Brincidofovir (CMX001) is Well Tolerated in Highly Immunocompromised Pediatric Patients

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2014 BMT Tandem Meetings, Grapevine, Texas, USA

Oral Abstracts: Session F: Supportive Care;
Thursday, February 27, 2014, 4:45 PM

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Disclosures

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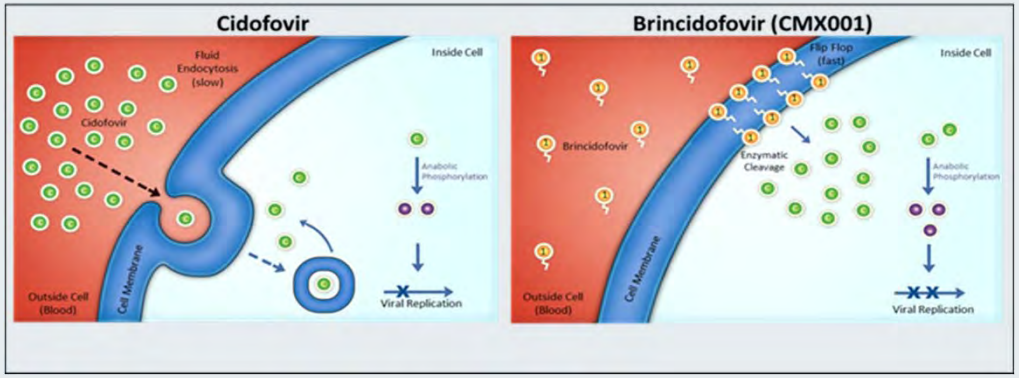
Brincidofovir (BCV, formerly CMX001): Background

- Lipid-conjugate of the nucleotide analog, cidofovir (Vistide®, CDV)
- Designed to use endogenous lipid uptake pathways to achieve high intracellular concentrations of BCV



- Long intracellular half-life (~ 4-6.5 days) of the active antiviral, cidofovir-diphosphate, allows twice-weekly (BIW) dosing
- Oral delivery (tablet and pediatric liquid suspension available)
- *In vitro* activity against all 5 families of double-stranded DNA viruses known to cause human disease
- No evidence of hematologic or renal toxicity to date:
  - Unlike Cidofovir, BCV is not a substrate of hOAT 1 (human organic anionic transporter) and thus is not concentrated in renal tubular cells
  - No drug-related renal dysfunction reported in > 800 subjects

Brincidofovir: Summary of *In Vitro* Antiviral Activity

Viral Family	dsDNA Virus	Brincidofovir EC_{50} (µM)	Cidofovir EC_{50} (µM)	Ganciclovir* EC_{50} (µM)	Foscarnet EC_{50} (µM)	Acyclovir EC_{50} (µM)	Maribavir EC_{50} (µM)	Letermovir EC_{50} (µM)
Herpes	Cytomegalovirus (CMV)	0.001	0.4	3.8	50-800	>200	0.31	0.005
	Epstein-Barr Virus (EBV)	0.03	65.6	0.9	<500	6.2	0.63	>10
	Human Herpesvirus 6A (HHV-6A)	0.003	2.7	5.8	16	10	Inactive	>10
	Human Herpesvirus 8 (HHV-8)	0.02	2.6	8.9	177	>100	Inactive	—
	Herpes Simplex Virus 1 (HSV-1)	0.01	3.0	0.7	92-95	3.8	Inactive	>10
	Herpes Simplex Virus 2 (HSV-2)	0.02	6.5	2.5	91-96	4.4	Inactive	>10
	Varicella Zoster Virus (VZV)	0.0004	0.5	1.3	39.8	3.6	Inactive	>10
Adenovirus	Adenovirus 7 (AdV7)	0.02	1.3	4.5-33	Inactive	>100	—	>10
Polyoma	BK Virus (BKV)	0.13	115	>200	Inactive	>200	—	—
	JC Virus (JCV)	0.045	>0.1	—	Inactive	—	—	—
Papilloma	Human Papillomavirus 11 (HPV-11)	17	716	Inactive	—	Inactive	—	—
Pox	Variola	0.1	27	—	—	—	—	—
	Vaccinia	0.8	46	>392	Inactive	>144	—	—

