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frontiers in drug development for viral hepatitis

Tenofovir Exalidex(TXL) Formulation: Optimization by Unique Physiochemical Properties

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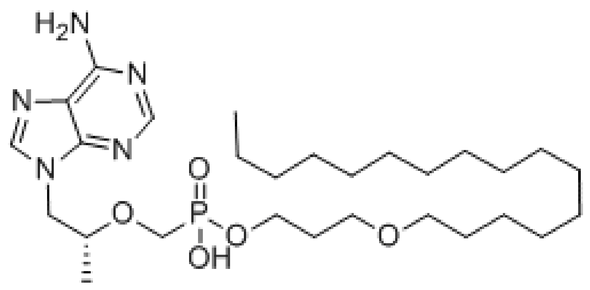
INTRODUCTION

- ✓ Tenofovir Exalidex (TXL) has been investigated clinically in phase 1 and 2 clinical trials. TXL was well tolerated and, in a phase 2 trial consisting of 62 patients, mean viral load reduction was approximately 3 logs after QD oral administration of 50-100 mg for 28 days.
- ✓ The solid dosage formulation of TXL was examined in detail and it was determined that further optimization of the tablet was possible, owing to the physicochemical properties of TXL.
- ✓ Prior to embarking on further testing of novel formulations in humans, a canine study was undertaken to determine possible improvements in formulation, including disintegration, dissolution/solubility and oral delivery.

Herein, is described the pharmacokinetics of TXL in a dog model to evaluate five different test formulations, compared to a reference.

Tenofovir Exalidex (TXL)

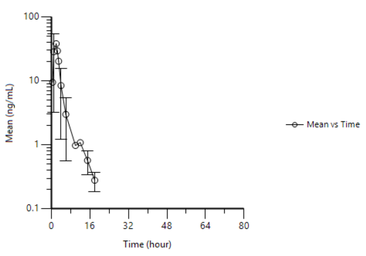
"Lipid" tail chemically modified tenofovir designed to target liver.



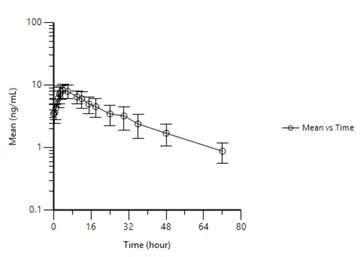
- ✓ TXL is designed to mimic lysophosphatidylcholine to take advantage of natural lipid uptake pathways and achieve high hepatic intracellular concentrations, while minimizing high circulating levels of TFV.
- ✓ TXL orally available as a once daily tablet.
- ✓ Physiochemical properties of TXL include: highly water soluble, 7.41 calculated LogP, and high liver extraction rate in rat, 86% .

Phase 2 HBV+ Patient Study Mean PK Profile (50mg/day)

Question: Can TXL formulation be optimized to enhance viral load reductions?



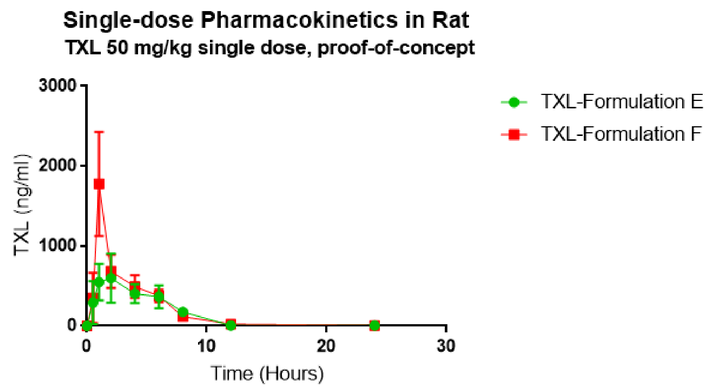
TXL prodrug rapidly declines



TFV metabolite persists, at low circulating levels

Rat TXL Exposure Increases by Formulation Enhancement

- ✓ Initial observations noted altering formulation made a significant difference to the PK profile.



Formulation F enhanced systemic exposure of TXL
1.3-Fold increase in AUC
3.2-Fold increase in Cmax

Materials and Methods

- ✓ A total of 24 beagle male dogs weighing between 8-12 kg were administered one of 6 possible formulations .
- ✓ Single oral dose of TXL. (n=4 dogs/group)
- ✓ Blood collected into EDTA tubes.
- ✓ Plasma determinations using LC-MS/MS.
- ✓ Pharmacokinetics parameters determined (WinNonLin Ver 7.0).
- ✓ Dogs were fasted for 12 hours prior to dosing until 4 hours post-dose. Water was given *ad libitum.*

Dose Group	Test Formulation	Dosing Route	n	Dose (mg/kg)	Blood Sampling Time Points
1	A (legacy)	PO	4	50mg/ dog	Pre-dose, 15, 30 min, 1, 2, 4, 6, 8 and 24 hrs
2	B	PO	4	50mg/ dog	Pre-dose, 15, 30 min, 1, 2, 4, 6, 8 and 24 hrs
3	C	PO	4	50mg/ dog	Pre-dose, 15, 30 min, 1, 2, 4, 6, 8 and 24 hrs
4	D	PO	4	50mg/ dog	Pre-dose, 15, 30 min, 1, 2, 4, 6, 8 and 24 hrs
5	E	PO	4	50mg/ dog	Pre-dose, 15, 30 min, 1, 2, 4, 6, 8 and 24 hrs
6	F	PO	4	50mg/ dog	Pre-dose, 15, 30 min, 1, 2, 4, 6, 8 and 24 hrs

Results

- ✓ The pharmacokinetics of TXL was determined for all six TXL formulations in beagle dogs.
- ✓ Formulation A was used in a previous clinical trial of TXL administered to chronic HBV patients.
- ✓ Formulation D, thus far, appeared to have the more favorable PK profile as indicated by mean increases is in both AUC and Cmax.
- ✓ All 5 formulations had greater AUC values compared with the reference.
- ✓ Only one formulation had a slightly lower Cmax compared with the reference.

