Pre-clinical Pharmacokinetics of Elsulfavirine/VM1500A Long Acting Injectable Formulations

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Background

New options for the prevention and treatment of HIV infection that allow infrequent dosing will facilitate adherence and likely improve long-term outcomes. Elsulfavirine (Elpida®, VM1500) is the prodrug of VM1500A, a new, potent non-nucleoside reverse transcriptase inhibitor (NNRTI), currently under review for registration as an oral QD regimen for HIV/AIDS treatment. Unique pharmacokinetic properties ($T_{1/2}$ is ~8 days) of VM1500A suggest a possibility for long-acting injectable (LAI) formulation development.

Methods

Aqueous nanosuspensions of Elsulfavirine or VM1500A (particle size 380 - 450 nm) were prepared by wet milling. Particle size was measured by dynamic light scattering DLS) using Malvern Zetasizer Nano ZSP system. Different surfactants and drug to surfactant ratios were used. Formulation safety and pharmacokinetics (PK) were studied in beagle dogs, following single 10 mg/kg dose administration by intramuscular (IM) or subcutaneous (SC) injection. Three animals were studied per dose and route of administration. Blood samples were collected frequently up to 72h after administration and every week up to 3 months. Elsulfavirine and VM1500A plasma concentrations were measured using LC-MS/MS.

Results

Optimal LA formulations composition (Table 1) with the desired properties (Table 2) were selected.

Table 1. Elsulfavirine or VM1500A LAI formulation composition

Components (mg/ml)	Cryoprotectant	
	Sucrose	Mannitol
API	95	95
P338	25	25
Cryoprotectant	29	29
PBS pH 7.4 (ml)	1	1
Process parameters		
Milling time (hr)	24	24
Grinding media dia. (mm)	0.5	0.5
Roller speed (rpm)	104	104

Table 2. VM1500A LAI formulation properties

Parameter	Cryoprotectant	
	Sucrose	Mannitol
pH	7.44	7.29
Appearance after lyophilization	Wite cake	White cake
Particle size (10 ml sample) Z-Ave (nm) /PDI	381.7 / 0.255	447.6 / 0.248
Particle size (30 ml sample) Z-Ave (nm) /PDI	386.1 / 0.252	442.6 / 0.252
Resuspendability	Readily resuspendable	Readily resuspendable
Syringeability	Easily syringeable	Easily syrimgeable
HPLC asssay (% label claim)	93.5	95

Using sucrose instead of mannitol as a cryoprotectant reduced particle aggregation (Figs 1-2).

