Elsulfavirine/VM1500A Long-Acting Injectable, Once Daily and Once Weekly Oral Formulations for Treatment and Prevention of HIV-1 Infections

Nikolay Savchuk[1], Vadim Bichko[1], Angela Koryakova[1], Ruben Karapetian[1], MiRa Huyghe[1], Elena Yakubova[1], Sergey Baranovsky[1], Alexander Khvat[1], Oksana Proskurina[1], Jenny Remeeva[1], Klaus Klumpp[1], Saranya Sankar[2], Igor Nikoulin[2], Gerald Yakatan[2], Winai Ratanasuwan[3], Peerawong Werarak[3], Baiba Berzins[4], Robert Murphy[4]

[1]Viriom, Inc., San Diego, USA, [2]IriSys, LLC, San Diego, USA, [3]Siriraj Hospital, Mahidol University, Thailand, [4]Northwestern University, Chicago, USA

BACKGROUND

VM1500A is a new, potent non-nucleoside HIV-1 reverse transcriptase inhibitor. Its orally bioavailable prodrug, Elsulfavirine/Elpida®, is marketed in Eastern Europe as an oral QD regimen for HIV/AIDS treatment. Red blood cells serve as a natural slow release depot for VM1500A. Unique pharmacokinetic properties ($T_{1/2}$~9 days) of VM1500A directed at development of long-acting formulations.

MATERIALS & METHODS

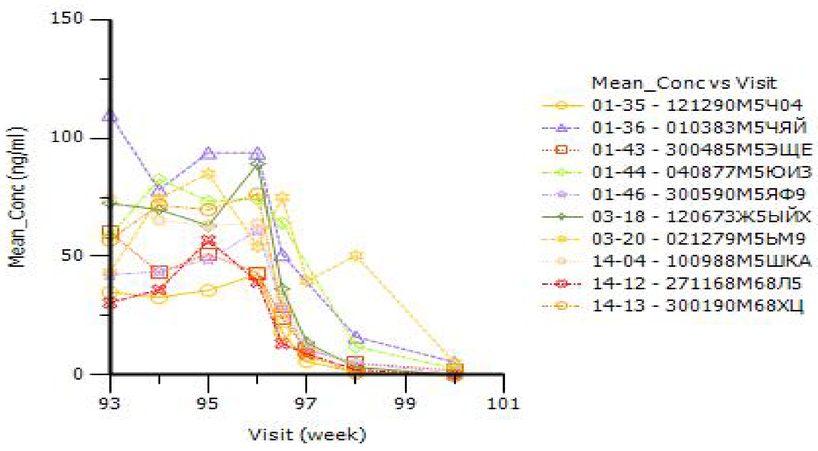
VM1500A was prepared and formulated as an aqueous nanosuspension. Formulation safety and pharmacokinetics were studied in beagle dogs, with a single or three once monthly intramuscular (IM) injections. Blood samples were collected frequently up to 72 hrs after administration and every week up to 4 months. Elsulfavirine and VM1500A plasma concentrations were measured using LC-MS/MS. In a phase I clinical study, uninfected healthy volunteers were randomized (7:1) to receive a single oral dose of VM1500 20 mg, 40 mg or placebo. Plasma samples were collected frequently over 48 hours after dosing and then until day 36. In phase IIb randomized, double-blind, multi-center study, ART-naïve HIV-1-infected patients received Elpida® 20 mg and various two NRTI regimens for 96 weeks. Plasma samples were collected at weeks 0-4 and 93-100. The VM1500 and VM1500A plasma concentrations were measured using LC-MS/MS method, and PK parameters were calculated.

RESULTS

In phase IIb study, the average C_{trough} level of VM1500A at the end of treatment (weeks 93-96) was 60.8±17.7 ng/ml (n=10), similar (within 25%) to that at the beginning of treatment (weeks 1-4), and declined after the end of treatment with kinetics similar to those after a single dose or 7-day dosing, suggesting that Elpida® neither significantly induced nor inhibited its own metabolism.

Figure 1. (A) A set of individual pharmacokinetic curves of VM1500A in patients' blood plasma. **(B)** The average pharmacokinetic curve of VM1500A in patients' blood plasma. (Mean±SD)

A



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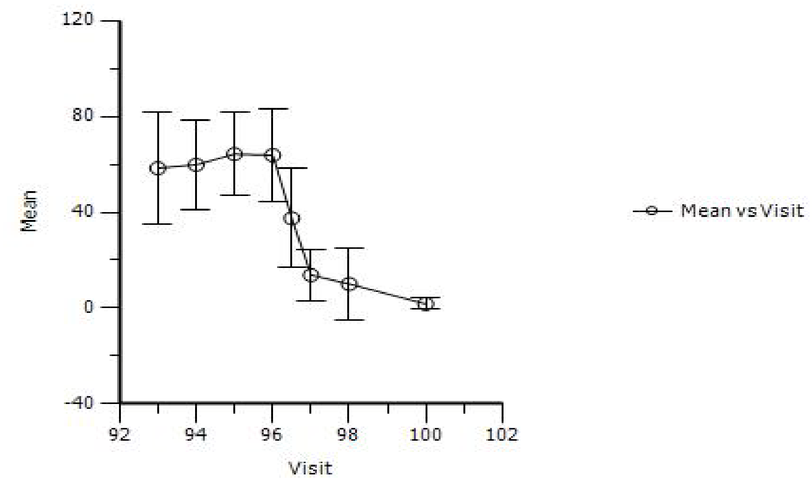
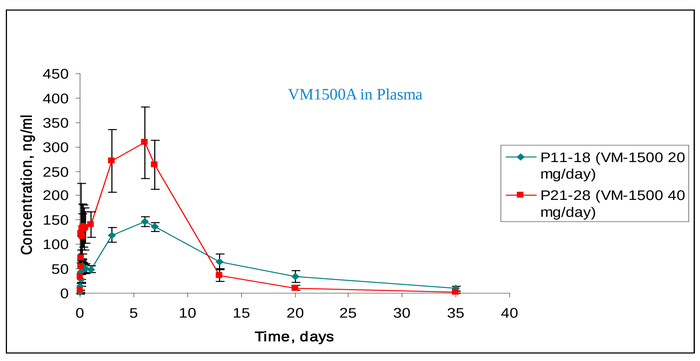


