Safety and PK Study of VM-1500A-LAI, a Novel Long-Acting Injectable Therapy for HIV

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BACKGROUND

VM1500A is a novel, potent NNRTI with unique clinical PK profile and broad-spectrum activity across HIV-1 variants. An oral dosage form of elsulfavirine (Elpida®), a pro-drug of VM1500A, has been approved in 2017 in Russia for treatment of HIV-infected patients in combination with standard ART. A long-acting injectable (LAI) form of VM1500A has been developed to expand the dosing options of VM1500A.

METHODS

This was a Phase 1 first-in-human open-label, single-center study to evaluate safety, tolerability and pharmacokinetics of single and multiple ascending intramuscular doses of the LAI nano-formulation of VM1500A (VM1500A-LAI) in HIV-uninfected volunteers. The study has been conducted in Russia.

RESULTS

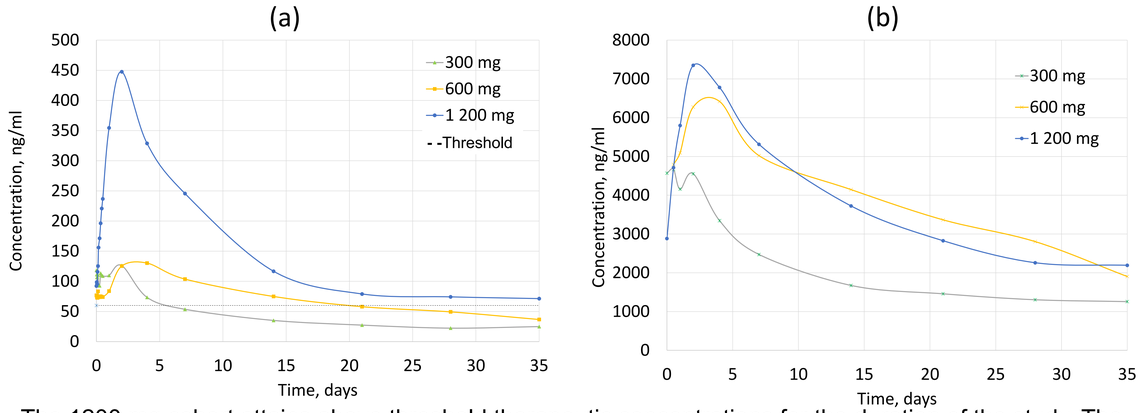
27 HIV-uninfected male volunteers (5 Asians, 22 Caucasians) with a mean age of 26 years and mean BMI of 23.9 kg/m^2 were enrolled and received single ascending doses (SAD) of VM-1500A of 150 mg, 300 mg, 600 mg, and 1200 mg once a month (qm) as well as multiple (2) doses of 600 mg qm, administered as an intramuscular (IM) injection in the gluteal muscle after a 2-week run-in period daily dosing of 20 mg Elpida® capsules orally. Each dose cohort consisted of 6 subjects, except for the pilot 150 mg cohort consisting of 3 subjects. There were no significant baseline differences between the groups. The subjects were evaluated for 35 days post-injection and during that period provided serial blood samples for PK assessments both in plasma and red blood cells (RBCs). Escalation to the next dose occurred in a step-wise manner, upon PK and safety data review. The main PK parameter was the sustained median plasma concentration of VM1500A above the target trough level C_{trough} of 61 ng/ml, as it was associated with efficacy of daily oral dose of 20 mg of Elpida® during 96 weeks treatment in the registration study in HIV-infected patients. Based on the results of SAD and previous preclinical data in dogs[1] the multiple dose part of the study of two qm IM doses of 600 mg VM1500A-LAI, split into 2 injections of 300 mg (1.5 ml each) has been initiated.