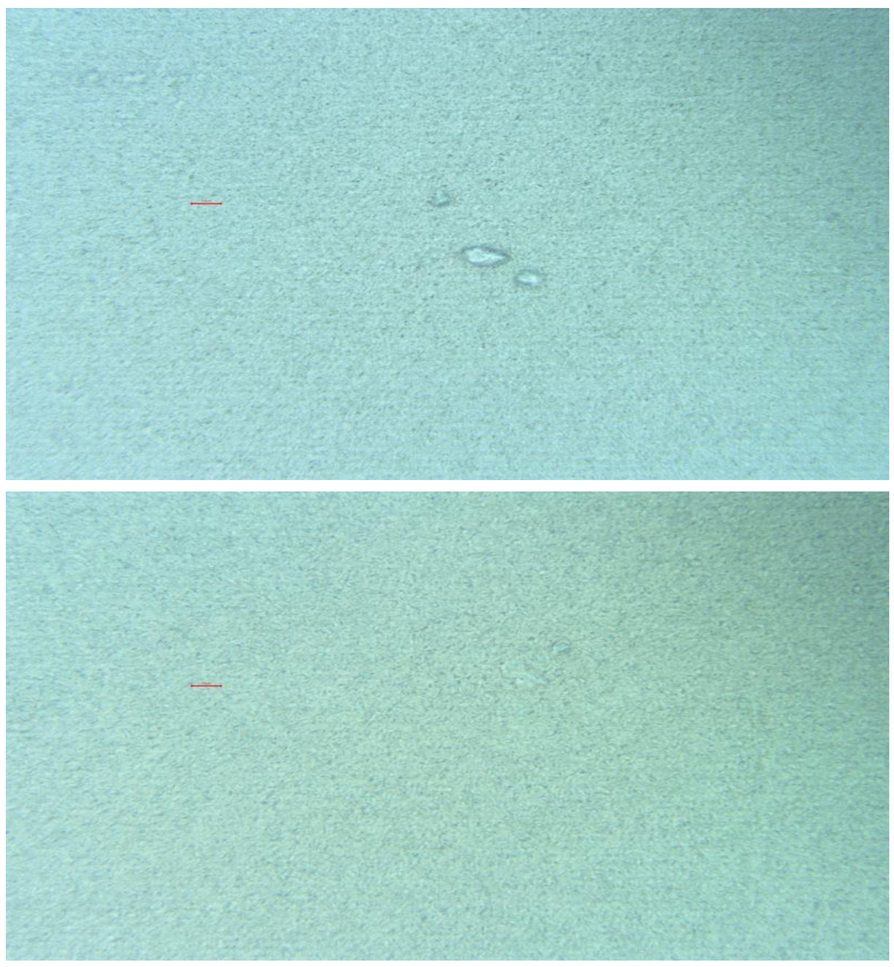

Fig. 1. Microscopic image of VM1500A LA formulation with mannitol (top) or sucrose (bottom) after lyophilization and reconstitution. Scale bar represents 10 microns.

Results (cont.)

No significant particle size changes were observed after lyophilization and reconstitution (Fig. 3).

