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Pharmacokinetics, Safety and Antiviral Activity of Tenofovir Exalidex(TXL™), a Novel Prodrug of Tenofovir, Administered as Ascending Multiple Doses to HBV-Infected Subjects: A 28 Day Study Final Analyses

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INTRODUCTION

Tenofovir exalidex (TXL) is a novel prodrug of the acyclic nucleotide phosphonate tenofovir (TFV). By chemically modifying TFV to include a lipid moiety, there is targeted cellular uptake in the liver through natural lipid absorption pathways and cellular conversion of TXL into TFV di-phosphate. This novel liver targeting structure results in decreased systemic circulating levels of TFV, thereby reducing the potential for renal and bone side effects. A single dose rat study of 20mg/kg TXL with an 86% first pass liver extraction demonstrated extensive liver targeting. The phase 1 multiple ascending oral dose study (CTRV-CMX-102) reported favorable safety, tolerability and pharmacokinetics. This multiple dose phase 2 study was designed to investigate safety, pharmacokinetics and HBV antiviral effects of TXL.

MATERIAL & METHODS

- Phase 2 study for the safety, tolerability, pharmacokinetics and antiviral activity in HBV-infected subjects.
- TXL 5, 10, 25, 50, and 100 mg orally administered for 28 days to sequential cohorts of 12 treatment naïve HBV-infected subjects randomized 10:2, TXL: Viread ®.
- Subjects were followed for a minimum of 28 days after last day of dosing.
- Sixty-two subjects were enrolled in the study, sixty-one subjects completed. One subject was discontinued for not meeting an inclusion criterion.

Baseline Characteristics

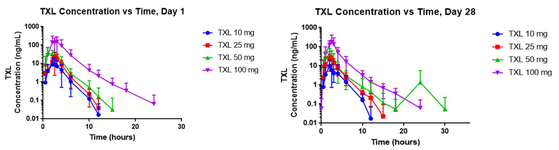
CMX-201	5 mg	10 mg	25 mg	50 mg	100 mg	Viread®
N=62	2[2]	9	10	10	20	10
Gender Male(n):Female(n)	1:1	4:5	9:1	6:4	11:10	4:6
Age [years][1]	31 (3.5)	32 (9.3)	34 (10.0)	31 (7.6)	37 (8.0)	34 (7.8)
Race - Asian (n)	2	9	10	10	21	10
BMI [kg/m][1]	20.2 (0.5)	21.8 (2.1)	23.5 (2.1)	21.7 (3.0)	22.1 (3.4)	22.9 (3.2)
HBV eAg+:eAg-	2:0	9:0	6:4	9:1	13:8	7:3
ALT [U/L][1]	40 (5)	103 (84)	47 (34)	91 (75)	60 (66)	58 (20)
Total Bilirubin [mg/dL][1]	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][1]	8.2 (.32)	7.0 (.68)	6.7 (2.0)	7.1 (1.8)	6.3 (1.8)	6.6 (1.4)

[1]Continuous variables are shown as Mean (SD)
[2]Recruitment stopped due to lack of antiviral activity

- Baseline characteristics were balanced, considering the small number of subjects per group.
- Subjects must have been HBsAg positive for greater than 6 months with a baseline viral load >2.0 x 10^3 IU/mL.

RESULTS

TXL Pharmacokinetics

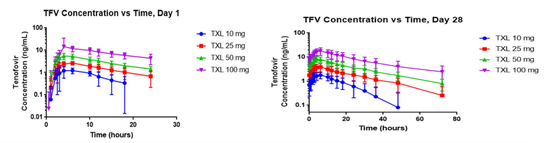


DAY 28	5 mg	10 mg	25 mg	50 mg	100 mg
	n=2	n=9	n=10	n=10	n=20
Cmax [ng/mL][1]	4.6 (--)	12.9 (9.5)	29.0 (15.5)	51.3 (39.9)	187 (176)
Tmax [h] Median (min, max)	3.0 (3, 3)	2.0 (0.9, 6)	2.0 (1, 2.5)	1.5 (1, 2.5)	2.0 (1, 4)
AUC_{0-24} [ng-h/mL]	15.6 (--)	26.0 (15.8)	66.7 (37.6)	110 (81.9)	433 (312)
$t_{½}$[h]	1.4 (--)	1.3 (0.5)	1.7 (0.5)	1.5 (0.7)	2.4 (0.7)

