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

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Objectives

Elsulfavirine/Elpida® is the prodrug of VM1500A, a new, potent non-nucleoside reverse transcriptase inhibitor (NNRTI, Fig.1). First marketing authorization for Elpida 20 mg oral QD regimen for HIV/AIDS treatment has been recently obtained in Eastern Europe. Drug properties include:

- High antiviral potency *in vitro*
  - EC_{50} = 1.2 nM, serum-adjusted EC_{50} = 13.8 nM
- High clinical efficacy, including patients with high viral titers (>10^5 HIV RNA copies/ml)
- Improved safety and tolerability (96 week comparator study vs. Efavirenz)
- Broad antiviral spectrum
  - Active against broad range of clinical HIV isolates, including isolates from NNRTI-experienced patients
  - No cross-resistance with other NNRTIs
- Higher genetic barrier to resistance
- Unique pharmacokinetic profile
  - Very long half-elimination time($T_{1/2}$ ~9 days)

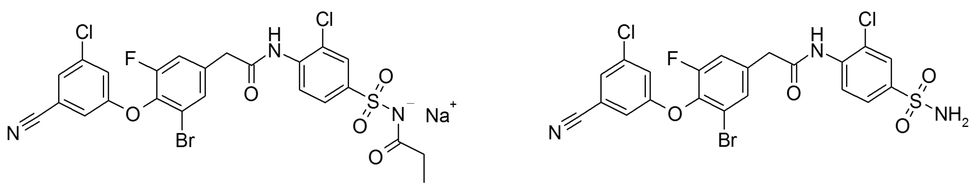

Fig. 1. Chemical structures of Elsulfavirine (left) and VM1500A (right).

New options for the prevention and treatment of HIV infection that allow infrequent dosing will facilitate adherence and likely improve long-term outcomes. This study evaluates Elsulfavirine/VM1500A potential for long-acting injectable (LAI) formulation development.

Methods

Aqueous nanosuspensions of Elsulfavirine or VM1500A (particle size 400-500 nm) were prepared by wet milling. Different surfactants and cryoprotectants 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 72 h after administration and then every week up to 6 months.Elsulfavirine/VM1500A in plasma and RBCs were analyzed using LC-MS/MS.

Results

Optimal LA formulations composition with the desired properties (Table 1) were selected (Table 2). Sucrose was chosen as a cryoprotectant as it led to less particle aggregation than mannitol.

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

Increasing Poloxamer/API ratio dramatically reduced particle aggregation (Fig. 2).

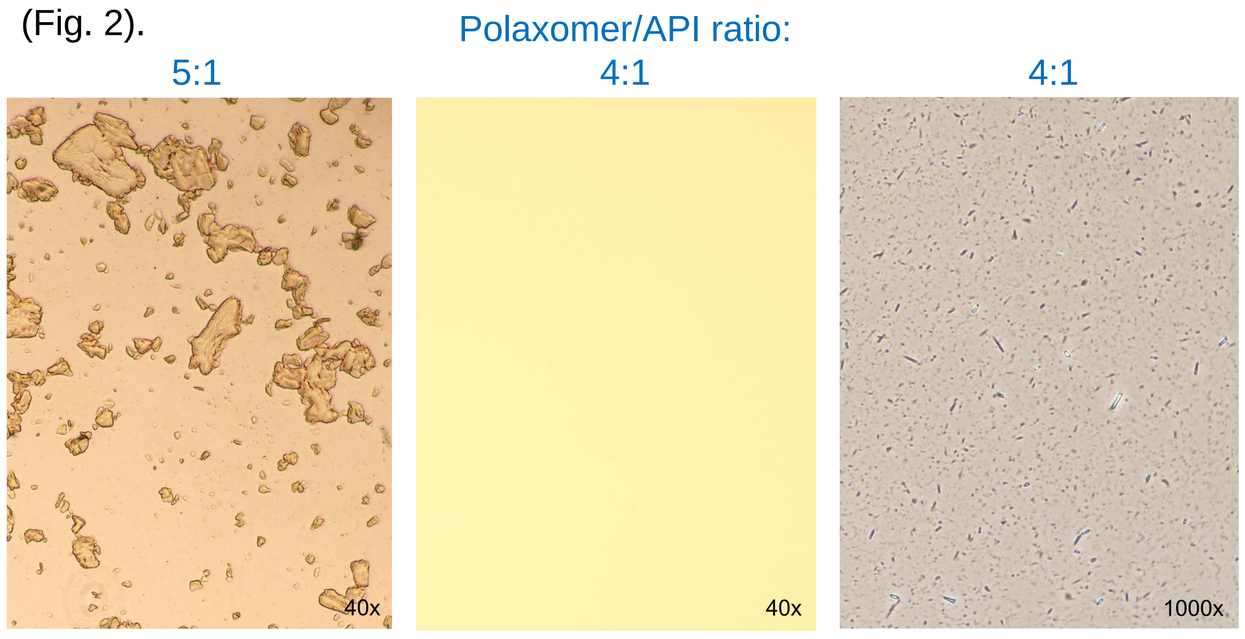

Fig. 2. Phase contrast microscopy of VM1500A LAI formulations after lyophilization and reconstitution. A rod-like VM1500A crystals are visible at higher magnification (right).