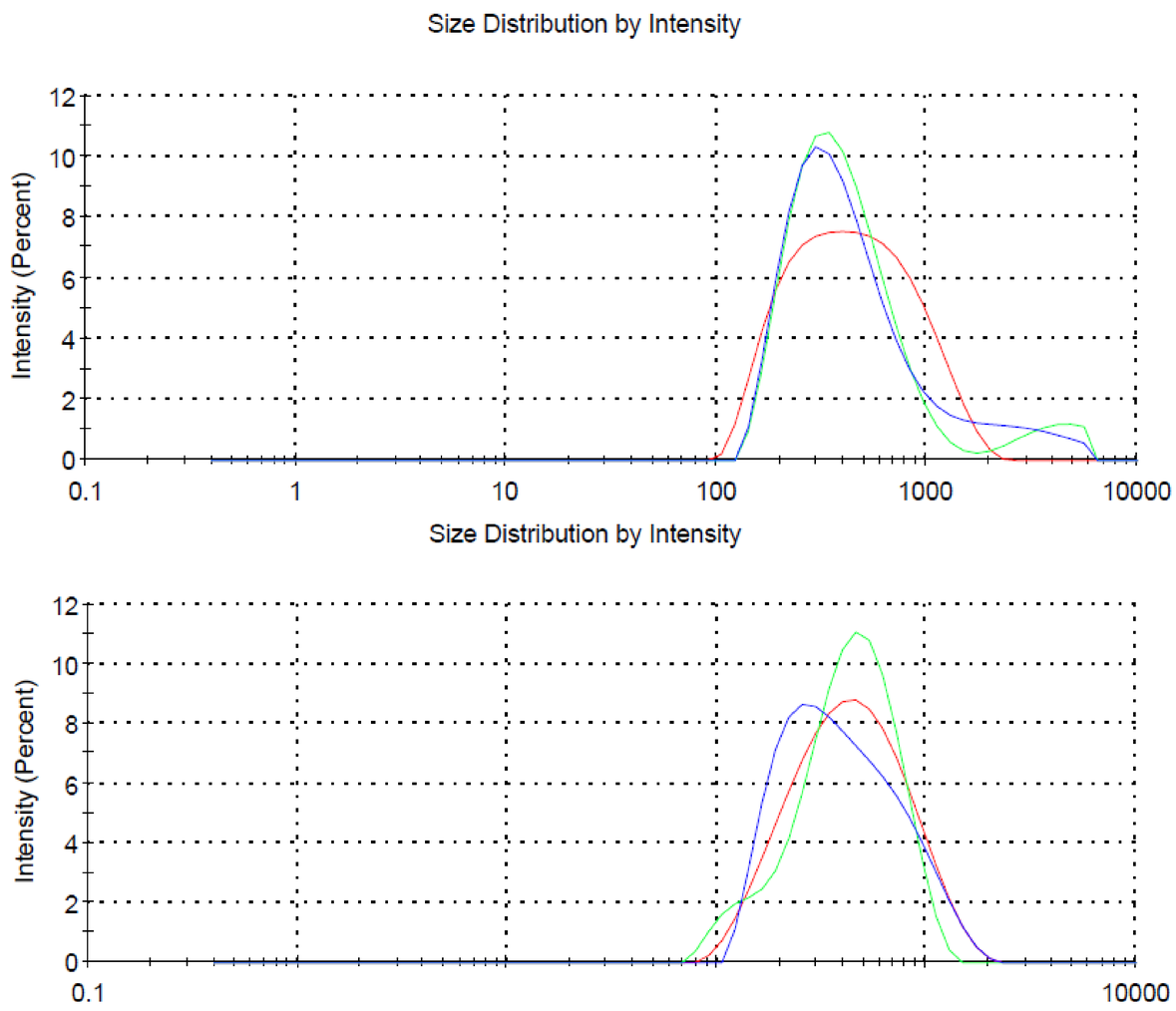

Fig. 3. VM1500A LAI formulation particle size distribution after ~9.5 hours of milling (top), and after lyophilization and reconstitution (bottom), as determined by DLS. The results of three consecutive measurements are shown.

In the animal studies, all tested formulations were well-tolerated, no adverse reactions were observed, including at the injection site. The PK analysis showed that dosing with VM1500A provided more stable drug plasma concentrations than dosing with the prodrug Elsulfavirine from these administration routes (Fig. 5). Following a single 10 mg/kg dose of VM1500A (either IM or SC), its plasma levels were maintained above 50 ng/ml for at least 4 weeks (SC). These levels exceeded the clinically-efficacious VM1500A plasma concentrations. After three months post-administration, VM1500A plasma levels were above or around 10 ng/ml, which exceeded the serum-adjusted EC_{50} value *in vitro*. No dose dumping was observed with the VM1500A LAI formulation (Fig. 4).

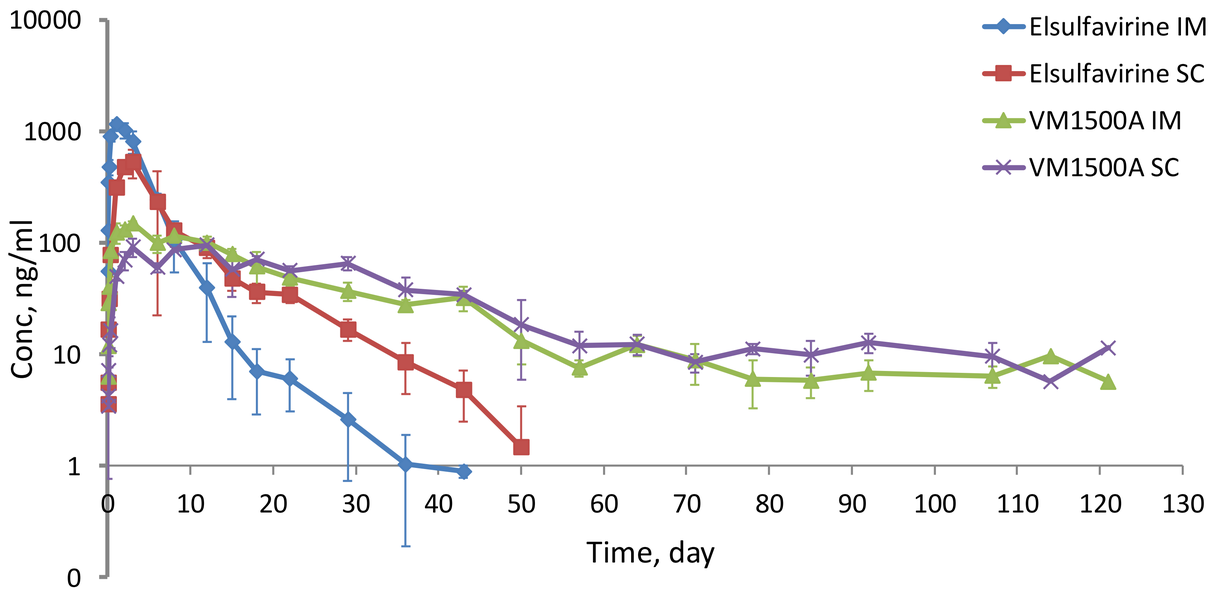

Fig. 4. VM1500A plasma concentrations over time after single IM or SC injections of 10 mg/kg Elsulfavirine or VM1500A LAI formulations.

Based on the results of this study, VM1500A was chosen for further LAI development.

Conclusions

This study provides proof-of-concept that VM1500A nanosuspensions could be developed into long-acting injectable formulations to enable infrequent dosing. Further pre-clinical development of these formulations is warranted.