Data are compiled from multiple sources and include multiple materials and methodologies: Andrei 2005; De Clercq 2006; Christensen/NIH; Foscavir® Data Sheet (Health Logistics 2012); Gershburg 2004; Hartline 2005; Huggins 2002; Ison 2006; Jiang 2010; Kern 2002; Marschall 2012; Neyts 1997; Öberg 1989; Randhawa 2006; Valtrex® package insert (GlaxoSmithKline 2008); Wildner 2003; Williams Aziz 2005

"—" indicates no data

EC_{50} = concentration in µM required to reduce viral replication by 50% *in vitro*

*Valganciclovir is rapidly converted to ganciclovir in vivo. Therefore, ganciclovir is the relevant compound for cell activity studies

Overview of BCV Clinical Development Program

- Currently enrolling Phase 3 SUPPRESS placebo controlled trial (Study CMX001-301; Clinical Trials.gov ID: NCT01769170) for CMV prevention in adult HCT recipients.
- Previously completed Phase 2 trial of BCV vs. placebo for CMV prevention in adult HCT recipients (Study CMX001-201; Clinical Trials.gov ID: NCT00942305). *Marty et al., NEJM 2013
  - GI symptoms, primarily diarrhea (often also reported as acute GvHD of the gut) was the dose-limiting toxicity in this study, particularly at the highest dose of 200 mg BIW
  - Dose-related, asymptomatic increases in serum transaminases, primarily ALT, were seen which typically resolved after the completion of treatment
  - A program-wide Safety Monitoring and Management Plan (SMMP) was implemented with standardized approaches for monitoring, characterizing, and managing GI symptoms and ALT elevations
  - Recommendation to dose BCV with food
- SMMP was implemented for Study CMX001-202 and midway through Study CMX001-350. Using the approaches described in SMMP, dose interruption or dose reduction allowed for continued study drug dosing.

***N Engl J Med. 2013 Sep 26;369(13):1227-36. doi: 10.1056/NEJMoa1303688**

Objective

Since pediatric patients pose unique toxicity challenges and dsDNA viral infections are common in this age group, we undertook this analysis.

We describe here the results of an analysis of the collective safety experience in pediatric subjects receiving BCV:

- Study CMX001-202
- Study CMX001-350
- Under EIND regulations

Study CMX001-202: Overview

Primary objective: To evaluate the safety and efficacy of early intervention with BCV vs. placebo for prevention of Adenovirus disease in pediatric and adult HCT recipients with asymptomatic viremia (positive plasma AdV PCR ≥ 100 copies/mL)

Design:

- Randomized, double-blind, placebo-controlled
- 29 sites in USA (from June 2011 to February 2013)

Enrollment: 48 subjects (35 pediatric subjects, 13 adults)

Randomization:

- 1:1 to dosing frequency (QW vs. BIW, unblinded)
- 2:1 to study treatment (BCV vs. placebo, blinded)
- stratified based on absolute lymphocyte count at screening.

Treatment:

- BCV or placebo BIW or QW for at least 6 weeks, up to a maximum of 12 weeks (treatment failures could discontinue blinded treatment and receive up to 12 weeks open-label BCV):
- Pediatric (< 18 yrs) dose: 2 mg/kg BIW or 4 mg/kg QW

Study CMX001-350: Overview

Primary objective: To provide access to BCV treatment for pediatric and adult subjects with life-threatening or serious illness caused by a dsDNA virus(es)

Study Design:

- Open-label, expanded access treatment protocol
- 36 sites in USA (from December 2010 to October 2012)
- No other treatment options and ineligible for BCV clinical trials
- Dec 2010 to July 2011, all dsDNA viruses included
- After July 2011 limited to CMV, AdV, or HSV-1/2

Enrollment: 210 subjects (77 pediatric subjects, 123 adults)

Treatment:

- BIW or QW for 3 months initially, up to a maximum of 6 months; FDA approval on case-by-case basis for treatment beyond 6 months
- Adolescents (13-17 yrs and ≥ 50 kg body weight): 100 mg BIW or 200 mg QW (prior to April 2011: 200 or 300 mg BIW)
- Pediatrics (≤ 12 yrs): 2 mg/kg BIW or 4 mg/kg QW (prior to April 2011: 4 mg/kg BIW)

EIND Patients: Overview

- Expanded access program for Brincidofovir
  - 100+ centers in USA, Canada, France, UK, Austria, Switzerland, Spain, Israel, and Chile for subjects with life-threatening or serious dsDNA viral infection
- A separate EIND (or local equivalent) for each subject by the investigator
- Enrollment: 230 patients; March 2009 to March 2012
- Limited safety data are available
  - 110 patients (including 43 children) who provided written consent for data collection
- Treatment:
  - Individualized treatment protocols were developed for each subject to allow flexibility in treating subjects with different medical histories and disease states.
  - Subjects received treatment for up to 13 weeks; treatment extension beyond 13 weeks required FDA or local regulatory approval.
  - Dosing was modified for all ongoing BCV clinical trials in April 2011 to limit treatment to a maximum of 200 mg/week (adults) or 4 mg/kg/week (pediatrics) following treatment-limiting GI events in HCT subjects at a dose of 200 mg BIW in Study CMX001-201.

Summary of Demographics: Pediatric Subjects

Demographic	CMX001-202 (n=35)	CMX001-350 (n=77)	EINDs (n=43)	All (N=155)
Age (yrs)				
Mean (SD)	6.9 (4.39)	6.5 (4.56)	8.5 (5.61)	7.1 (4.88)
Median (Range)	7.0 (0 – 17)	6.0 (0 – 17)	10.0 (0 – 17)	7.0 (0 – 17)
Age Range, n (%)				
< 2 yrs	4 (11.4%)	13 (16.9%)	8 (18.6%)	25 (16.1%)
2 to 11 yrs	25 (71.4%)	53 (68.8%)	19 (44.2%)	97 (62.6%)
12 to 17 yrs	6 (17.1%)	11 (14.3%)	16 (37.2%)	33 (21.3%)
Race, n (%)				
Asian	1 (2.9%)	4 (5.2%)	1 (2.3%)	6 (3.9%)
Black	6 (17.1%)	13 (16.9%)	6 (14.0%)	25 (16.1%)
Other	2 (5.7%)	15 (19.5%)	14 (32.6%)	31 (20.1%)
White	26 (74.3%)	45 (58.4%)	22 (51.2%)	93 (60.0%)
Gender, n (%)				
Female	10 (28.6%)	31 (40.3%)	23 (53.5%)	64 (41.3%)
Male	25 (71.4%)	46 (59.7%)	20 (46.5%)	91 (58.7%)

Patient Characteristics: Pediatric Subjects

Characteristic	CMX001-202 (n=35)	CMX001-350 (n=77)	EINDs (n=43)	All (N=155)
Primary dsDNA virus				
AdV	35 (100%)	31 (40.3%)	10 (23.3%)	76 (49.0%)
CMV	N/A	33 (42.9%)	5 (11.6%)	38 (24.5%)
EBV	N/A	3 (3.9%)	1 (2.3%)	4 (2.6%)
HHV-6	N/A	2 (2.6%)	1 (2.3%)	3 (1.9%)
HSV-1/2	N/A	3 (3.9%)	3 (7.0%)	6 (3.9%)
BKV, VZV, Molluscum	N/A	5 (6.5%)	4 (9.3%)	9 (5.9%)
Multiple dsDNA viruses[1]	N/A	N/A	19 (44.2%)	19 (12.3%)
Disease subgroup				
Transplant[2]	N/A	N/A	38 (88.4%)	38 (24.5%)
HCT	35 (100%)	59 (76.6%)	N/A	94 (60.7%)
SOT	N/A	9 (11.7%)	N/A	9 (5.8%)
Non-transplant	N/A	9 (11.7%)	5 (11.6%)	14 (9.0%)