Results (cont.)

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. 3).

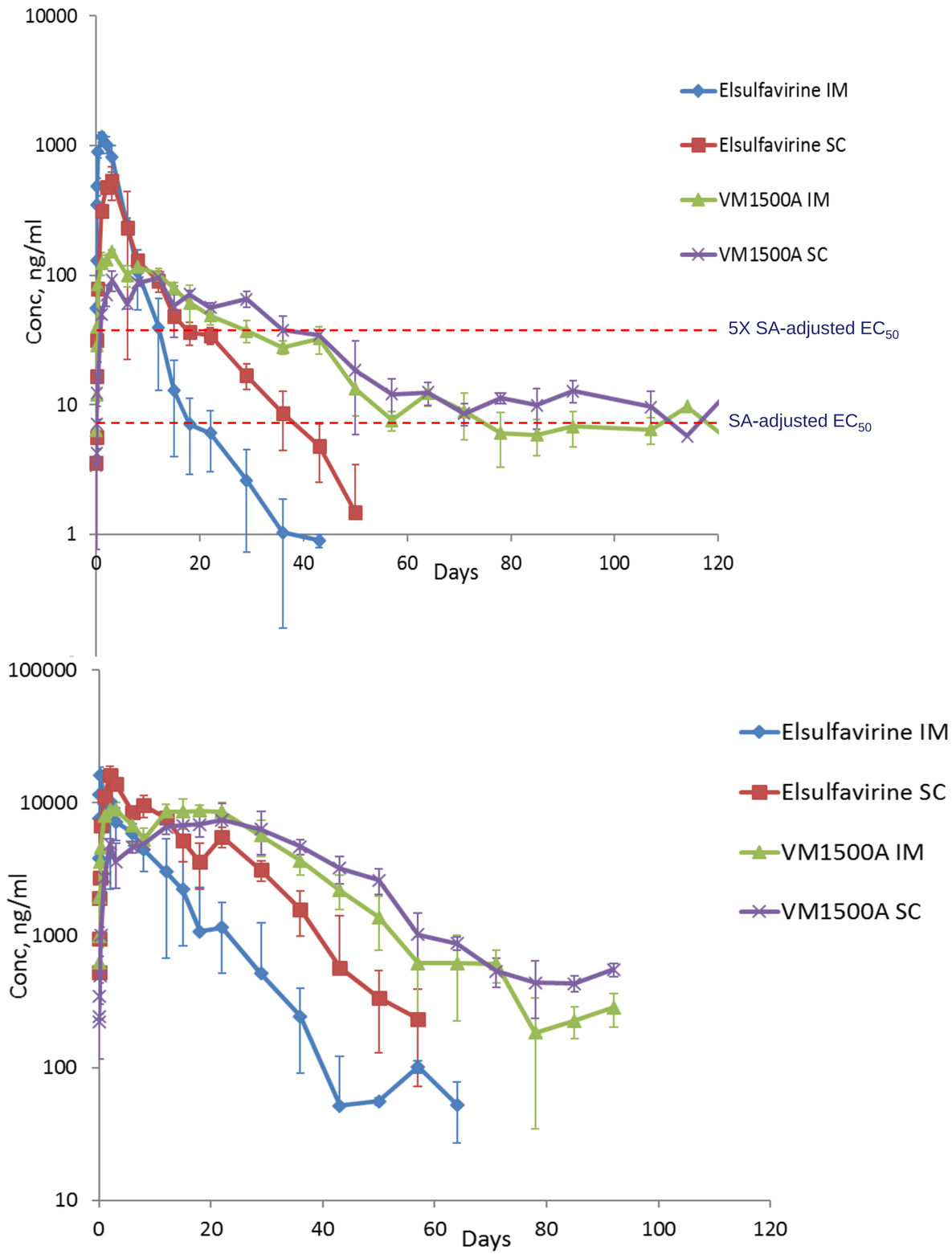

Fig. 3. VM1500A plasma (top) or blood cells (bottom) concentrations over time after single IM or SC injections of 10 mg/kg Elsulfavirine or VM1500A LAI formulations.

Following a single 10 mg/kg dose of VM1500A LAI (either IM or SC), drug plasma levels were maintained above target value (40 ng/ml) for 4 weeks, and above or around 10 ng/ml for > 4 month, which exceeded the serum-adjusted EC_{50} value *in vitro*. No dose dumping was observed with the VM1500A LAI formulation (Fig. 3). Based on the results of this study, VM1500A was chosen for further LAI development.

VM1500A extensively and reversibly partitioned to blood cells, presumably *via* reversible binding to erythrocyte carbonic anhydrase [Bichko et. al., ESCV 2017, Abstract O18].

Conclusions

- Elsulfavirine is an orally-bioavailable prodrug of an effective and well tolerated NNRTI (VM1500A) with excellent antiviral efficacy, resistance profile, pharmacokinetic properties and safety profile
- Elsulfavirine oral administration has potential to be greater than QD (once weekly, $T_{1/2}$ ~ 9 days)
- VM1500A has potential as an LAI, either IM or SC, with an administration schedule that could be every 1-3 months
- 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 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 proof-of-concept that VM1500A nanosuspensions could be developed into LAI formulations to enable infrequent dosing
- Further preclinical development of these formulations is warranted