EASL The Home of Hepatology | THE INTERNATIONAL LIVER CONGRESS™ 2017 19-23 APRIL, AMSTERDAM, THE NETHERLANDS

ContraVir

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 #: **PS-040**

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

Presenter Disclosure Information

Tawesak Tanwandee, MD

Presentation #: **PS-040**

FINANCIAL DISCLOSURE:

Grants/Research Support: Roche, Inovio, ContraVir, Eisai and MSD

Unlabeled/Unapproved Uses Disclosure:

Use of TXL™ is investigational ONLY

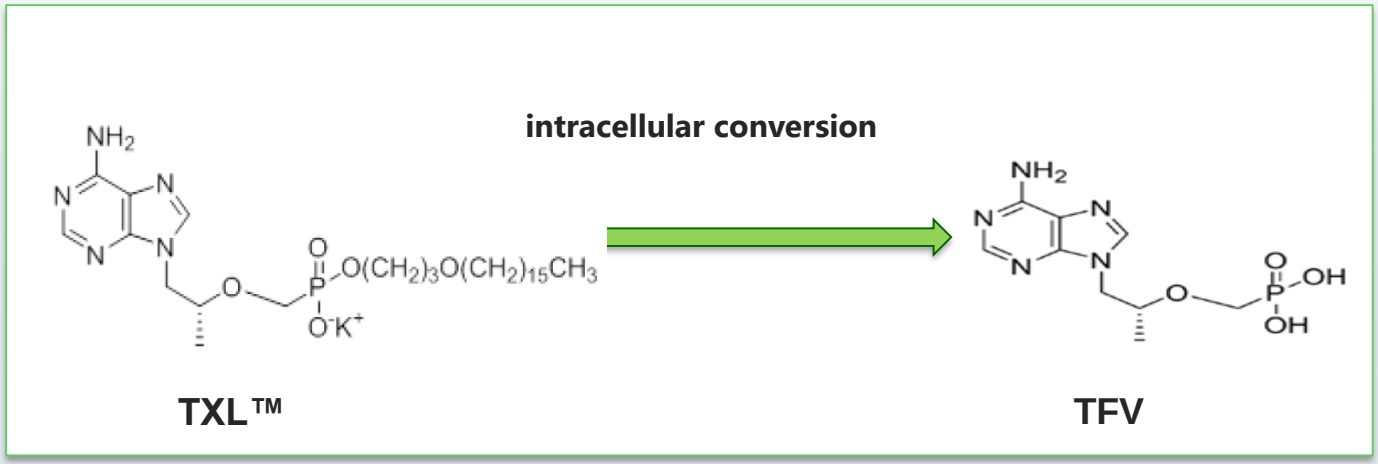
Tenofovir exalidex
Background

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

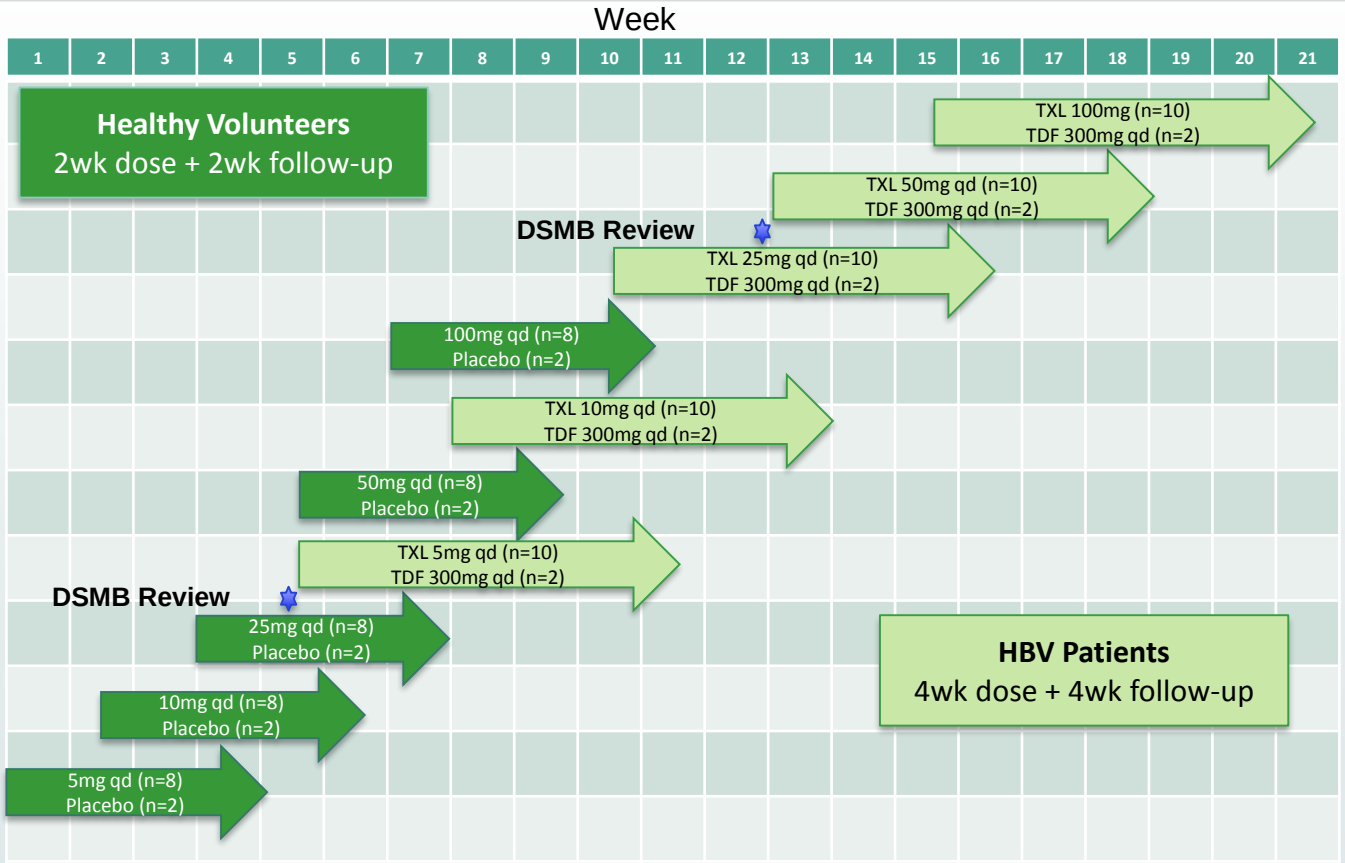
- 97 fold more potent in HBV than TFV *in vitro*