[1] Multiple (2+) dsDNA viruses listed, primary virus not identified for EINDs
[2] Data collection did not differentiate between HCT and SOT for EINDs

Brincidofovir Treatment Duration: Pediatric Subjects

Treatment Duration (days)	CMX001-202 (n=35)	CMX001-350 (n=77)	EINDs (n=43)	All (N=155)
Mean (SD)	45.0 (26.3)	63.2 (55.0)	91.4 (74.0)	66.9 (58.5)
Median (Range)	42 (1 - 99)	46 (1 - 185)	71 (15 - 308)[1]	47 (1 - 308)[1]

[1] 1 EIND subject was still receiving BCV; at the time of analysis, the subject was Day +78

Drug-related AEs of Particular Interest

Study CMX001-202, Pediatric Subjects

System Organ Class[1] Preferred Term[2]	Randomized Phase			Open-label
	BCV 2 mg/kg BIW (n=11)	BCV 4 mg/kg QW (n=12)	Placebo (n=12)	BCV 2 mg/kg BIW (n=8)
Subjects with ≥ 1 event	**3 (27.3%)**	**4 (33.3%)**	**4 (33.3%)**	**5 (62.5%)**
Gastrointestinal Disorders				
Diarrhea	3 (27.3%)	3 (25.0%)	2 (16.7%)	4 (50.0%)
Abdominal pain	1 (9.1%)	0	1 (8.3%)	2 (25.0%)
Investigations				
Neutrophil count decreased	0	2 (16.7%)	0	1 (12.5%)
ALT increased	0	0	2 (16.7%)	0
AST increased	0	0	2 (16.7%)	0
Immune System Disorders				
Acute GvHD	0	0	1 (8.3%)	0

[1] Subjects are counted once within each SOC or for each PT regardless of the number of AEs.
[2] All investigator verbatim terms were coded using MedDRA dictionary version 14.0.

Drug-related AEs (Grade 3, 4, or 5 of Particular Interest

Study CMX001-202, Pediatric Subjects

System Organ Class[1] Preferred Term[2]	Randomized Phase			Open-label
	BCV 2 mg/kg BIW (n=11)	BCV 4 mg/kg QW (n=12)	Placebo (n=12)	BCV 2 mg/kg BIW (n=8)
Gastrointestinal Disorders				
Diarrhea	0	1 (8.3%)	1 (8.3%)	2 (25.0%)
Investigations				
Neutrophil count decreased	0	2 (16.7%)	0	1 (12.5%)
Immune System Disorders				
Acute GvHD	0	0	1 (8.3%)	0

[1] Subjects are counted once within each SOC or for each PT regardless of the number of AEs.
[2] All investigator verbatim terms were coded using MedDRA dictionary version 14.0.

Drug-related AEs in >1 Subject by Dose

Study CMX001-350, Pediatric Subjects

System Organ Class[1] Preferred Term[2]	Recommended or Lower BCV Doses: ≤ 200 mg/wk or 4 mg/kg/wk (n=36)	Higher than Recommended BCV Doses: > 200 mg/wk or 4 mg/kg/wk (n=41)
No. of subjects with ≥ 1 event	**14 (38.9%)**	**22 (53.7%)**
Gastrointestinal Disorders		
Abdominal pain	1 (2.8%)	3 (7.3%)
Diarrhea	6 (16.7%)	14 (34.1%)
Nausea	2 (5.6%)	3 (7.3%)
Vomiting	1 (2.8%)	4 (9.8%)
Investigations		
ALT increased	2 (5.6%)	2 (4.9%)
Bilirubin increased	0	2 (4.9%)
Metabolism and Nutrition Disorders		
Decreased appetite	0	4 (9.8%)
Dehydration	0	2 (4.9%)

[1] Subjects are counted once within each SOC or for each PT regardless of the number of AEs.
[2] All investigator verbatim terms were coded using MedDRA dictionary version 13.1.