[1]Mean (SD) for all except Tmax

- Median T_{max} ranged from 2.0 to 3.0 hours.
- Mean t½ ranged from 1.1 to 2.4 hr, the highest being at the 100mg dose level.
- No accumulation after 28 days of QD administration.

TFV Pharmacokinetics



DAY 28	5 mg	10 mg	25 mg	50 mg	100 mg	Viread®
	n=2	n=9	n=10	n=10	n=20	n=10
Cmax [ng/mL][1]	1.0 (--)	1.8 (0.5)	4.0 (1.5)	8.5 (2.0)	18.4 (5.0)	370 (102)
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 (0.5, 2)
AUC_{0-24} [ng-h/mL]	23.4 (--)	28.8 (9.6)	63.7 (22.5)	136 (33.3)	302 (98.5)	2870 (656)
$t_{½}$[h]	21.0 ND	23.1 (28.5)	23.0 (5.5)	23.3 (3.4)	26.8 (6.1)	18.1 (3.1)

[1]Mean (SD) for all except Tmax

- Median T_{max} ranged from 3.0 to 6.0 hours.
- Metabolite t½ values were notable longer than parent drug values.
- Trough C_{24} levels and AUCs for TFV increased with escalating TXL dose and were consistent with modest accumulation of TFV at steady state.
- Mean accumulation ratios ranged from 1.48 to 1.95 and increased with dose.

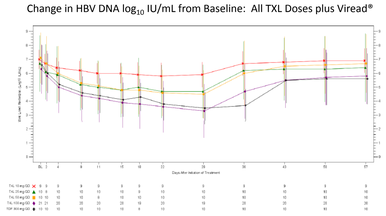
Number of Subjects with AEs by SOC

	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	62	10
Any AE	2	2	5	4	7	20	5
Blood and Lymphatic System Disorders	1					1	
Gastrointestinal Disorders		1	1	1	1	4	3
General Disorders and Administration Site Conditions	1				1	2	1
Infections and Infestations			3	1	3	7	
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	

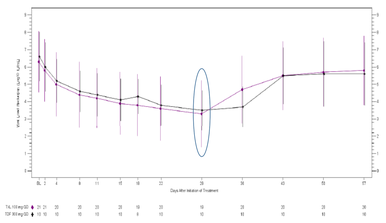
- There were no SAEs or deaths and no AEs leading to study drug discontinuation.
- There were no patterns or dose-related trends in the nature, frequency or severity of AEs. The majority of events were mild and resolved during the study.
- Results are consistent with the disease and the study population.
- There were no clinically significant abnormalities, patterns or dose-related trends in PE findings, vital signs, ECGs or safety laboratory parameters.

HBV DNA Decreases Over Time

Change in HBV DNA log_{10} IU/mL from Baseline: All TXL Doses plus Viread®



Change in HBV DNA log_{10} IU/mL from Baseline: 100mg TXL versus 300mg Viread®



- Day 28 was last day of dosing.
- No non-responders.
- No on treatment rebounders.

CONCLUSIONS

- TXL was safe and well tolerated when administered fasted to HBV-infected subjects at 5, 10, 25, 50, and 100 mg PO QD for 28 days.
- Systemic exposure, Cmax, AUCs, for TXL and TFV in fasted subjects increased with escalating TXL dose for both single and repeated daily doses of TXL.
- There were no AEs leading to study drug discontinuation, no SAEs, and no deaths during the study. There were no dose-related or other patterns observed in the types, frequency or severity of AEs.
- The magnitude of viral load reduction in the TXL dosing groups was dose-dependent and comparable to that seen in the TDF dosing group.
- 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.

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CONTRAVIR

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