



BACKGROUND

VM1500A is a new, potent non-nucleoside HIV-1 reverse transcriptase inhibitor (NNRTI). Its orally-bioavailable prodrug, El sulfavirine (Elpida®, VM1500), is currently marketed in Eastern Europe as an oral QD regimen for HIV/AIDS treatment. Unique pharmacokinetic properties (T_{1/2} ~ 9 days) of VM1500A suggest a possibility for long-acting formulation development.

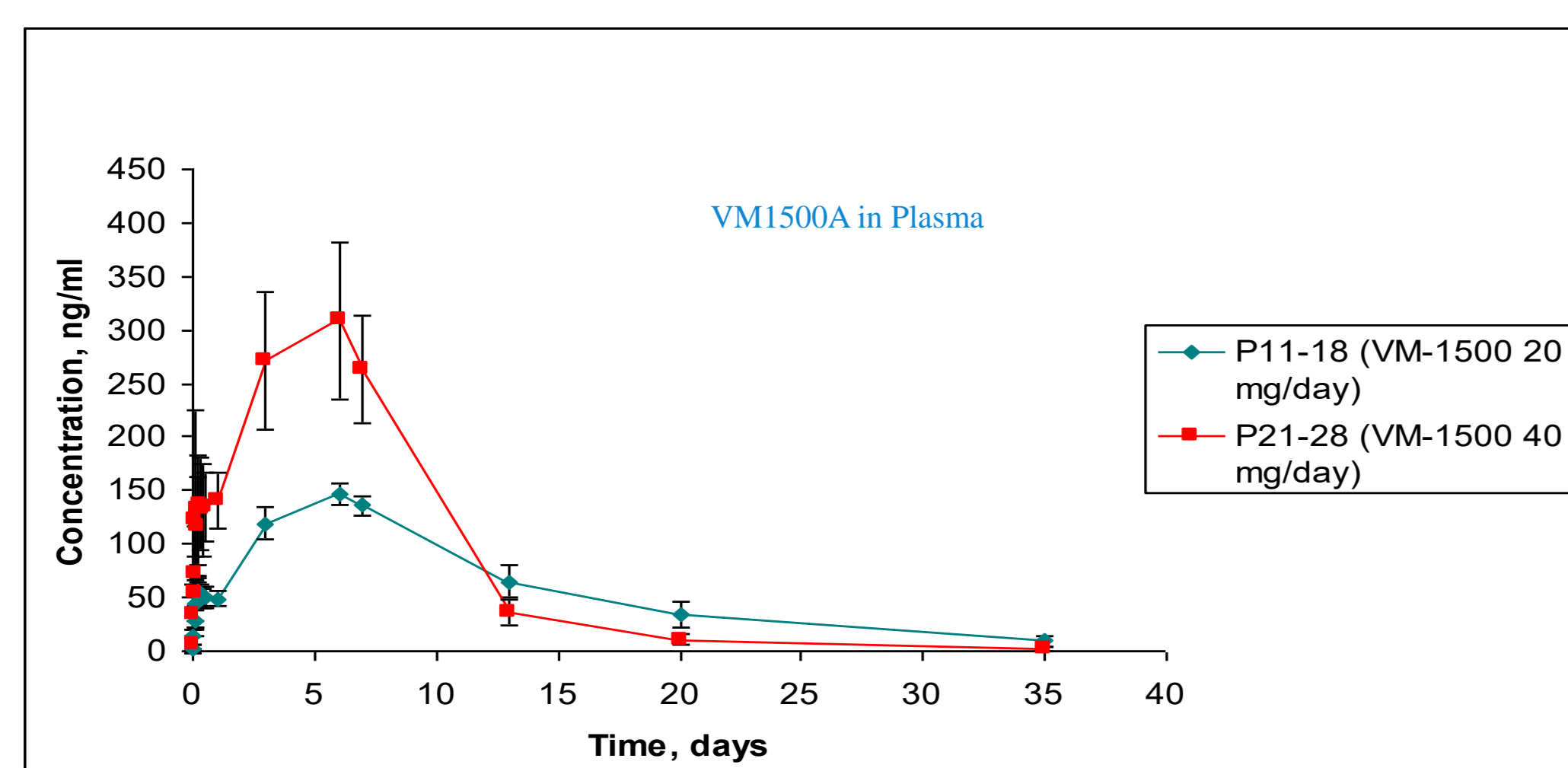
MATERIALS & METHODS

Polymorph analysis of VM1500A resulted in selection of 2 aqueous nanosuspensions of VM1500A polymorphs with 2 specific particle size distribution and development of corresponding formulations. Formulation safety and pharmacokinetics (PK) were studied in beagle dogs, following three once-monthly 10 mg/kg dose administration by intramuscular (IM) injection. Three animals per group were studied for each formulation. Blood samples were collected frequently up to 72 h after administration and every week up to 3 months after last administration. VM1500A plasma concentrations were measured using LC-MS/MS.

RESULTS

VM1500A Advantages for LAI Development: Prolonged Half-elimination Time

Figure 1. Treatment-naïve HIV-infected patients received 20 or 40 mg oral doses of El sulfavirine QD for 7-days



El sulfavirine/VM1500A Parameter	20 mg (n=7)		40 mg (n=7)	
	Mean	SD	Mean	SD
T _{1/2} (h/days)	1.9/8.9	0.5/2.8	2.1/8.8	1.2/1.4
T _{max} (h/days)	0.9/6.3	0.4/0.5	1.0/6.2	0.4/0.1
C _{max} (ng/mL)	8.4/148	4.6/8	13.4/383	7.5/86
AUC _t (h*ng/mL/d*ng/mL)	16.6/2009	5.9/217	32.6/2872	13.5/605
AUC _{inf} (h*ng/mL/d*ng/mL)	16.8/2123	6.0/266	33.0/2889	13.9/612
MRT (h/days)	2.4/10.7	0.6/1.4	3.2/6.4	1.3/0.5

T_{1/2} value for VM1500A was 8.9 and 8.8 days for the 20 and 40 mg doses, respectively

The half-elimination time suggests the potential for once weekly oral dosing as well as an advantage for long-acting injectable (LAI) formulations development.