Table1. Study design

	Months	0				1				2				3				4				5				6				7				8				9				10				11			
	W	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
Single Dose	150 mg (0,75 ml)	Screening				20 mg				LAI #1 IM				F/U																																	
	300 mg (1,5 ml)									Screening				20 mg				LAI #1 IM				F/U																								
	600 mg (3 ml)													Screening				20 mg				LAI #1 IM				F/U																			
	1200 mg= 3 ml x 2																					Screening				20 mg				LAI #1 IM				F/U											
Multiple Dose	600 mg 1,5 ml x 2																													Screening				20 mg				LAI #1 IM				LAI #2 IM				F/U		

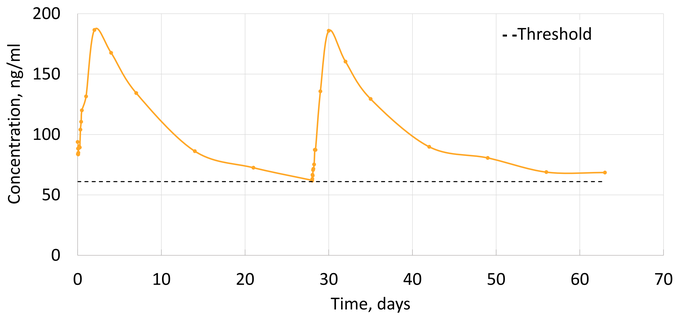
RESULTS

Figure 1. VM1500A median concentrations in plasma (a) and RBCs (b) after single VM-1500A-LAI IM injection for 300, 600 and 1200 mg cohorts.



The 1200 mg cohort attains above threshold therapeutic concentrations for the duration of the study. The level of VM1500A in RBCs indicates to the possible drug storage depot with the prolonged release function.

Figure 2. VM1500A plasma median concentrations after multiple VM-1500A-LAI IM injection for 600 mg (300mg x 2).



The 600 mg dose split into 2 injections attains above threshold therapeutic concentrations after both the first and the second months of the study.

RESULTS

All doses were well tolerated and no-dose limiting toxicities were reported. Injection site related pain was notable at the highest dose tested, i.e. 1200 mg. This pain was very mild and transient. There have been no death or serious adverse event. Most AEs were mild (Grade 1) and resolved. The majority (91%) of AEs were minor lab parameters deviations not-related to the study drug.

The observed PK profile of IM VM-1500A-LAI is consistent with sustained delivery. Median (range) plasma concentrations of VM1500A at 28 days post-single injection were 74 (55, 87), 49 (34, 64), 22 (17, 28) and 25 (14, 25), ng/ml for the 1200, 600, 300 and 150 mg dose levels, respectively. For the multiple dosing part of the study, median (range) plasma concentrations of VM1500A were 62 (35, 92) and 69 (51, 106) ng/ml for the 28 days after the 1st and 28 days after the 2nd IM injections with 600 mg (300 mg x 2) qm respectively. These results show that being split into 2 simultaneous injection the dose of 600 mg/ml supports the required therapeutic Ctrough level.

CONCLUSIONS

Pharmacokinetic parameters demonstrated dose-proportionality over the range of four doses tested in this study.

- Single monthly injection with 600 mg of VM-1500A-LAI achieved median plasma C_{trough} above target level for at least 3 weeks.
- Single monthly injection with 1200 mg achieved median plasma C_{trough} for 35 days.
- Two consecutive monthly injections of 600mg split into 2 x 300 mg achieved target level for 4 weeks after 1st and 5 weeks after 2nd injections also showing drug accumulation in plasma.

In summary, VM1500A LAI was well tolerated and had an acceptable PK profile in healthy volunteers following single and multiple IM dosing.

These data support further development of VM1500A-LAI as a novel, long-acting antiretroviral agent for the treatment of HIV-1 infection.

[1]*Pharmacokinetics of VM1500A Long Acting Injectable Formulations for HIV-1 Infections Treatment and Prevention after Repeat-Dose Administration in Dogs. Yakubova E. et al; 22nd International Aids Conference (Aids 2018) Amsterdam, Netherlands 23-27 July 2018*