A Shape-Shifting Tail Decay is the Pharmacokinetic Profile of an Ultra-Long Acting Bictegravir Prodrug

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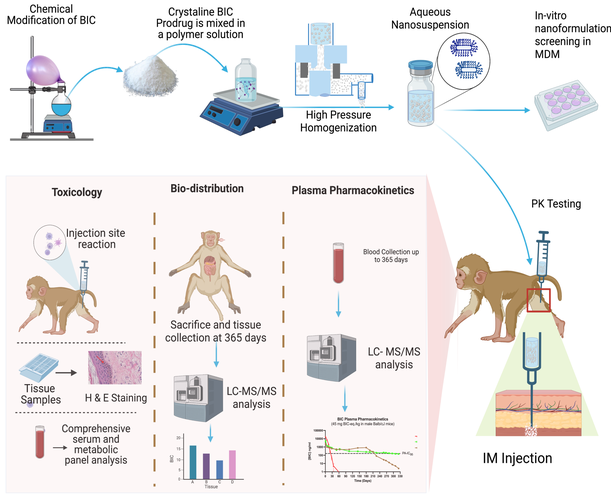
INTRODUCTION

The advantages of long-acting (LA) antiretroviral therapy (ART) for regimen adherence and sustained viral suppression are unquestioned. However, the requirement for frequent clinic visits, injection site reactions, large dosing volumes, and long pharmacokinetic (PK) tail pose notable challenges to widespread LA ART use. Consequently, there is an immediate need for ultra-LA (ULA) ART capable of synchronizing dosing intervals with established six-month clinic visits. We report the PK and biodistribution profiles of two lead bictegravir (BIC) prodrug formulations in rodents and rhesus macaques, in pursuit of a ULA formulation with a short PK tail.

METHODS

Dimeric (MXBIC) and monomeric (M2BIC) prodrug formulations were synthesized by esterification and then converted into surfactant-stabilized aqueous solid drug nanosuspensions. Stability, size, homogeneity, particle surface charge, pharmacokinetic (PK) profiles, biodistribution, and terminal decay were evaluated in Balb/cJ mice, Sprague Dawley (SD) rats, and rhesus macaques (RM) after IM injection.



A potential every six-months bictegravir prodrug nanosuspension with a short PK tail

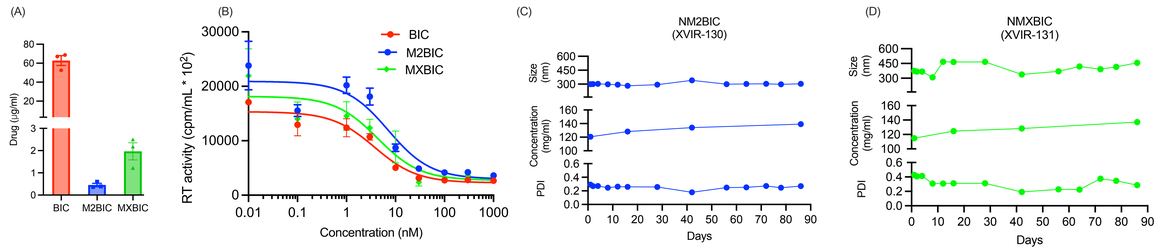


Figure 1. Characterization of BIC prodrugs and nanoformulations. ***(A)*** *Aqueous solubility of native BIC, M2BIC, and MXBIC.* ***(B)*** *The antiretroviral half-maximal inhibitory concentrations (IC_{50}) of native BIC, M2BIC, and MXBIC solutions (0.1%v/v in DMSO) in MDMs were assessed at 0.1-1,000 nM concentrations by measuring HIV-1 reverse transcriptase (RT) activity in culture supernatants. The stability of* ***(C)*** *M2BIC and* ***(D)*** *MXBIC nanoformulations (designated here as NM2BIC (XVIR-130) and NMXBIC (XVIR-131), respectively) was evaluated over 90 days following manufacture at room temperature as determined by size (nm), polydispersity index (PDI), and prodrug concentration in nanoformulation (mg/ml). Results are expressed as the mean ± SEM for N = 3. The experiments were repeated at least twice.*