TXL™ **TFV**

Tenofovir exalidex

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



Tenofovir exalidex

Study CTRV-CMX-102 and 201; Baseline Characteristics

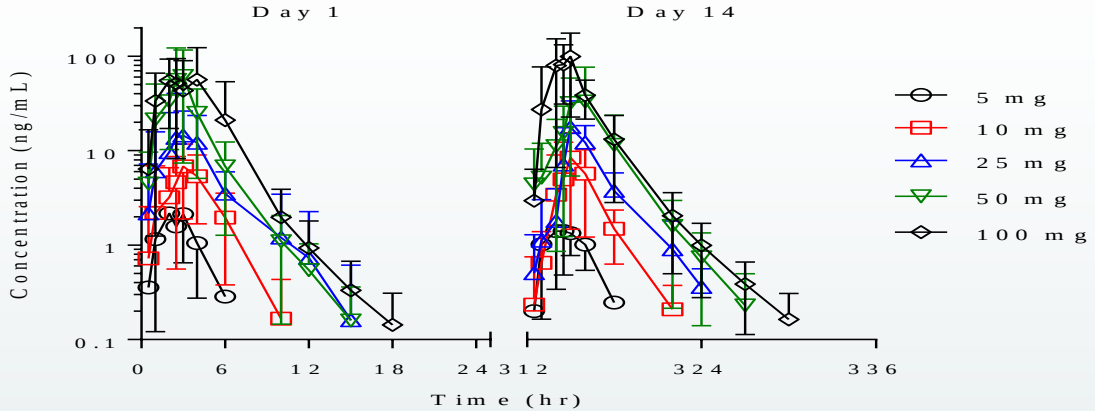
CMX-102	5 mg	10 mg	25 mg	50 mg	100 mg	Placebo
N=50	8	8	8	8	8	10
Gender Male(n):Female(n)	5:3	5:3	6:2	7:1	6:2	8:2
Age [years][1]	33.6 (6.9)	33.9 (6.8)	38.3 (6.8)	30.9 (10.8)	32.6 (7.8)	30.2 (8.8)
Race - Asian (n)	8	8	8	8	8	10
BMI [kg/m]	22.6 (2)	23.5 (2.2)	23.4 (2.6)	21.1 (3.5)	22.3 (2.2)	23.2 (2.3)
CMX-201	**5 mg**	**10 mg**	**25 mg**	**50 mg**	**100 mg**	**Viread®**
N=62	2[2]	9	10	10	21	10
Gender Male(n):Female(n)	1:1	4:5	9:1	6:4	11:10	4:6
Age [years]	30.5 (3.5)	31.8 (9.3)	33.7 (10.0)	31.3 (7.6)	36.5 (8.0)	34.2 (7.8)
Race - Asian (n)	2	9	10	10	21	10
BMI [kg/m]	20.2 (0.5)	21.8 (2.1)	23.5 (2.1)	21.7 (3.0)	22.1 (3.4)	22.9 (3.2)

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

[2]Recruitment stopped due to lack of antiviral activity

Tenofovir exalidex

Study CTRV-CMX-102 TXL PK



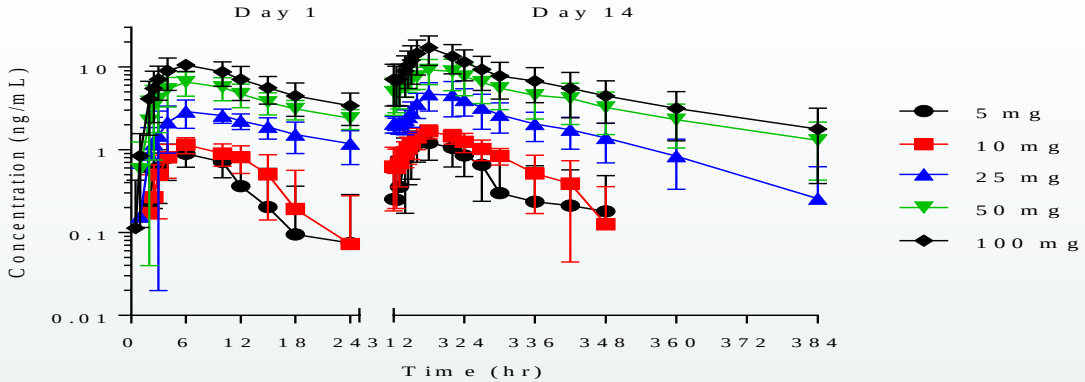
DAY 14	5 mg	10 mg	25 mg	50 mg	100 mg
	n=8	n=8	n=8	n=8	n=8
Cmax[1] [ng/mL]	1.92 (0.85)	10.7 (8.05)	21.2 (14.3)	47.1 (42.6)	132 (70.6)
Tmax [h] Median (min, max)	2.5 (1, 4)	3.0 (2.5,4)	3.5 (2.5, 10)	3.0 (2, 6)	3.0 (2,4)
AUC_{0-24} [ng-h/mL]	6.6 (2.7)	24.8 (17.2)	52.4 (13.2)	126 (90.9)	285 (136)
$t_{½}$ [h]	1.2 (0.3)	1.4 (0.4)	1.6 (0.3)	1.8 (0.6)	2.4 (0.7)

[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=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: Healthy Volunteer