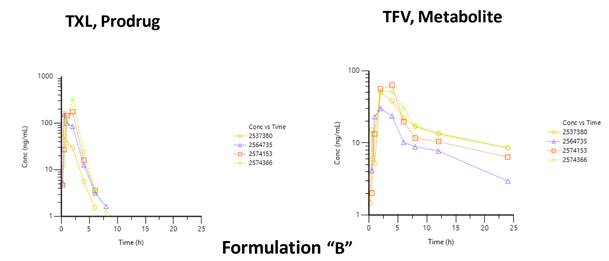
Mean TXL PK Systemic Exposure by Formulation

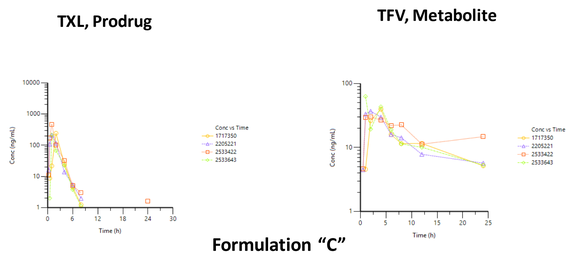
Formulation	Mean AUC_{inf} ng.h/mL	Mean $AUC_{0\text{-}2hr}$ ng.h/mL	Mean $AUC_{2\text{-}8hr}$ ng.h/mL	Mean $AUC_{8\text{-}24hr}$ ng.h/mL	Cmax ng/mL
A(legacy)	379.15/538.26	187.11/35.96	190.81/190.04	1.46/49.65	204.5/48.95
B	470.42/547.16	266.81/39.30	190.15/149.40	3.69/50.28	284.25/42.4
C	582.83/523.08	276.24/42.64	300.72/196.78	7.25/54.50	294.25/56.85
D	849.83/497.31	691.73/55.86	153.69/143.63	6.03/171.49	753.75/47.82
E	539.16/480.11	403.51/46.42	134.56/149.61	1.13/163.07	344.00/39.58
F	421.83/387.92	147.45/18.5	262.53/108.57	15.17/125.99	146.78/24.03

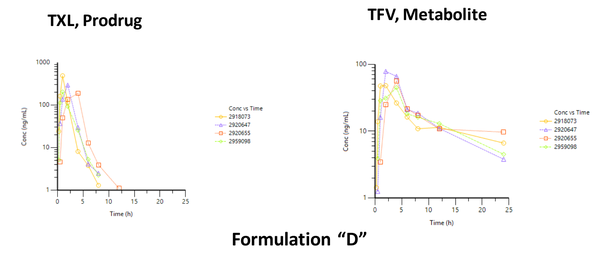
Results continued

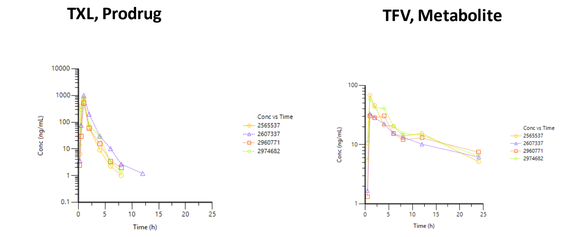
- ✓ Formulation "D", relative to Formulation "A" had increased systemic exposure of TXL, but only appreciably enhanced exposure of TFV from 8-24 hours, consistent with liver uptake.

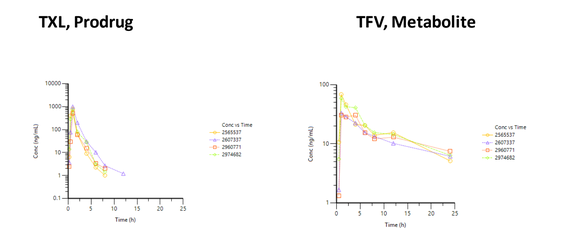
"Legacy" product (reference product, Formulation "A")

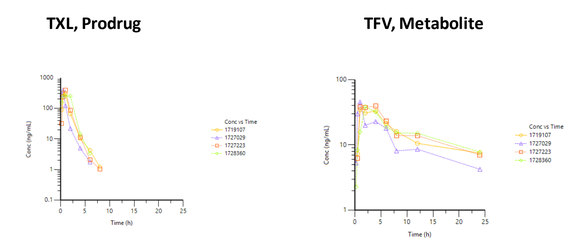












DISCUSSION AND CONCLUSIONS

- ✓ TXL is a novel lipid-conjugated prodrug of tenofovir that confers altered physicochemical properties relative to existing commercial versions of tenofovir
- ✓ Unique physicochemical properties may be exploited to further optimize TXL formulation(e.g., logP, aqueous solubility, polar surface area)
- ✓ Canine model suggests that TXL formulation may be altered in meaningful ways
- ✓ The impact of altering TXL pharmacokinetics will be further studied in chronic HBV patients