Pharmacokinetic Profile of Multi-Dose Bictegravir Stearate (XV-130) in Rhesus Macaques

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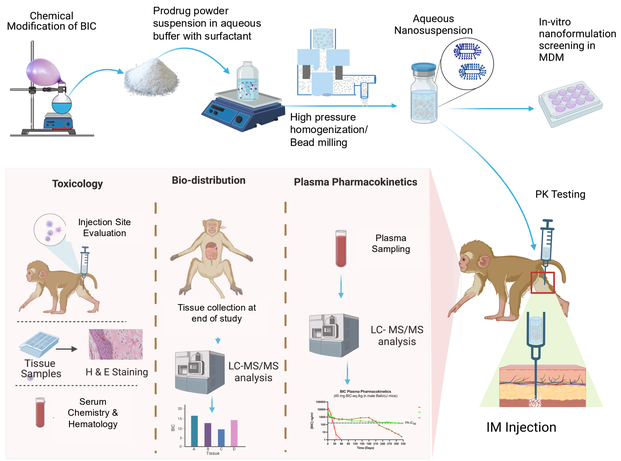
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BACKGROUND

Long-acting (LA) antiretroviral therapies (ART) have transformed HIV care through reductions in dose frequency and regimen adherence. The significant preference for ultra-long acting (ULA) ART led to the development of monomeric and dimeric integrase strand transfer inhibitor prodrug nanosuspensions. For bictegravir (BIC), a single injection of the dimeric prodrug nanosuspension (XV-131) into rodents and rhesus macaques (RM) led to sustained plasma BIC levels ≥4x PA-IC_{95} for six months, followed by a shorter terminal elimination phase. By contrast, the monomeric prodrug nanosuspension of BIC (XV-130) produced lower (<1.5x PA-IC_{95}) but substantially prolonged BIC levels. The current study evaluated the effect of repeated low and high dose IM injections on the pharmacokinetic profile of XV-130 in RM over 132 weeks.

METHODS

XV-130, a nanocrystalline aqueous nanosuspension of bictegravir stearate (NM2BIC), was produced by high-pressure homogenization. Three female rhesus macaques (RM, 10–13 years; 14–15 kg) received IM injections (quadriceps) over a period of 132 weeks. Two doses of 50 mg BIC-eq./kg were administered to RM on days 0 and 217, followed by 100 mg BIC-eq./kg doses on days 511 and 539. Visual and histopathologic assessments of the injection sites were conducted by a certified pathologist. In addition to complete blood counts and serum chemistry tests, plasma and tissue samples were collected for BIC and prodrug quantitation by validated LC–MS/MS methods.



Multiple ascending doses of XV-130 in rhesus macaques are well tolerated and sustain therapeutic bictegravir concentrations (≥4× PA-IC_{95}) for over a year after the last dose

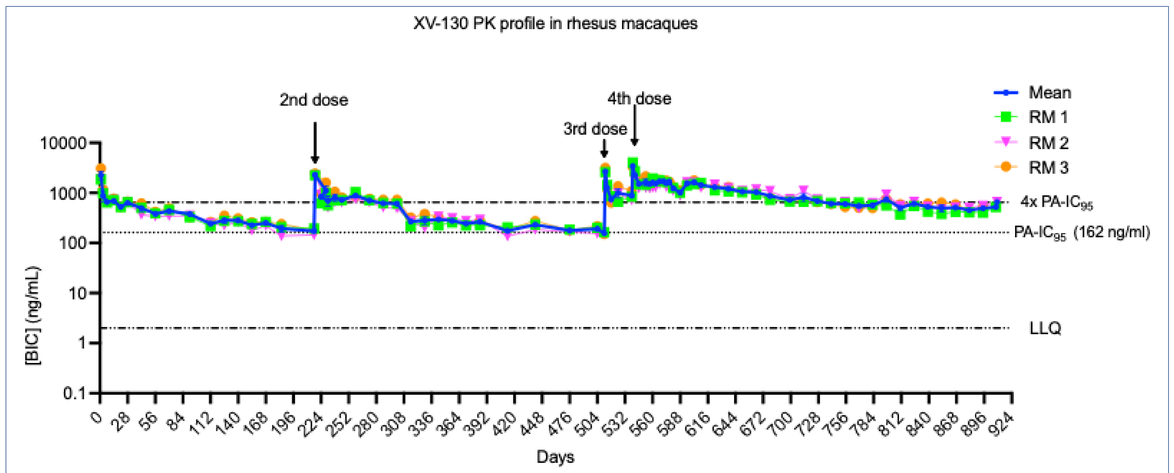


Figure 1: Plasma concentration-time profiles of BIC following repeat doses of XV-130 in rhesus macaques. Three female rhesus macaques were administered 50 mg. BIC-eq./kg IM dose of XV-130 on day 0, followed by an equivalent second dose on day 217. The third and fourth IM injections of 100 mg BIC eq./kg XV-130 were administered on days 511 and 539, respectively. Drug levels were quantified by UPLC-MS/MS. Results are expressed as mean ± SEM for N=3