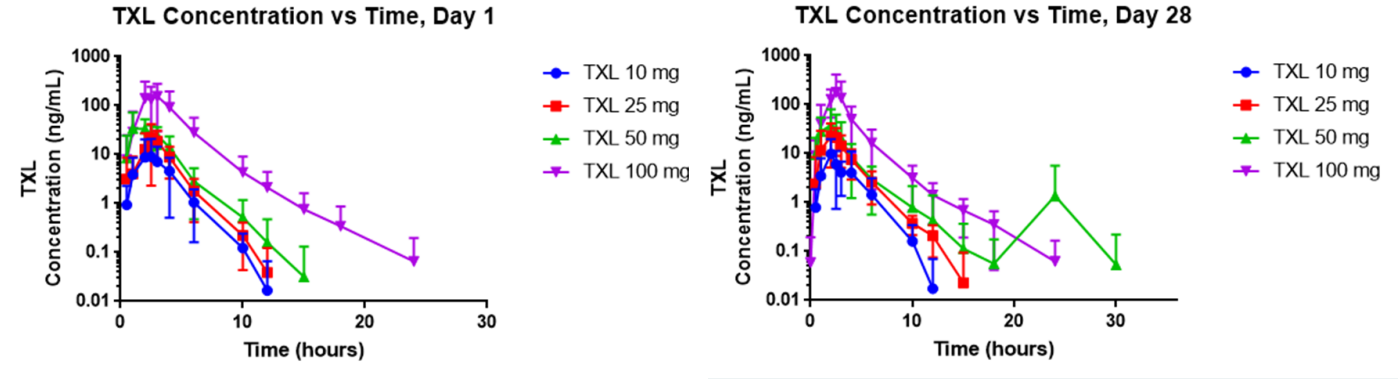
Study CTRV-CMX-102; Number of subjects with AEs, by SOC

	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-201; TXL Pharmacokinetics



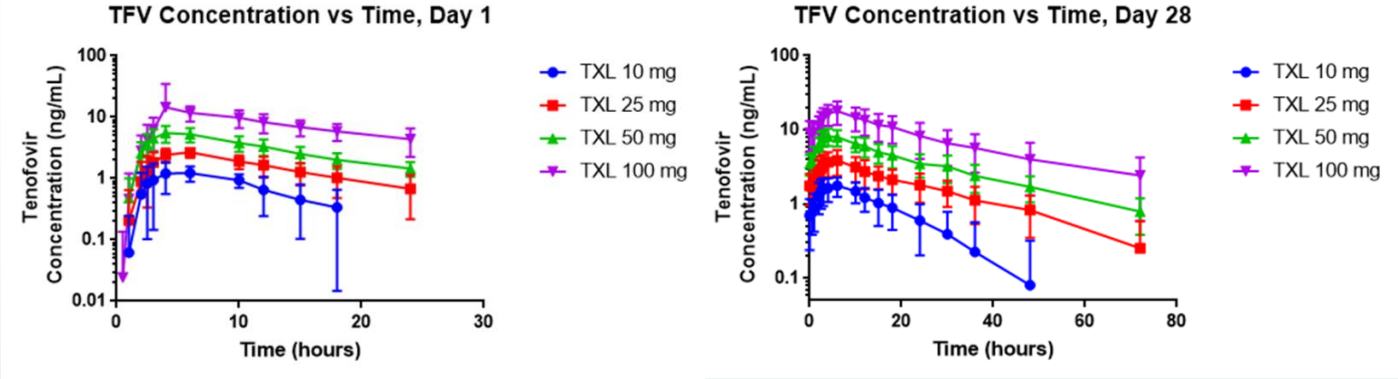
DAY 1	5 mg	10 mg	25 mg	50 mg	100 mg
	n=2	n=9	n=10	n=10	n=21
Cmax[1] [ng/mL]	2.5 (--)	14.0 (11.3)	27.8 (16.2)	52.2 (26.9)	232 (169)
Tmax [h] Median (min, max)	2.5 (1, 4)	2.0 (1, 4)	2.5 (0.5, 4)	2.0 (1, 3)	3.0 (2, 6)
AUC_{0-24} [ng-h/mL]	2.36 (--)	29.1 (21.7)	56.0 (27.0)	112 (38.2)	519 (354)
$t_{½}$ [h]	1.0 (--)	1.2 (0.3)	1.1 (0.3)	1.3 (0.3)	2.2 (0.5)

