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

Presentation #: OP221

Tawesak Tanwandee, MD, Somruedee Chatsiricharoenkul, MD, Pisit Tangkijvanich, MD, Satawat Thongsawat, MD, Wattana Sukeepaisarnjaroen, MD, Anchalee Avihigsanon, MD, Piyawat Komolmit, MD, and Teerha Piratvisuth, MD

Tenofovir exalidex
Background

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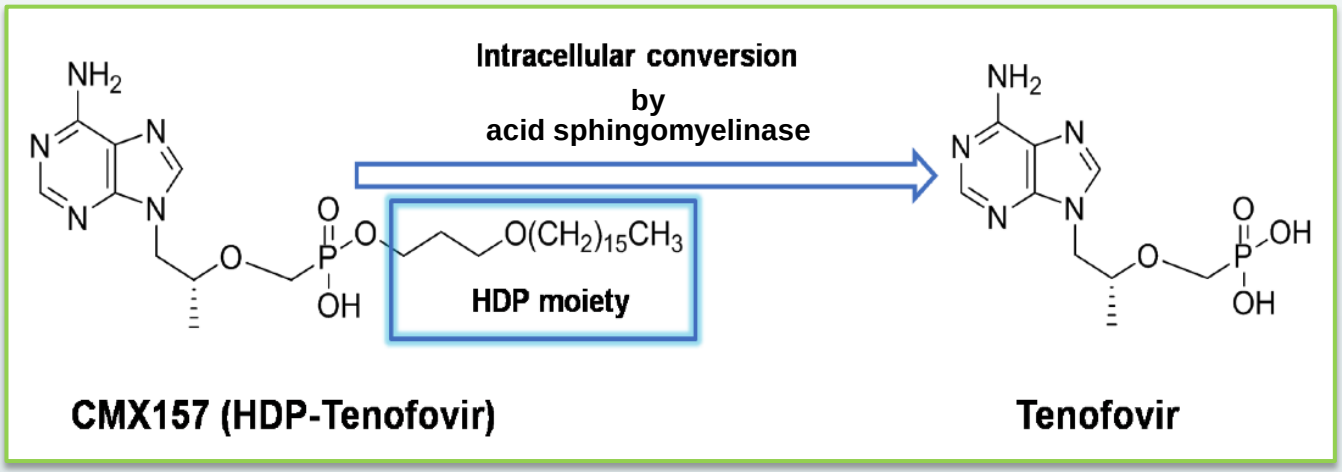
Enhanced Efficacy and Safety

- Increased bioavailability by harnessing lipid uptake mechanisms
- Enhanced target tissue penetration
- Decreased renal and bone toxicity by reducing circulating TFV