VM1500A Advantages for LAI Development: Prolonged Half-elimination Time

Figure 2. Treatment-naïve HIV-infected patients received 20 or 40 mg oral doses of Elsulfavirine QD for 7-days



Elsulfavirine/VM1500A Parameter	20 mg (n=7)		40 mg (n=7)	
	Mean	SD	Mean	SD
T1/2 (h/days)	1.9/8.9	0.5/2.8	2.1/8.8	1.2/1.4
Tmax (h/days)	0.9/6.3	0.4/0.5	1.0/6.2	0.4/0.1
Cmax (ng/mL)	8.4/148	4.6/8	13.4/383	7.5/86
AUCt(h*ng/mL//d*ng/mL)	16.6/2009	5.9/217	32.6/2872	13.5/605
AUCinf (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

T1/2 value for VM1500A was 8.9 and 8.8 days for the 20 and 40 mg doses, respectively

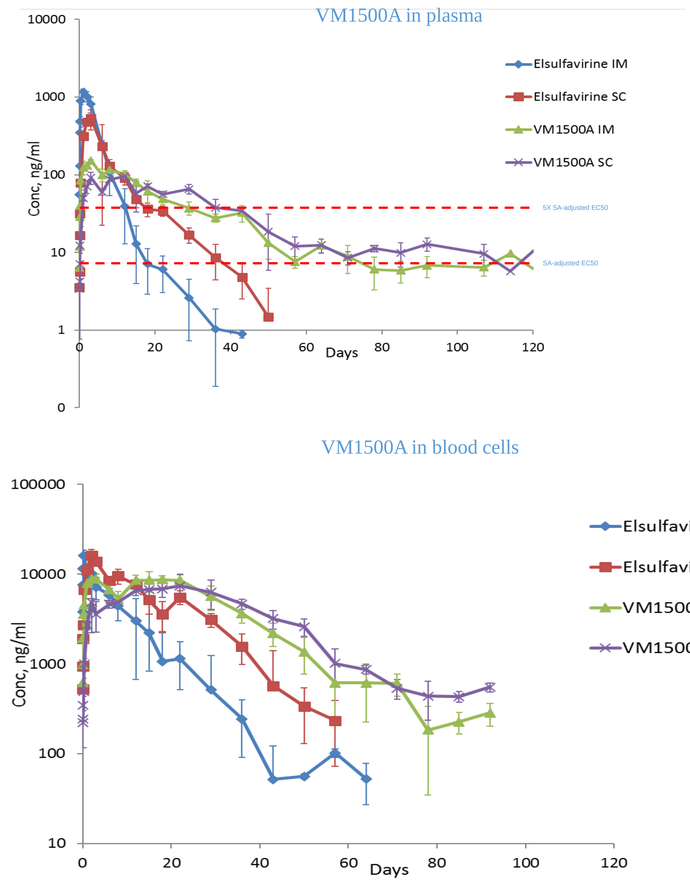
The half-elimination time suggests the potential for once weekly oral dosing as well as an advantage for long-acting injectable (LAI) formulations development.

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

Upon oral administration, Elsulfavirine 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 Elsulfavirine/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.

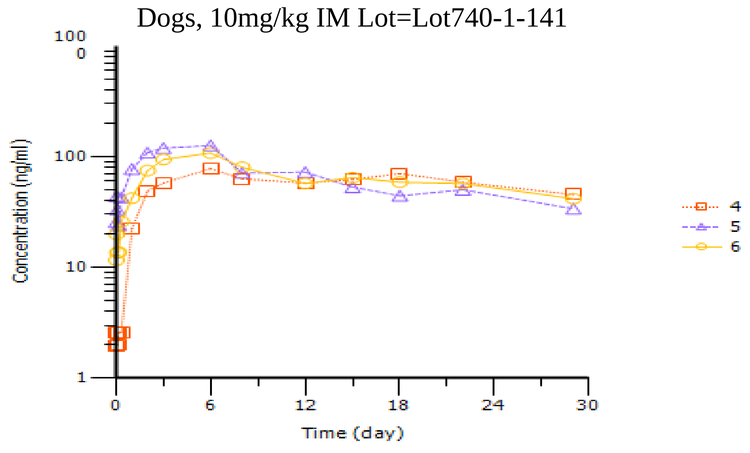
LAI formulation development: PK Study in Dogs

Figure 3. Proof-of-concept that VM1500A nanosuspensions could be developed into long-acting injectable (LAI) formulations



Following a single 10 mg/kg dose of VM1500A LAI (either IM or SC), drug plasma levels were maintained above target value (50 ng/ml) for 4 weeks, and above or around 10 ng/ml for > 4 months. Administration of Elsulfavirine LAI led to faster elimination of VM1500A from plasma and blood cells. VM1500A extensively and reversibly partitioned to blood cells, presumably via reversible binding to erythrocyte carbonic anhydrase [Bichko et. al., ESCV 2017, Abstract O18]

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



CONCLUSIONS

These studies support further development of VM1500A long-acting injectable formulations and Elsulfavirine once weekly oral formulations to enable infrequent dosing for treatment and prevention of HIV-1 infections.