[1]Mean (SD) for all except Tmax

- Approximately dose proportional
- Short half-life
- Supports QD dosing

Tenofovir exalidex

Study CTRV-CMX-201; TFV Pharmacokinetics



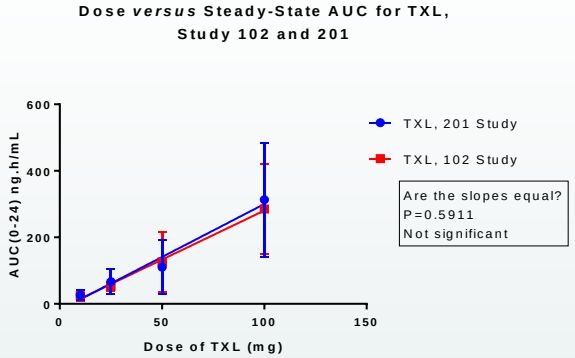
DAY 1	5 mg	10 mg	25 mg	50 mg	100 mg	Viread®
	n=2	n=9	n=10	n=10	n=21	n=10
Cmax[1] [ng/mL]	1.2 (--)	1.4 (0.5)	2.9 (0.4)	5.8 (1.3)	16.6 (20)	382 (120)
Tmax [h] Median (min, max)	3.0 (3, 3)	4.0 (3, 6)	6.0 (2.7, 10)	4.0 (4,6)	6.0 (4, 10)	0.9 (0.5, 2)
AUC_{0-24} [ng-h/mL]	15.8 (--)	17.5 (3.8)	34.9 (8.3)	71.7 (18.9)	176 (52.9)	2060 (514)
$t_{½}$ [h]	ND ND	8.0 (3.7)	10.4 (2.7)	11.4 (2.3)	14.8 (10.7)	11.5 (1.0)

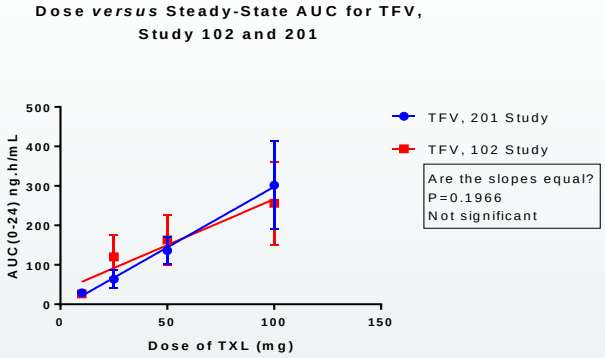
[1]Mean (SD) for all except Tmax

- **Dose proportional PK**
- **Supports QD dosing**
- **Low levels of free TFV compared to Viread®**

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 across all doses of TXL 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: HBV+ Patients

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	21	52	10
Any AE	2	2	5	4	7	20	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	3	3	9	
Injury, Poisoning and Procedural Complications			1		1	2	
Investigations	1				1	2	
Metabolism and Nutrition Disorders			1	1		2	
Musculoskeletal Disorders			1	1		2	1
Nervous System Disorders	1	1	3		1	6	2
Reproductive System Disorders	1			1		2	
Skin Disorders	1				1	2	
Hepatobiliary Disorder				1		1	
Respiratory, Thoracic and Mediastinal Disorder	1					1	
Cardiac Disorders					1	1	

- 62 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; Virologic Baseline Characteristics