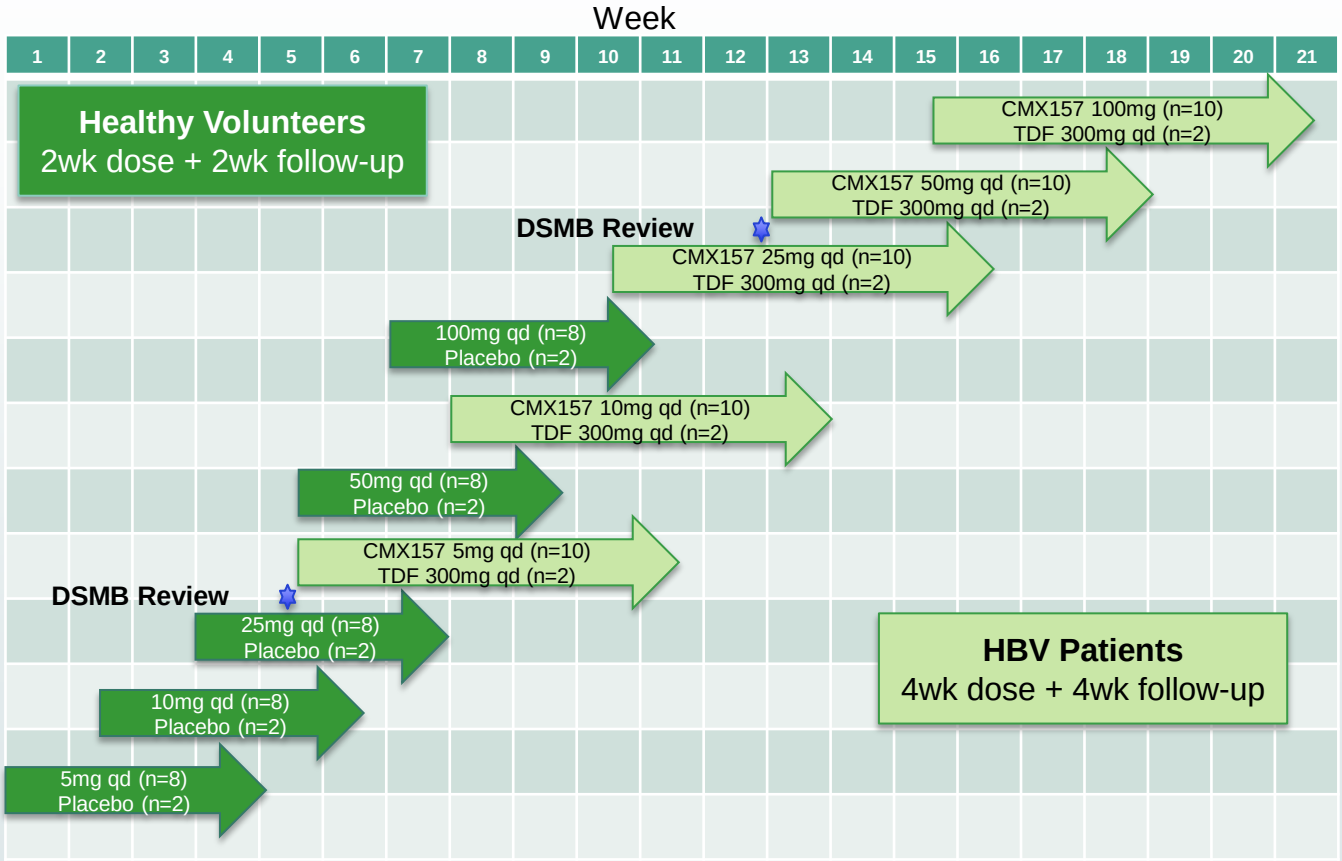
Enhanced Potency

- 97 fold more potent in HBV than TFV *in vitro*
- 200 fold more potent in HIV than TFV *in vitro*



Overview

Studies CRTV-CMX-102 and CRTV-CMX-201



Tenofovir exalidex

Study CTRV-CMX-102 and 201; Baseline Characteristics

CMX-102	5 mg	10 mg	25 mg	50 mg	100 mg	Placebo
N=50	8	8	8	8	8	10
Gender Male(n):Female(n)	5:3	5:3	6:2	7:1	6:2	8:2
Age [years][3]	33.6 (6.9)	33.9 (6.8)	38.3 (6.8)	30.9 (10.8)	32.6 (7.8)	30.2 (8.8)
Race - Asian (n)	8	8	8	8	8	10
CMX-201	**5 mg**	**10 mg**	**25 mg**	**50 mg**	**100 mg**	**Viread®**
N=49	2[1]	9[2]	10	10	10	8
Gender Male(n):Female(n)	1:1	4:5	9:1	6:4	6:4	3:5
Age [years][3]	30.5 (3.5)	31.8 (9.3)	33.7 (10.0)	31.3 (7.6)	38.9 (7.7)	33.8 (8.5)
Race - Asian (n)	2	9	10	10	10	8
BMI [kg/m^2]	20.2 (0.5)	21.8 (2.1)	23.5 (2.1)	21.7 (3.0)	23.0 (3.7)	22.4 (3.4)
ALT [U/L]	40 (5)	103 (84)	47 (34)	91 (75)	56 (58)	62 (19)
HBV eAg+/eAg-	2:0	9:0	6:4	9:1	2:8	5:3

[1]Recruitment stopped due to lack of antiviral activity

[2]Recruitment stopped at 9 tenofovir exalidex (not the planned 10) and 2 TFV due to logistical problems

[3]Continuous variables are shown as Mean (SD)