Study Drug Discontinuation due to AE or Death

	CMX001-202				CMX001-350 (N=77)	EINDs (N=42[1])
	Randomized Phase			Open-label BCV 2 mg/kg BIW (n=8)		
	BCV 2 mg/kg BIW (n=11)	BCV 4 mg QW (n=12)	Pooled Placebo (n=12)			
Death	0	1 (8.3%)	0	1 (12.5%)	18 (23.4%)	10 (23.8%)
Adverse event	0[2]	1 (8.3%)	2 (16.7%)	2 (25.0%)	11 (14.3%)	4 (9.5%)

- No deaths were related to study drug

[1] One EIND subject was continuing BCV treatment at time of analysis.
[2] One subject in BCV BIW group discontinued at legal guardian's request had an ongoing AE of GI hemorrhage that required study drug discontinuation.

AEs Leading to Study Drug Discontinuation

Study CMX001-202, Pediatric Subjects

System Organ Class[1] Preferred Term[2]	Randomized Phase			Open-label BCV 2 mg/kg BIW (n=8)
	BCV 2 mg/kg BIW (n=11)	BCV 4 mg/kg QW (n=12)	Placebo (n=12)	
Subjects reporting ≥ 1 event	**1 (9.1%)**	**2 (16.7%)**	**1 (8.3%)**	**1 (12.5%)**
Gastrointestinal Disorders				
Diarrhea	0	1 (8.3%)	0	0
Lower GI hemorrhage	1 (9.1%)	0	0	0
Infections and Infestations				
BK virus infection	0	0	0	1 (12.5%)
General Disorders and Administration Site Conditions				
Fatigue	0	1 (8.3%)	0	0
Investigations				
Neutrophil count decreased	0	1 (8.3%)	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	0	1 (8.3%)	0	0
Skin and Subcutaneous Tissue Disorders				
Toxic epidermal necrolysis	0	0	1 (8.3%)	0

[1] Subjects are counted once within each SOC or for each PT regardless of the number of AEs.
[2] All investigator verbatim terms were coded using MedDRA dictionary version 14.0.

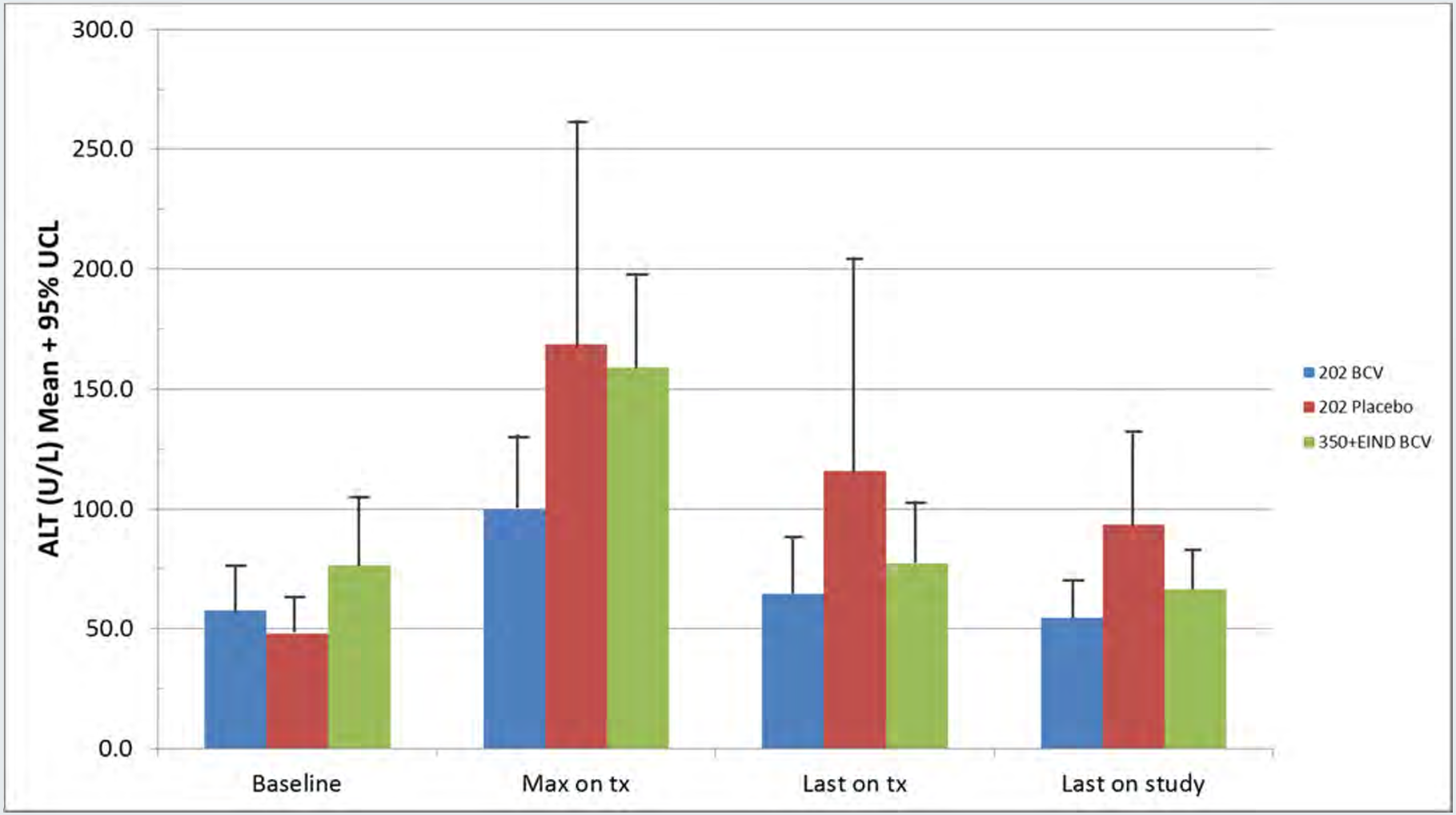
AEs of Particular Interest Leading to Study Drug Discontinuation by Dose