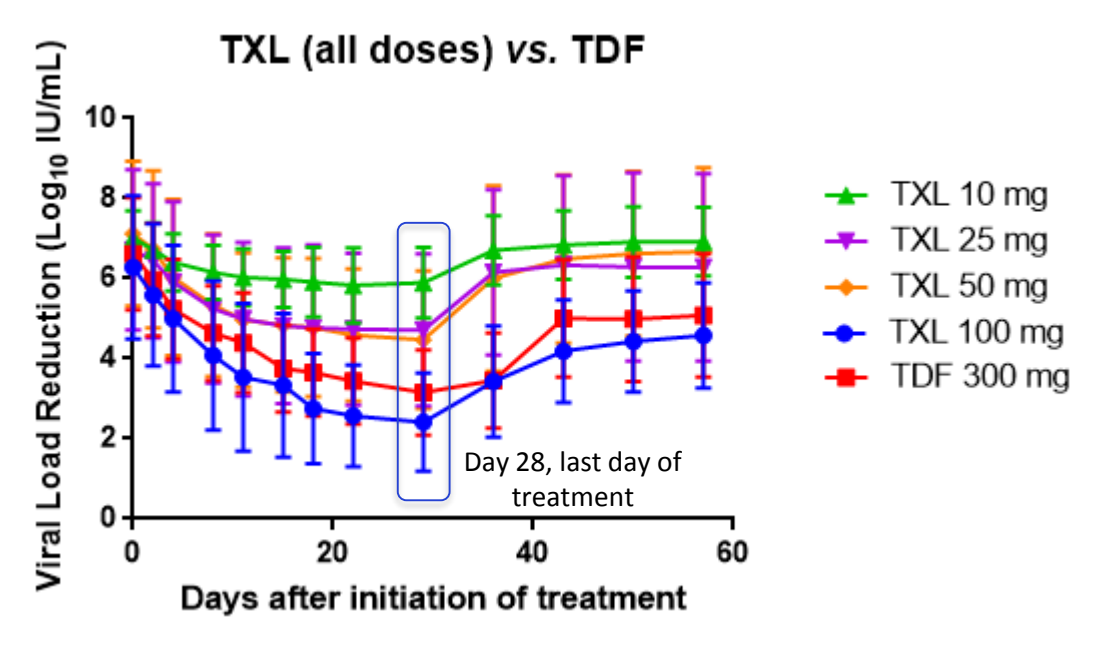
CMX-201	5 mg	10 mg	25 mg	50 mg	100 mg	Viread®
N=62	2[1]	9	10	10	21	10
Gender Male(n):Female(n)	1:1	4:5	9:1	6:4	11:10	4:6
Age [years][2]	30.5 (3.5)	31.8 (9.3)	33.7 (10.0)	31.3 (7.6)	36.5 (8)	34.2 (7.8)
HBV eAg+/eAg-	2:0	9:0	6:4	9:1	13:8	7:3
ALT [U/L]	40 (5)	103 (84)	47 (34)	91 (75)	60 (66)	58 (20)
Total Bilirubin [mg/dL]	0.53 (0.11)	0.56 (0.11)	0.67 (0.29)	0.57 (0.35)	0.59 (0.27)	0.51 (0.2)
HBV DNA [log_{10} IU/mL]	8.2 (.32)	7.0 (.68)	6.7 (2.0)	7.1 (1.8)	6.3 (1.7)	6.6 (1.4)