Tenofovir exalidex: Healthy Volunteer

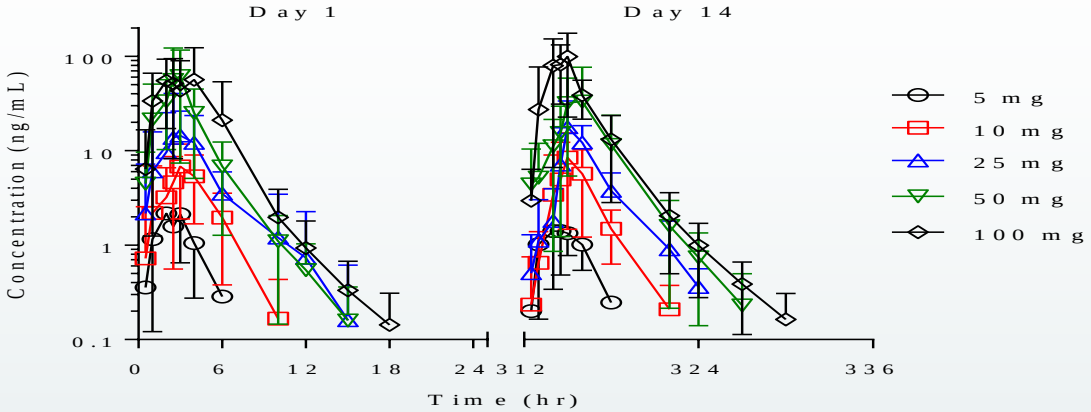
Study CTRV-CMX-102; Number of subjects with AEs, by SOC

	Tenofovir exalidex						Placebo
System Organ Classification	5 mg	10 mg	25 mg	50 mg	100 mg	Total	
NUMBER OF SUBJECTS	8	8	8	8	8	40	10
Any AE	2	2	1	3	3	11	3
Gastrointestinal Disorders	1		1	1	1	4	1
Infections and Infestations					1	1	1
Injury, Poisoning and Procedural Complications							1
Cardiac Disorders			1			1	
Nervous System Disorders	1	1	1	1	1	5	
Respiratory, Thoracic and Mediastinal Disorder	1	1		1		3	

- 50 subjects dosed
- No SAEs or discontinuations for AEs
- ECGs, vital signs, safety laboratory results show no patterns or any relationship to dose

Tenofovir exalidex

Study CTRV-CMX-102 TXL PK



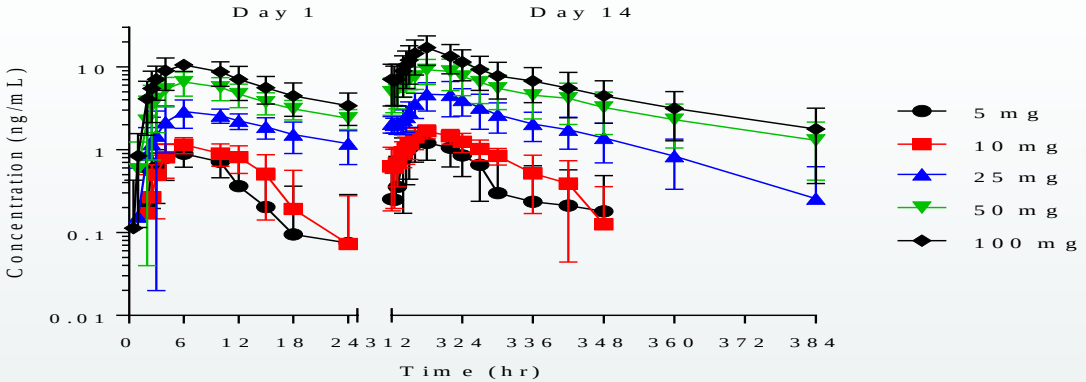
DAY 14	5 mg	10 mg	25 mg	50 mg	100 mg
n	n=8	n=8	n=8	n=8	n=8
Cmax[1] [ng/mL]	1.92 (0.85)	10.7 (8.05)	21.2 (14.3)	47.1 (42.6)	132 (70.6)
Tmax [h] Median (min, max)	2.5 (1, 4)	3.0 (2.5,4)	3.5 (2.5, 10)	3.0 (2, 6)	3.0 (2,4)
AUC_{0-24} [ng-h/mL]	6.6 (2.7)	24.8 (17.2)	52.4 (13.2)	126 (90.9)	285 (136)
$t_{½}$ [h]	1.2 (0.3)	1.38 (0.35)	1.64 (0.33)	1.84 (0.57)	2.4 (0.69)

[1]Mean (SD) for all except Tmax

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

Tenofovir exalidex

Study CTRV-CMX-102 TFV PK



DAY 14	5 mg	10 mg	25 mg	50 mg	100 mg
n	n=8	n=8	n=8	n=8	n=8
Cmax[1] [ng/mL]	1.3 (0.5)	1.7 (0.3)	4.9 (2.0)	9.6 (3.3)	17.3 (6.4)
Tmax [h] Median (min, max)	6.0 (3, 10)	6.0 (4, 10)	6.0 (6, 12)	6.0 (3, 12)	6.0 (6, 10)
AUC_{0-24} [ng-h/mL]	22.2 (9.2)	26.3 (6.0)	78.7 (28.3)	163 (62.7)	256 (106)
$t_{½}$ [h]	16.8 (11.5)	14.4 (3.3)	20.9 (6.3)	27.4 (5.0)	26.1 (8.1)