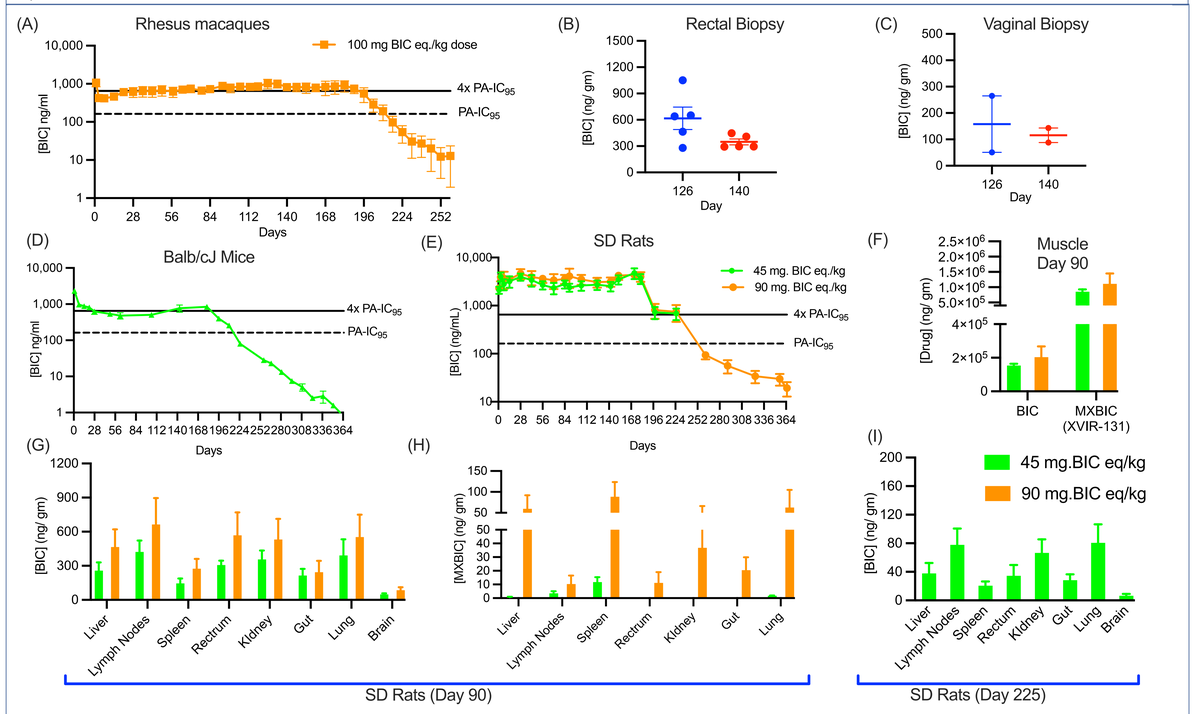
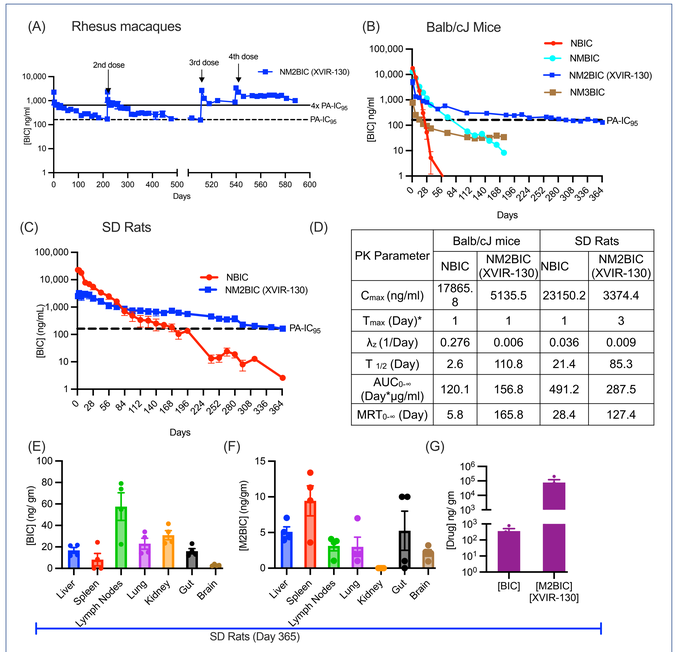