[1]Recruitment stopped due to lack of antiviral activity

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

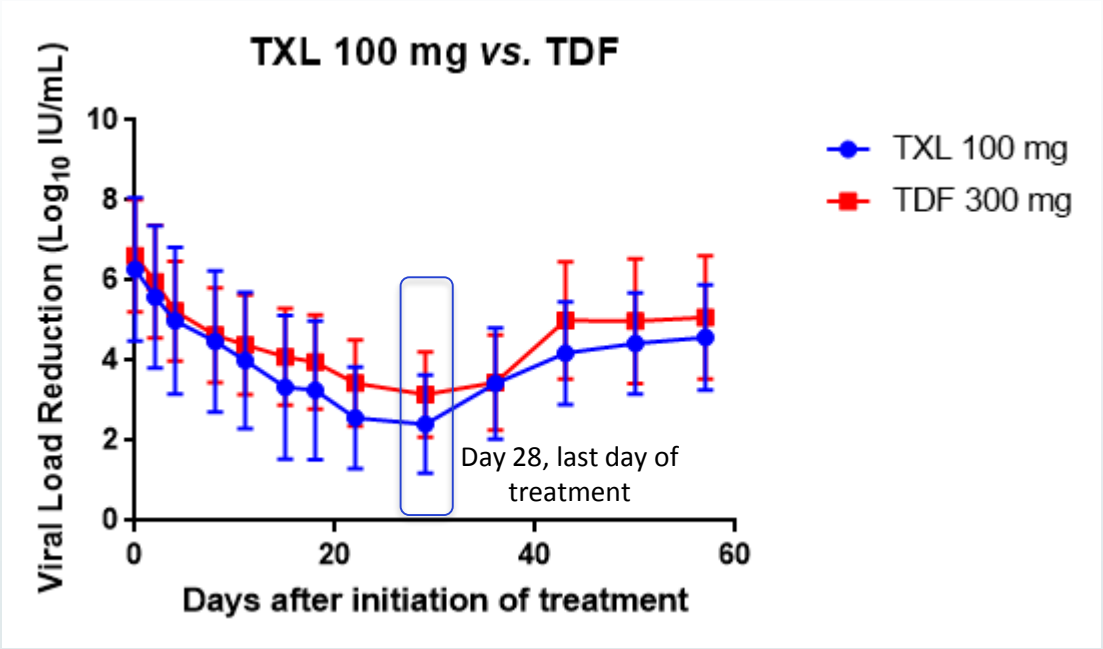
Tenofovir exalidex

Study CTRV-CMX-201; HBV DNA over time (mean +/- SD)



Tenofovir exalidex

Study CTRV-CMX-201; HBV DNA over time (mean +/- SD)



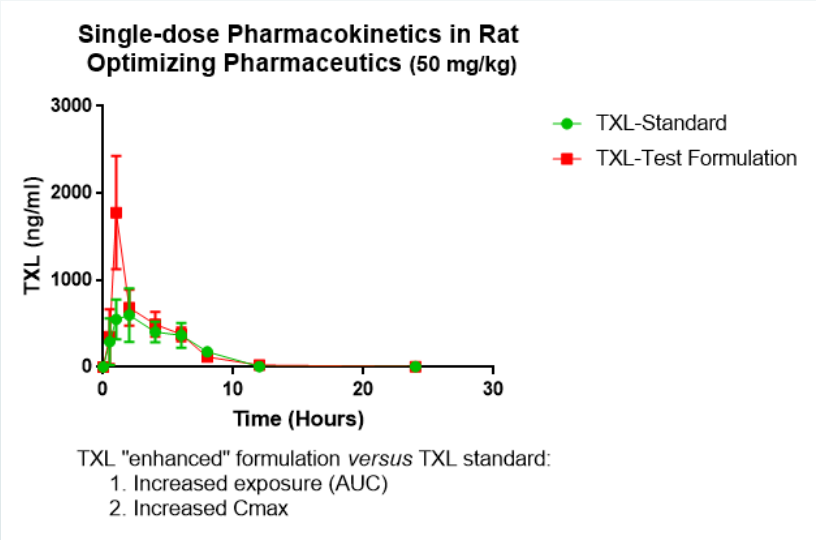
Tenofovir exalidex
CONCLUSIONS

- **TXL was safe and effective**
- **Lower systemic circulating TFV levels may mitigate bone and kidney toxicities previously reported for Viread**
- **First generation prototype formulation is now being optimized to enhance pharmaceutical properties**

Tenofovir exalidex
CONCLUSIONS

- **Second generation, 'optimized formulation', designed to reduce drug loading (mg/tablet), allowing for:**
  1. **Reduced dosing; and**
  2. **Potential for drug combinations**

- **Proof of Principle animal model:**



Thank you

- **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.**