Study CMX001-350, Pediatric Subjects

	Recommended or Lower BCV Doses: ≤ 200 mg/wk or 4 mg/kg/wk (n=36)	Higher than Recommended BCV Doses: > 200 mg/wk or 4 mg/kg/wk (n=41)
No. of subj. with ≥ 1 event	**8 (22.2%)**	**7 (17.1%)**
Gastrointestinal		
Diarrhea	0	1 (2.4%)
Ileus	1 (2.8%)	1 (2.4%)
Lower GI hemorrhage	2 (5.6%)	0
Pancreatitis	0	2 (4.9%)
Hepatobiliary		
ALT increased	1 (2.8%)	0
AST increased	1 (2.8%)	0
Hepatic failure	0	1 (2.4%)
Immune System		
Acute GvHD	1 (2.8%)	1 (2.4%)
Renal and Urinary		
Renal failure acute	1 (2.8%)	0

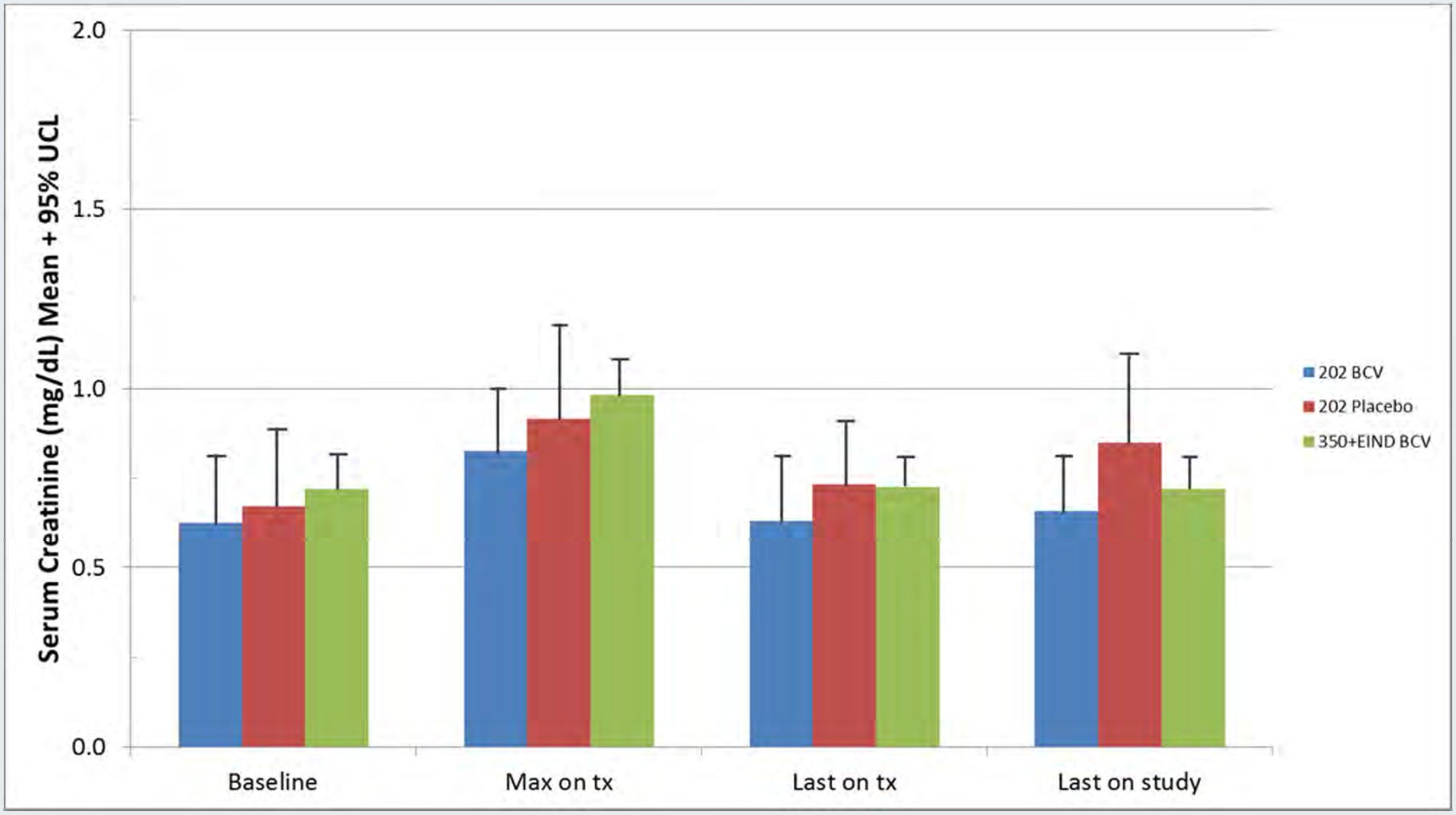
ALT: Baseline, Maximum On-Treatment, Last On-treatment and Last On-study Values

