Pharmacokinetics and Safety of CMX157, a Novel Prodrug of Tenofovir, Administered as Ascending Multiple Doses to Healthy Volunteers and HBV-Infected Subjects

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CONTRAVIR

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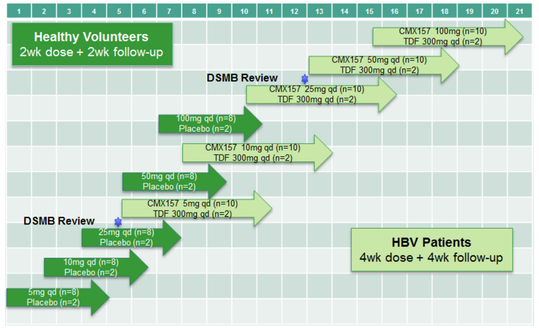
INTRODUCTION

CMX157 (3-(hexadecyloxy)propyl hydrogen ((R)-1-(6-amino-9H-purin 9-yl)propan-2-yloxy) methylphosphonate; hexadecyloxypropyl tenofovir; HDP-TFV) is a novel lipid conjugated prodrug of tenofovir (TFV), designed to take advantage of natural lipid uptake pathways and achieve high intracellular concentrations of the active antiviral TFV diphosphate, while decreasing plasma TFV, thereby lessening the potential for off-target toxicity.

Studies CTRV-CMX-102 and CTRV-CMX-201



CMX157-102: Healthy Subjects

- Phase 1 study for safety, tolerability and pharmacokinetics (PK) fasted and with food effect in healthy subjects.
- CMX157 5, 10, 25, 50, and 100 mg orally administered for 14 days to sequential cohorts of healthy subjects randomized 8:2, active: placebo.
- Fifty enrolled, 48 completed.
- Two discontinued (1 pregnancy, 1 consent withdrawn) study drug and completed safety follow up.

CMX157-201: HBV Infected Subjects

- Phase 2 study for the safety, tolerability, PK and antiviral activity in HBV-infected subjects.
- CMX157 5, 10, 25, and 50 mg orally administered for 28 days to sequential cohorts of 12 treatment -naïve HBV-infected subjects randomized 10:2, CMX157: Viread ®.
- Thirty-seven enrolled to date. Two completed . Twenty-three are in follow-up, 12 currently on treatment.

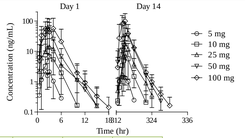
Both studies conducted in Thailand

CMX157-102 Demographics and Baseline Characteristics

CMX157-102:

- Healthy Subjects
- Mean age 33.9 years, SD 7.95
- 100% Asian
- 3:1, male : female
- BMI, eGFR and other baseline variables balanced across cohorts

CMX157-102: Pharmacokinetics of CMX157 in Healthy Subjects

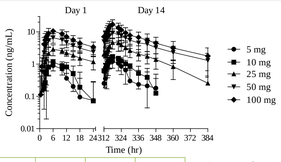


Day 1	5 mg	10 mg	25 mg	50 mg	100 mg
n	8	8	8	8	8
Cmax* (ng/mL)	3.1 (2.4)	9.7 (4.7)	27.1 (22.4)	78.4 (55.7)	110 (41.5)
Tmax (h) Median (min,max)	2.0 (1,4)	3.1 (1,4)	3.0 (1,10)	2.3 (1,3)	2.5 (1,4)
$AUC_{0-\infty}$* (ng-h/mL)	10.0 (6.5)	26.3 (6.6)	60.5 (32.5)	170 (112)	261 (135)
$t_{½}$* (h)	1.1 (0.3)	1.3 (0.4)	1.3 (0.3)	1.8 (0.5)	2.1 (0.4)

- No safety signals
- Approximately dose proportional PK
- Short half-life
- Supports QD dosing
- ~ 30% decrease in AUC with high fat meal
- No observable difference between Day 1 and Day 14

* Mean(SD)

CMX157-102: Pharmacokinetics of TFV in Healthy Subjects



Day 1	5 mg	10 mg	25 mg	50 mg	100 mg
n	8	8	8	8	8
Cmax* (ng/mL)	0.9 (0.3)	1.2 (0.3)	3.2 (0.6)	6.7 (2.0)	11.4 (2.5)
Tmax (h) Median (min,max)	6.0 (2.7,6)	6.0 (4,12)	6.0 (3,15)	6.0 (6,10)	6.0 (4,10)
$AUC_{0-\infty}$* (ng-h/mL)	23.1 (7.9)	18.8 (6.4)	59.0 (12.6)	146 (32.8)	205 (66.1)
$t_{½}$* (h)	11.4 (1.7)	8.1 (1.5)	10.8 (1.3)	15.6 (7.7)	11.6 (2.7)

- Approximately dose proportional PK
- Supports QD dosing
- ~50% increase in AUC with high fat meal
- No observable difference between Day 1 and Day 14

* Mean(SD)

Contributors

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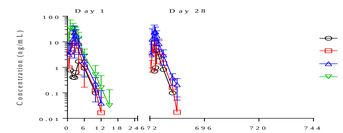
CMX157-201 Demographics and Baseline Characteristics