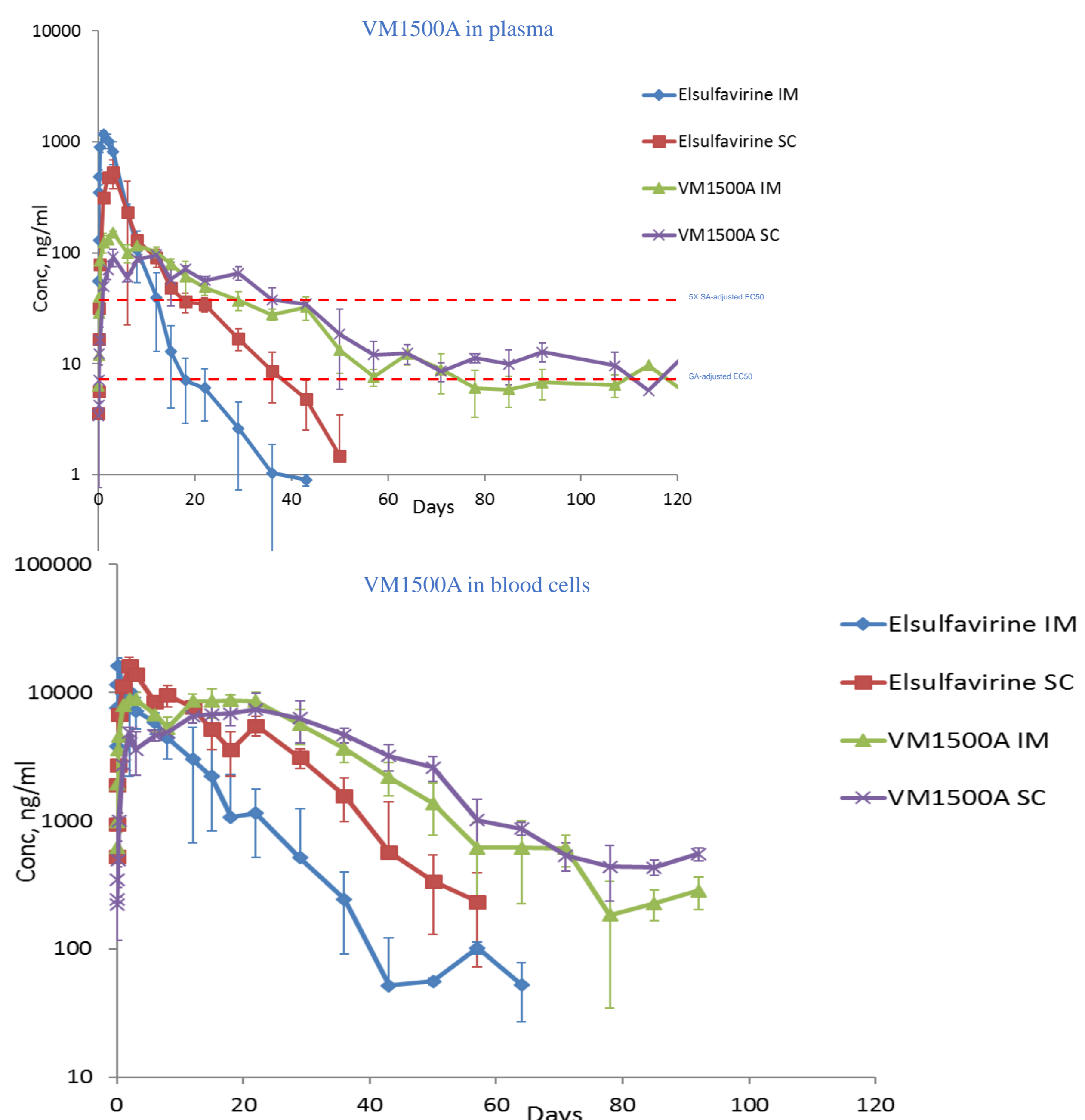
Ratanasuwana W et al. 2014 Annual IAS conference AIDS, Abstract LBPE20

Upon oral administration, El sulfavirine is quickly converted to VM1500A that reversibly accumulates in red blood cells (RBCs) via binding to RBC carbonic anhydrase. The reversible red blood cell distribution allows the compound to be slowly released back to plasma, and from plasma to PBMCs, the target cells. In this way, red blood cells serve as a natural slow release depot for VM1500A, leading to prolonged plasma exposure of the drug and a very slow elimination of the drug from plasma. This phenomenon gives El sulfavirine/VM1500A advantage for long-acting oral and parenteral formulation development. This study provides a proof-of-concept that VM1500A nanosuspensions could be developed into LAI formulations to enable infrequent dosing.

RESULTS (cont.)