[1]Mean (SD) for all except Tmax

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

Tenofovir exalidex: HBV+ Patients

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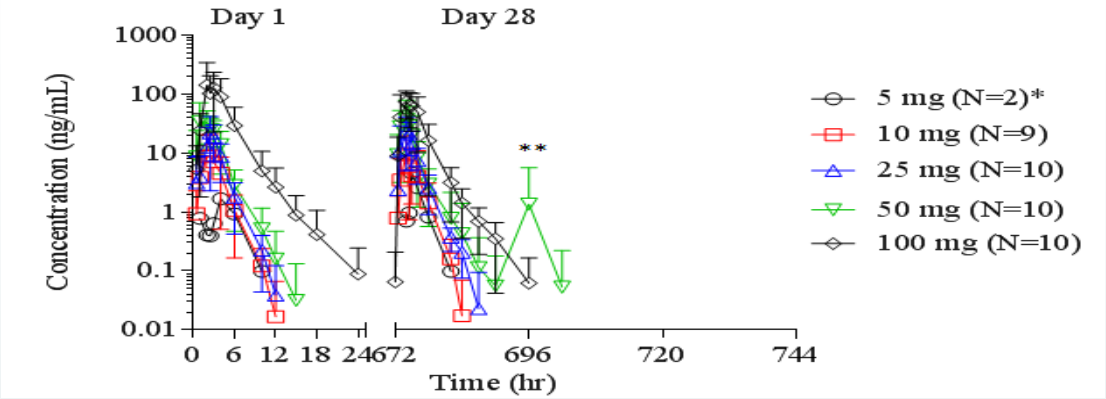
Study CTRV-CMX-201; Number of subjects with AEs, by SOC

	Tenofovir exalidex						
System Organ Classification	5 mg	10 mg	25 mg	50 mg	100 mg	Total	Viread®
NUMBER OF SUBJECTS	2	9	10	10	10	41	8
Any AE	2	2	5	3	3	15	4
Blood and Lymphatic System Disorders	1					1	
Gastrointestinal Disorders		1	1	1	1	4	2
General Disorders and Administration Site Conditions	1				1	2	
Infections and Infestations			3	2	1	6	
Injury, Poisoning and Procedural Complications			1			1	
Investigations	1					1	
Metabolism and Nutrition Disorders			1	1		2	
Musculoskeletal Disorders			1			1	1
Nervous System Disorders		1	3			4	2
Reproductive System Disorders	1					1	
Skin Disorders	1					1	
Hepatobiliary Disorder				1		1	
Respiratory, Thoracic and Mediastinal Disorder	1					1	

- 49 subjects dosed
- No SAEs or discontinuations for AEs
- ECGs, vital signs, safety laboratory results show no patterns or any relationship to dose
- Results are consistent with the disease and the study population

Tenofovir exalidex

Study CTRV-CMX-201; TXL Pharmacokinetics



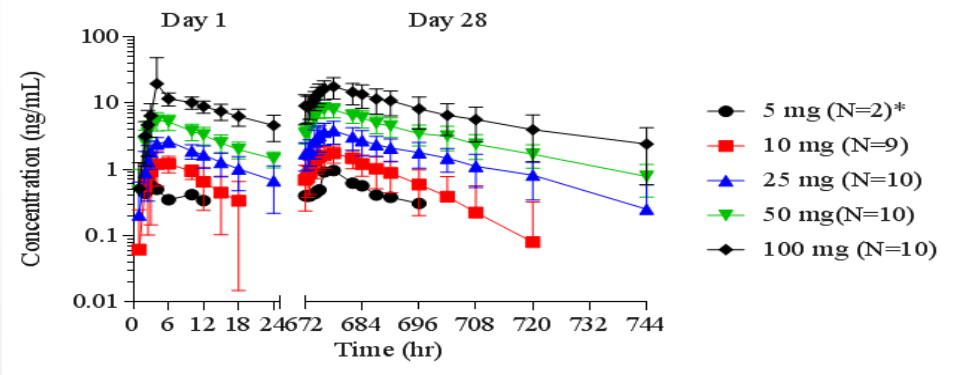
DAY 28	5 mg	10 mg	25 mg	50 mg	100 mg
n	n=2	n=9	n=10	n=10	n=10
Cmax[1] [ng/mL]	4.6 (--)	12.9 (9.5)	29.0 (15.5)	51.3 (39.9)	102 (38.9)
Tmax [h] Median (min, max)	3.0 (3, 3.02)	2.0 (0.8, 6)	2.0 (1, 2.5)	1.5 (1, 2.5)	2.3 (1, 4)
AUC_{0-24} [ng-h/mL]	15.6 (--)	26 (15.8)	66.7 (37.6)	110 (81.9)	313 (170)
$t_{½}$ [h]	1.4 (--)	1.3 (0.48)	1.7 (0.46)	1.5 (0.69)	2.6 (0.72)