	5 mg	10 mg	25 mg	50 mg	TDF
n	2	9	10	10	6
Gender Male(n) : Female(n)	1:1	4:5	9:1	6:4	2:4
Age [years]	30.5 (3.5)	31.8 (9.3)	33.7 (10.0)	31.3 (7.6)	34.5 (9.7)
Race - Asian (n)	2	9	10	10	6
HBV DNA Log_{10} [IU/mL]	8.17 (0.32)	7.01 (0.68)	6.72 (2.01)	7.12 (1.81)	6.68 (0.94)
ALT [U/L]	40 (5)	103 (84)	47 (34)	91 (75)	67 (20)
HBV eAg+	2	9	6	9	4
HBV eAg-	0	0	4	1	2
BMI [kg/m^2]	20.2 (0.5)	21.8 (2.1)	23.5 (2.1)	21.7 (3.0)	22.2 (2.9)
Total Bilirubin [mg/dL]	0.53 (0.11)	0.56 (0.11)	0.67 (0.29)	0.57 (0.35)	0.57 (0.20)

- Continuous variables are shown as Mean (SD)
- Subjects with a Metavir score > F2 excluded

CMX157-201: Pharmacokinetics of CMX157 in HBV-Infected Subjects

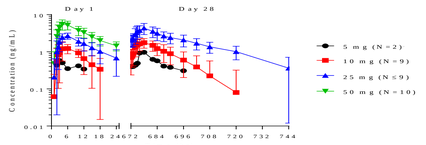


Day 1	5 mg	10 mg	25 mg	50 mg
n	2	9	10	10
Cmax* (ng/mL)	2.5 (--)	14.0 (11.3)	27.8 (16.2)	52.2 (26.9)
Tmax (h) Median (min,max)	2.5 (1,4)	2.0 (1,4)	2.5 (0.5,4)	2.0 (1,3)
$AUC_{0-\infty}$* (ng-h/mL)	2.3 (--)	29.1 (21.7)	56.0 (26.9)	112 (38.5)
$t_{½}$* (h)	1.0 (--)	1.2 (0.3)	1.1 (0.3)	1.3 (0.3)

- Dose-dependent PK
- Approximately dose-proportional
- Short half-life (prodrug)
- PK and safety support fully exploring the dose range
- No observable difference between Day 1 and Day 28

* Mean(SD)

CMX157-201: Pharmacokinetics of TFV in HBV-Infected Subjects



Day 1	5 mg	10 mg	25 mg	50 mg
n	2	9	10	10
Cmax* (ng/mL)	1.2 (--)	1.4 (0.5)	2.9 (0.4)	5.8 (1.3)
Tmax (h) Median (min,max)	3.0 (3,3)	4.0 (3,6)	6.0 (2.7,10)	4.0 (4,6)
$AUC_{0-\infty}$* (ng-h/mL)	ND (--)	20.7 (5.0)	46.9 (15.5)	94.7 (22.2)
$t_{½}$* (h)	ND (--)	8.0 (3.7)	10.4 (2.7)	11.4 (2.3)

- Dose-dependent PK
- Approximately dose-proportional
- Low TFV consistent with potential for improved safety over TDF
- No observable difference between Day 1 and Day 28

* Mean(SD) ND – Not Determined

CMX157-102: Safety

Overall treatment with CMX157 was safe and well-tolerated by healthy subjects. There were no patterns or dose-related trends in the nature, frequency or severity of AEs, safety laboratory parameters, vital signs or ECGs. The majority of AEs were mild and resolved during the study.

CMX157-102: Safety (continued)

- Adverse events were most frequently reported in Nervous System Disorders (5 of 40) and Gastrointestinal Disorders (4 of 40) System Organ Classifications. Dizziness (4 of 40), headache (2 of 40), diarrhea (2 of 40), nausea (2 of 40) and rhinorrhea (2 of 40) were most frequently reported. Diarrhea (1 of 10) was also reported in the placebo group.

CMX157-201: Safety

	CMX157					TDF
By SOC	5 mg	10 mg	25 mg	50 mg	Total	300 mg
n	2	9	10	10	31	6
Any AE	2	2	5	2	11	3
Blood and Lymphatic System Disorders	1				1	1
Gastrointestinal Disorders		1	3		4	
General Disorders and Administration Site Conditions	1				1	
Infections and Infestations	1		3	1	5	
Injury, Poisoning and Procedural Complications			1		1	
Investigations	1		1		2	
Metabolism and Nutrition Disorders			2		2	
Musculoskeletal Disorders			1		1	1
Nervous System Disorders		1	3		4	1
Reproductive System Disorders	1				1	
Skin Disorder	1				1	

- No SAEs or discontinuations for AEs.
- ECGs, vital signs, safety laboratory results are unremarkable.
- Safety evaluations show no patterns or any relationship to dose.
- Consistent with the disease and the study population.

CONCLUSION

- CMX157 and TFV exposures dose proportional from 10 to 100 mg without accumulation.
- PK in healthy and HBV-infected subjects comparable and supports QD dosing.
- Minimal food effect not clinically significant.
- Safe and well tolerated in healthy and HBV-infected subjects. No drug related safety signals.
- Low levels of circulating TFV may mitigate risk of kidney and bone toxicities associated with approved treatment.
- Data support continuing dose escalation to fully define CMX157 pharmacokinetics, safety and antiviral activity.
- Clinical investigation for HBV endpoints is ongoing.