Figure 2: NMXBIC (XVIR-131) PK and biodistribution in RM and rodents. ***(A)*** *Plasma BIC levels in NMXBIC (XVIR-131)-treated rhesus macaques. Five female rhesus macaques were given a 100 mg BIC-eq./kg intramuscular (IM) dose of NMXBIC (XVIR-131) in the quadriceps muscles. BIC levels in the* ***(B)*** *rectal and* ***(C)*** *vaginal tissues were quantified on day 126 and day 140.* ***(D)*** *Plasma BIC level after a single IM injection of 45 mg BIC-eq./kg NMXBIC (XVIR-131) into the caudal thigh of Balb/cJ mice.* ***(E)*** *Plasma BIC levels in Sprague Dawley (SD) rats following a single IM injection of NMXBIC (XVIR-131) at doses of 45 or 90 mg BIC-eq./kg in the caudal thigh. The study began with 8 rats in each group. 4 rats from each group were sacrificed on day 90, and the remaining 4 were sacrificed on days 225 and 365 for 45 and 90 mg. BIC eq./kg groups, respectively.* ***(F)*** *BIC and MXBIC levels at the injection site muscle on day 90 for both groups* ***(G)*** *Tissue BIC and H) MXBIC levels on day 90 (n=4) for both groups.* ***(I)*** *Tissue BIC levels of the SD rats treated with 45 mg BIC eq./kg NMXBIC (XVIR-131). Prodrug levels were undetectable on day 225. All analytes were quantified by UPLC-MS/MS, and results expressed as Mean ± SEM. The horizontal dotted and solid line indicates the protein-adjusted IC_{95} ($PA\text{-}IC_{95}$ = 162 ng/mL) and 4x above the $PA\text{-}IC_{95}$ for BIC, respectively.*



PK Parameter	Balb/cJ mice		SD Rats	
	NBIC	NM2BIC (XVIR-130)	NBIC	NM2BIC (XVIR-130)
C_{max} (ng/ml)	17865.8	5135.5	23150.2	3374.4
T_{max} (Day)*	1	1	1	3
λ_z (1/Day)	0.276	0.006	0.036	0.009
$T_{1/2}$ (Day)	2.6	110.8	21.4	85.3
$AUC_{0-\infty}$ (Day*µg/ml)	120.1	156.8	491.2	287.5
$MRT_{0-\infty}$ (Day)	5.8	165.8	28.4	127.4

Figure 3. Monomeric Prodrugs PK and BD in rhesus macaques and rodents. ***(A)*** *Plasma BIC levels of NM2BIC (XVIR-130) treated rhesus macaques. Three female rhesus macaques were given 50 mg. BIC-eq./kg NM2BIC (XVIR-130) IM dose in the quadriceps muscles on day 0, followed by an equivalent booster dose on day 217 (arrow). A third and fourth dose (arrow) of 100 mg BIC eq./kg NM2BIC (XVIR-130) dose was administered intramuscularly on days 511 and 539, respectively.* ***(B)*** *Plasma BIC levels after a single IM injection of either NBIC, NMBIC, NM2BIC (XVIR-130), or NM3BIC at a dose of 45 mg BIC-eq./kg in the caudal thigh of male Balb/cJ mice.* ***(C)*** *Plasma BIC levels after a single IM injection of either NBIC or NM2BIC (XVIR-130) at a dose of 45 mg BIC-eq./kg in the caudal thigh of SD rats.* ***(D)*** *PK parameters for monomeric prodrugs nanoformulations were determined using non-compartmental analyses.* ***(E)*** *Tissue BIC and* ***(F)*** *M2BIC levels of NM2BIC (XVIR-130) treated SD rats on day 365.* ***(G)*** *BIC and M2BIC levels at the injection site of NM2BIC (XVIR-130)-treated SD rats on day 365. All the drug levels were quantified by UPLC-MS/MS and results are expressed as Mean ± SEM, n= 3 or 5. The horizontal dotted and solid line indicates the protein-adjusted IC_{95} ($PA\text{-}IC_{95}$ = 162 ng/mL) and 4x above the $PA\text{-}IC_{95}$ for BIC, respectively.*

CONCLUSIONS

- Both NM2BIC (XVIR-130) and NMXBIC (XVIR-131) extend BIC's apparent half-life retaining drug potency.
- NMXBIC (XVIR-131) exhibits high BIC exposure for six months with a short PK tail in rodents and RM.
- NM2BIC (XVIR-130) showed slow and prolonged plasma BIC decay curve in rodents and RM.
- NMXBIC (XVIR-131) and NM2BIC (XVIR-130) are under evaluation as potential every-6-months subcutaneous and IM injectables.

ACKNOWLEDGEMENTS

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