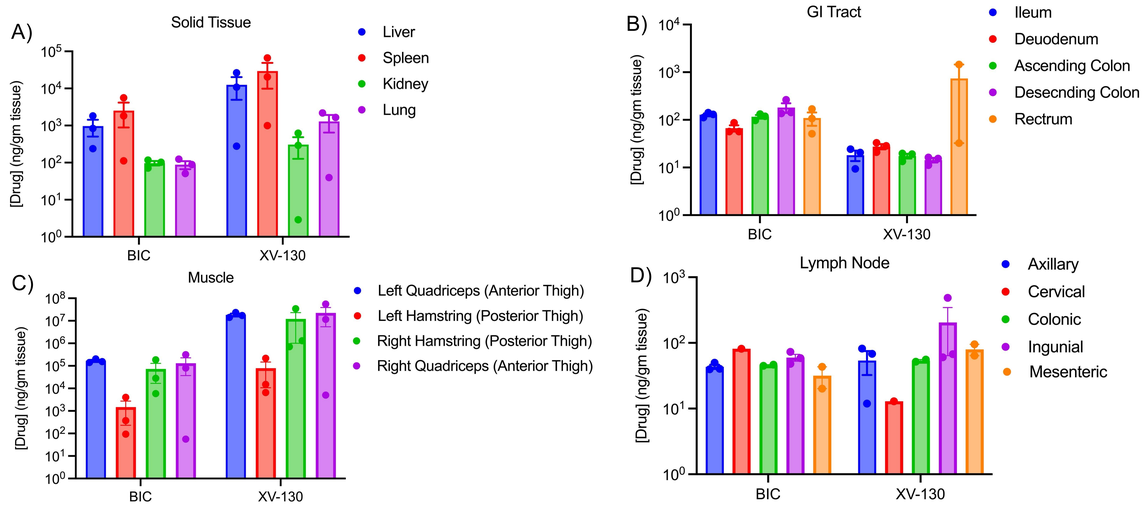


Figure 2: Tissue distribution of BIC and XV-130 following intramuscular administration. Rhesus macaques were euthanized and drug concentrations were measured in (A) solid tissues (liver, spleen, kidney, lung), (B) GI tract segments, (C) injection-site muscles (quadriceps and hamstrings), and (D) lymph nodes. XV-130 demonstrates enhanced tissue and lymphoid distribution. Drug levels were quantified by UPLC-MS/MS. Results are expressed as mean ± SEM for N=3

Treatment	XV-130 (1st dose, 50 mg. BIC-eq./kg) on day 0	XV-130 (2nd dose, 50 mg. BIC-eq./kg) on day 217	XV-130 (post 3rd and 4th dose, 100 mg. BIC-eq./kg) on day 539
$T_{½}$ (Day)	164.4	86.6	118.2
C_{max} (ng/ml)	3411.1	2299.5	2254.3
$AUC_{0-\infty}$	464056.3	136642.0	108555.9
$MRT_{0-\infty}$	278.9	142.5	165.3

Table 1. PK parameters of XV-130 were calculated using non-compartmental analysis. C_{max}, peak plasma concentration; individual estimate of the terminal elimination rate constant; $T_{½}$, elimination half-life; $AUC_{0-\infty}$, area under the plasma concentration time curve (AUC) from 0 hours to infinity; $MRT_{0-\infty}$, mean residence time from 0 hours to infinity. All results are expressed as the Mean days.

CONCLUSION

Repeated dosing of XV-130 (bictegravir stearate nanosuspension) in rhesus macaques sustains BIC concentrations above 4xPA-IC95 for up to a year after the last dose. The injections were well tolerated. These findings support further evaluation of XV-130 as an ultra-long acting candidate for HIV-1 treatment and prevention.

ACKNOWLEDGEMENT

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