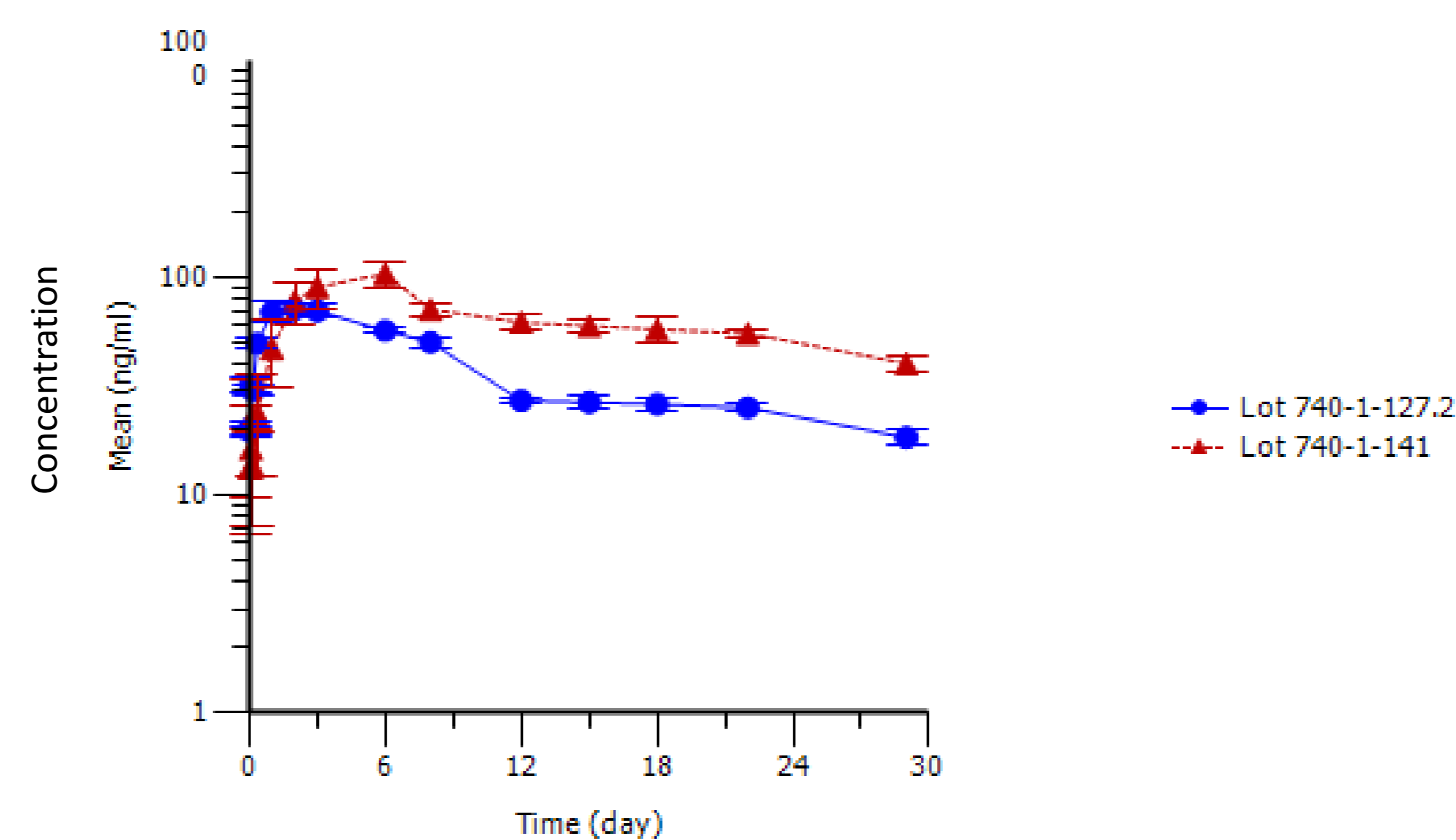
LAI formulation development: PK Study in Dogs

Figure 2. Proof-of-concept that VM1500A nanosuspensions could be developed into long-acting injectable (LAI) formulations



- All studied formulations were well-tolerated, no adverse reactions were observed, including at the injection site. Dosing with formulation 1 (smaller particle size) provided more stable drug plasma concentrations than dosing with larger particle size formulation 2.

