Pharmacokinetics of VM-1500 20 mg and 40 mg in Healthy and HIV-Infected Patients

Poster #: LBPE20

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Background

VM-1500 is the prodrug of the active compound VM-1500A, a highly selective HIV non-nucleoside reverse transcriptase inhibitor. Its short-term antiviral profile demonstrated a high level of activity in HIV-infected patients naïve to antiretroviral therapy. HIV RNA decreased 1.73 and 1.8 $\log_{10}$ after 7 days of VM-1500 20 mg and 40 mg therapy, respectively. Minimal side effects have been reported supporting the statement that VM-1500 is well tolerated over a 7 day period in both dosing groups.

Methods

Uninfected healthy subjects were randomized (4:2) to receive a single oral dose of VM-1500 20 mg or placebo, and another dose cohort received VM-1500 40 mg or placebo. Plasma samples were collected over 24 hours on Day 1.

In the second part of the study, HIV-infected treatment-naive patients were randomized (7:1) to VM-1500 20 mg or placebo, and another dose cohort received VM-1500 40 mg or placebo once daily for 7 days. Plasma samples were collected over 24 hours after the Day 1 and Day 7 doses and at 14, 21, and 36 days of follow-up.

VM-1500 and VM-1500A (metabolite) plasma concentrations were measured using the LC-MS/MS method, and PK parameters were calculated.

Results

Uninfected Healthy Subjects

4 uninfected subjects in each dose cohort received VM-1500.
The mean half-life (T1/2) of a single 20 mg dose of VM-1500 in healthy patients was 1.7 hours, and 2.6 hours for the 40 mg dose. T1/2 of the metabolite VM-1500A was 8.9 and 8.8 days for the 20 and 40 mg doses, respectively (Table 1).

Table 1: Pharmacokinetics of Single Oral Dose of VM-1500

VM-1500	20 mg (n=4)		40 mg (n=4)	
Parameters	Mean	SD	Mean	SD
T1/2 (hours)	1.7	0.8	2.6	1.2
Tmax (hours)	1.1	0.8	1.9	1.5
Cmax (ng/mL)	7.5	2.3	10.8	4.7
AUCt (h*ng/mL)	15.5	5.0	27.4	6.6
AUCinf (h*ng/mL)	15.7	5.0	28.1	6.9
MRT (hours)	2.1	0.5	3.7	0.8
VM-1500A metabolite	20 mg (n=4)		40 mg (n=4)	
Parameters	Mean	SD	Mean	SD
T1/2 (days)	8.9	2	8.8	1.4
Tmax (days)	0.15	0.04	0.38	0.16
Cmax (ng/mL)	98	74.3	85.3	36.3
AUCt (days*ng/mL)	790	503	627	115
AUCinf (days*ng/mL)	829	507	651	106
MRT (days)	8.6	1.5	6.9	1.6

Results (cont.)

HIV-infected Patients

7 HIV-infected patients in each dose cohort received VM-1500.

The mean half-life (T1/2) of 7 days of VM-1500 20 mg dosing in HIV-infected patients was 1.9 hours on Day 1; T1/2 of 40 mg dosing was 2.1 hours on Day 1 and 2.4 hours on Day 7.

T1/2 of the metabolite VM-1500A was 7.4 and 5.4 days for the 20 and 40 mg doses, respectively. (Table 2)

Table 2: Pharmacokinetics of 7-day Oral Dosing of VM-1500 in HIV-infected Patients

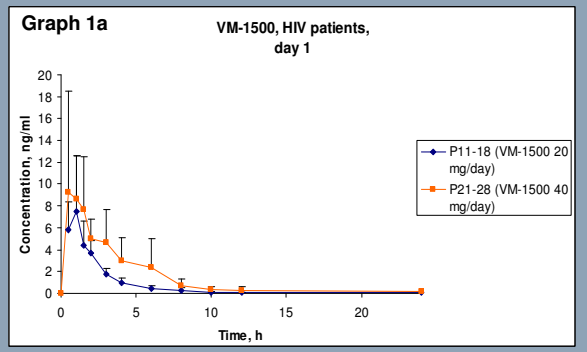
VM-1500	20 mg (day 1) (n=7)		40 mg (day1/day7) (n=7)	
Parameters	Mean	SD	Mean	SD
T1/2 (hours)	1.9	0.5	2.1/2.4	1.2/1.2
Tmax (hours)	0.9	0.4	1.0/1.1	0.4/0.4
Cmax (ng/mL)	8.4	4.6	13.4/8.7	7.5/4.7
AUCt (h*ng/mL)	16.6	5.9	32.6/23.6	13.5/9.8
AUCinf (h*ng/mL)	16.8	6.0	33.0/24.2	13.9/10.1
MRT (hours)	2.4	0.6	3.2/3.5	1.3/0.7
VM-1500A metabolite	20 mg x 7 days (n=7)		40 mg x 7 days (n=7)	
Parameters	Mean	SD	Mean	SD
T1/2 (days)	7.4	1.6	5.4	0.6
Tmax (days)	6.3	0.5	6.2	0.1
Cmax (ng/mL)	148	8	383	86
AUCt (days*ng/mL)	2009	217	2872	605
AUCinf (days*ng/mL)	2123	266	2889	612
MRT (days)	10.7	1.4	6.4	0.5

Conclusions

- The pharmacokinetic profile supports once daily dosing of VM-1500 at either the 20 mg or 40 mg dosage, with neither dose showing superiority.
- VM-1500 at 20 mg and 40 mg doses given once daily showed optimal antiviral activity over a 7 day period and was well tolerated.
- Further development of VM-1500 is warranted.

Mean Plasma Concentration Profiles of VM-1500 and VM-1500A (Graph 1c) Following Oral Administration of VM-1500 20 and 40 mg/day for 7 days: Day 1 (Graph 1a), Day 7 (Graph 1b)

Graph 1a



Graph 1b

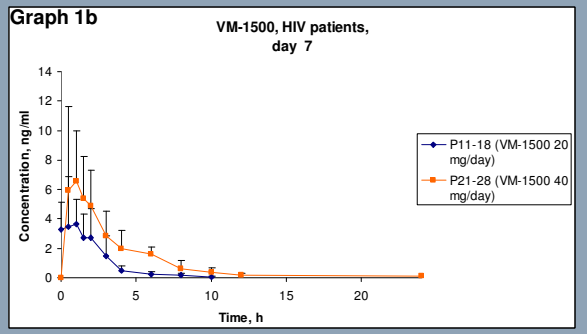
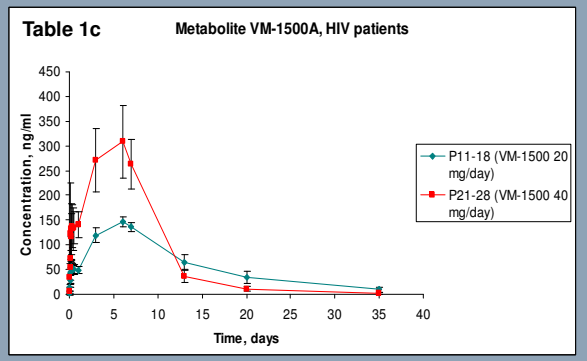


Table 1c



Acknowledgment

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