[1]Mean (SD) for all except Tmax

- Approximately dose proportional PK with numerical increase at 100 mg
- Short half-life
- Supports QD dosing
- No accumulation between Day 1 and Day 14

Tenofovir exalidex

Study CTRV-CMX-201; TFV Pharmacokinetics



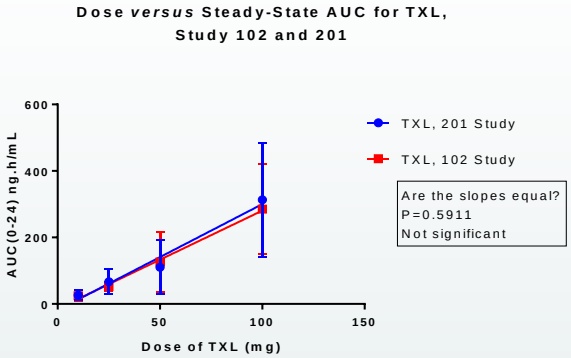
DAY 28	5 mg	10 mg	25 mg	50 mg	100 mg	Viread®
n	n=2	n=9	n=10	n=10	n=10	n=8
Cmax[1] [ng/mL]	1.0 (--)	1.8 (0.5)	4.0 (1.5)	8.5 (2.0)	18.3 (6.0)	344 (97.8)
Tmax [h] Median (min, max)	6.0 (6, 6)	6.0 (2.5, 6)	6.0 (4, 12)	4.0 (2.5, 10)	6.0 (3, 10)	1 (0.5, 2)
AUC_{0-24} [ng-h/mL]	23.4 (--)	28.8 (9.6)	63.7 (22.5)	136 (33.3)	302 (111)	2690 (575)
$t_{½}$ [h]	21 (--)	23.1 (28.5)	23 (5.5)	23.3 (3.4)	28.1 (7.2)	18.7 (2.9)

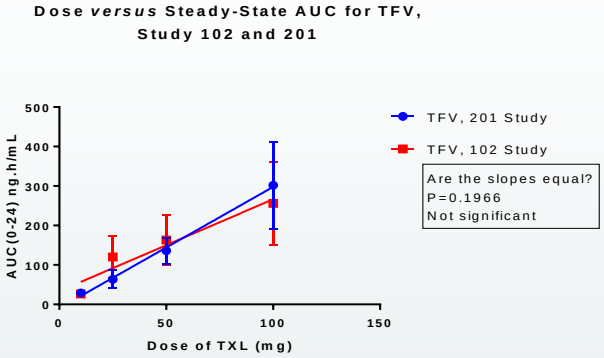
- Approximately dose proportional PK with numerical increase at 100 mg
- Supports QD dosing
- No accumulation between Day 1 and Day 14
- Low levels of free TFV compared to Viread®

[1]Mean (SD) for all except Tmax

Tenofovir exalidex

Exposures in Healthy vs. HBV-infected Subjects





- $AUC_{0\text{-}24h}$ of TXL across all doses tested was not statistically different in healthy vs. HBV-infected subjects
- $AUC_{0\text{-}24h}$ of TFV TXL across all doses tested was not statistically different in healthy vs. HBV-infected subjects
- $AUC_{0\text{-}24h}$ of TXL and TFV, at 100 mg, were numerically higher in HBV-infected subjects

Tenofovir exalidex
Conclusions

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- 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.

Thank you

ContraVir

- **Study subjects**
- **Clinical research sites and staff**
  - Siriraj Hospital, Mahidol University
  - Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University
  - Srinagarind Hospital, Khon Kaen University
  - King Chulalongkorn University Hospital, Chulalongkorn University
  - HIV-NAT, Bangkok
  - Songklanagarind Hospital, Prince of Songkla University
- **ACLIRES International Ltd.**