Studies CMX001-202 and CMX001-350, EINDs, Pediatric Subjects



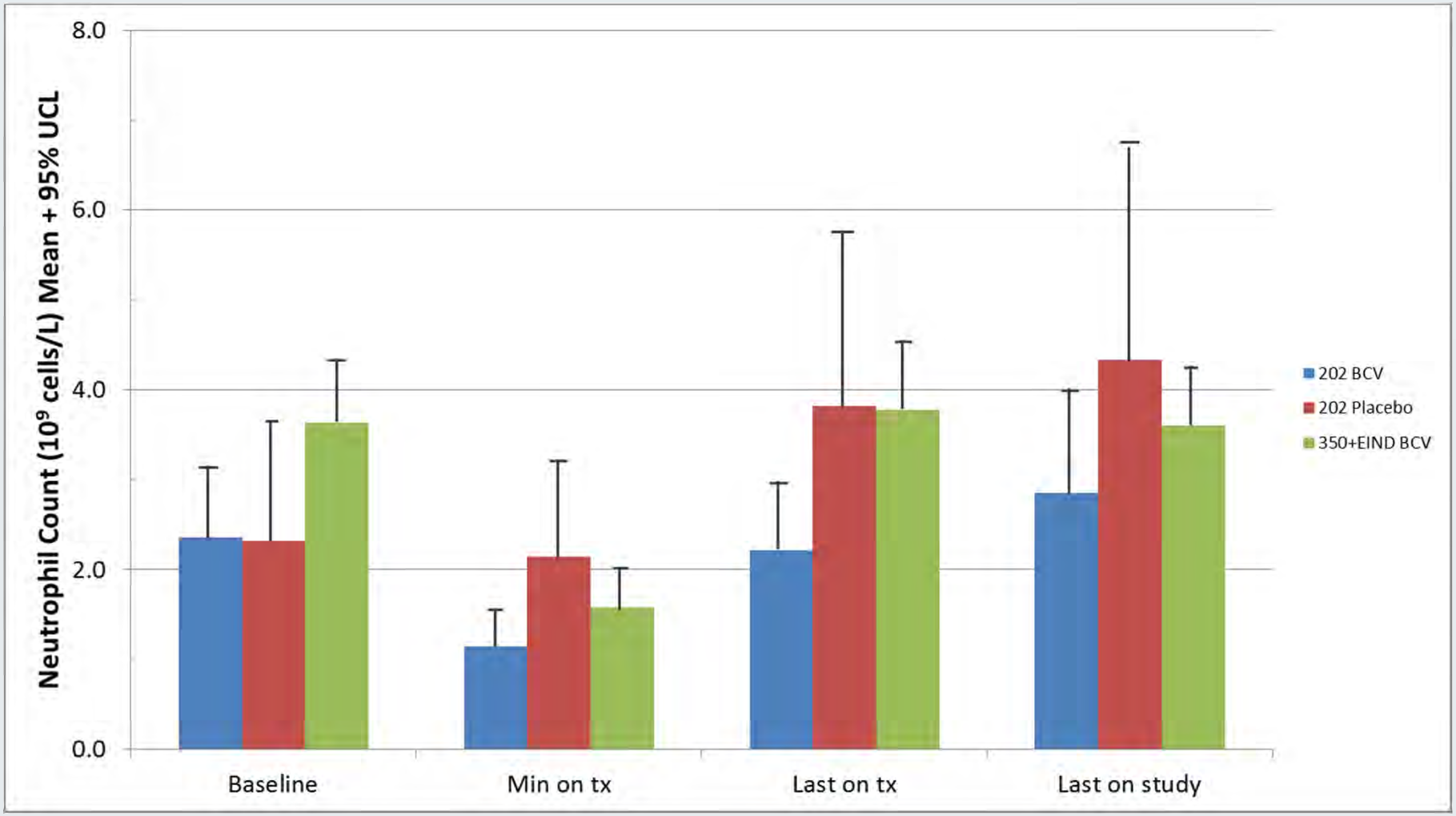
Serum Creatinine: Baseline, Max On-Treatment, Last On-treatment and Last On-study Values

Studies CMX001-202 and CMX001-350, EINDs, Pediatric Subjects



Neutrophils: Baseline, Minimum On-Treatment, Last On-treatment and Last On-study Values

Studies CMX001-202 and CMX001-350, EINDs, Pediatric Subjects



Conclusions

- Data from 143 pediatric patients in CMX001-202 and CMX001-350 trials and EIND revealed no previously unidentified safety signals
- Similar to the adult experience, the most frequently reported AEs were GI disturbances, primarily diarrhea (26%)
- The overall rate of discontinuation due to AEs in pediatric subjects receiving BCV therapy was 11% (16/143)
- Similar to the adult experience, increased serum transaminases (primarily ALT) with no corresponding bilirubin increases were reported in pediatric subjects
- In the placebo-controlled study (CMX001-202), the incidence of ALT/AST elevations in BCV-treated subjects was not higher than placebo recipients, although the sample size was very small
- Following implementation of the SMMP for Study CMX001-202, few subjects were discontinued due to GI events, acute GvHD, or increased serum transaminase concentrations
- As in adult patients, there was no indication of renal or hematologic toxicity in pediatric subjects

Acknowledgements

Funding: CMX001-350 Expanded Access Protocol was funded in part with Federal funds from the Biomedical Advanced Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, Department of Health and Human Services, under Contract No. HHSO1002O1100013C.

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