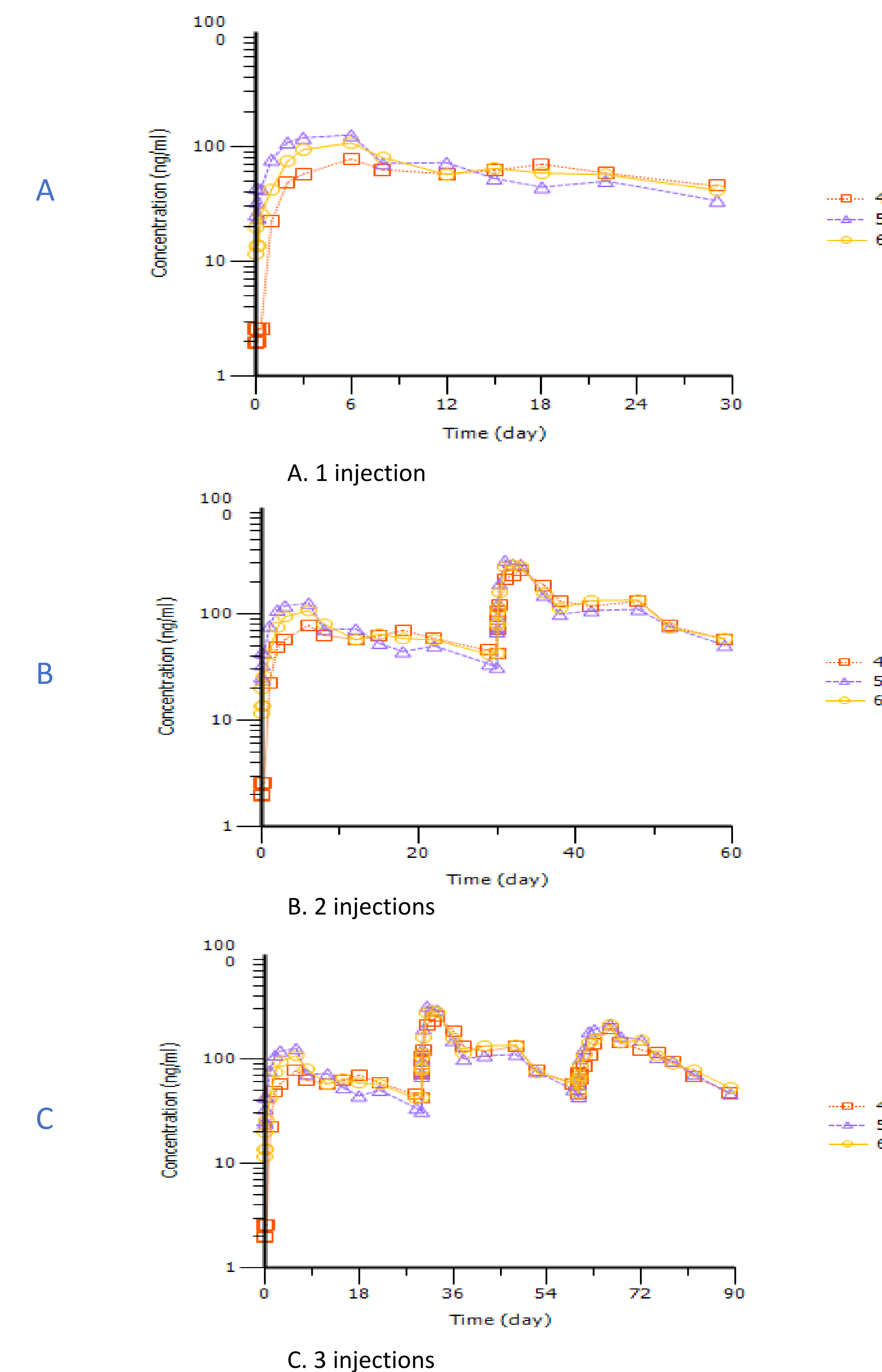
Figure 3. PK in plasma VM-1500A, Dogs, 10 mg/kg IM, Mean +/-SE (n=3)



RESULTS (cont.)

Following three once-monthly 10 mg/kg IM injections of VM1500A formulation 1, drug plasma levels were maintained above 40 ng/ml for at least three month. These levels exceeded the clinically-efficacious VM1500A plasma concentrations.

Figure 4. VM1500A-LAI PK in plasma, Dogs, 10mg/kg IM, Lot740-1-141



CONCLUSIONS

This study supports further development of VM1500A long-acting injectable formulations to enable infrequent dosing. It was discovered that variation of a particle size affects pharmacokinetic properties. Future formulation development will be directed at decreasing the particle size and increasing the half-elimination time of the substance, which can potentially allow for a once per quarter administration. This new development is very promising for both HIV treatment and prevention.