxicity in the form of diarrhea in adults at high doses (200 mg twice weekly or above) appears dose limiting, yet common in this patient population

Conclusion

- ▶ CMX001 is a promising agent for the treatment of refractory dsDNA infections
- ▶ Safety profile is differentiated from cidofovir and other antivirals in these indications
- ▶ Further randomized controlled trials are needed to define the adequate dose and dosing regimens in these indications with various risk/benefit ratios

Acknowledgements: Participating Institutions

Medical College of Wisconsin, Milwaukee
University of Washington Seattle , Fred Hutchinson
Seattle Children's Hospital
University of Utah School of Medicine, Salt Lake City
Salt Lake City, UT- LDS Hospital
University of Texas, Houston- MD Anderson Cancer Center
The Methodist Hospital, Houston TX
Cook Children's Medical Center, TX Fort Worth
University of TX Southwestern Medical Center, Dallas TX
Zurich, Switzerland, Oncology Center Zürich (Clinic in the Park)
Lausanne, Switzerland, Centre Hospitalier Universitaire Vaudois
Bern, Switzerland, Institut für Spitalpharmazie
Spain, Madrid, Hospital Niño Jesús
Neurology Associates, Sioux Falls SD
VA Medical Center, Pittsburgh, PA
Children's Hospital of Pittsburgh, PA
Greenstein Neurology Associates, Philadelphia, PA
Northshore Neurosciences, Erie, PA
Lehigh Valley Hospital, Allentown, PA
Oregon Health and Science University, Doernbecher Children's Hospital
Toledo, University of Toledo Medical Center
Columbus, Nationwide Children's Hospital
Cleveland, Cleveland Clinic
Cincinnati Children's Hospital Medical Center
Rochester, University of Rochester
Weill Medical College of Cornell University, New York Presbyterian Hospital
NY, Mount Sinai Medical Center
Memorial Sloan Kettering Cancer Center
Columbia University
Buffalo, Buffalo General Hospital
Hackensack Medical Center
University of Nebraska Medical Center
Duke University Medical Center
Charlotte, Carolina Healthcare Charlotte
University of North Carolina at Chapel Hill
St. Louis, Washington University School of Medicine
MN, Rochester, Mayo Clinic
Minneapolis, University of Minnesota
Detroit, Wayne State University School of Medicine
Ann Arbor, University of Michigan
The National Institutes of Health Clinical Center
Johns Hopkins University School of Medicine
Baltimore, Johns Hopkins
Tufts Medical Center
LSUHSC
Heath Care Campus
Chicago, University of Chicago
Chicago, Northwestern University
Emory University School of Medicine, Emory Children's Center
France, Paris, Robert Debré Hospital
Tampa, Moffitt Cancer Center
Walter Reed Army Medical Center
Georgetown University Hospital
George Washington University School of Medicine
Children's National Medical Center
Canada, Quebec, Montreal, University of Montreal, Ste Justine Hospital
Canada, Quebec, Montreal, McGill University Health Centre
Canada, Alberta, Edmonton, University of Alberta
San Diego, Rady Children's Hospital
San Diego, Naval Medical Center San Diego
Stanford University School of Medicine
Loma Linda, Loma Linda University Medical Center
Children's Hospital of Los Angeles
Duarte, City of Hope, National Medical Center
Tucson, University of Arizona Medical Center
Phoenix, Maricopa Medical Center
Austria, Graz, Medical University of Graz
AL, Cullman, North Central Neurology Associates
Birmingham, University of Alabama at Birmingham