Elsulfavirine as Compared to Efavirenz in Combination with TDF/FTC: 48-week Study

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Pharmacokinetics of VM-1500 20 mg and 40 mg in Healthy and HIV-Infected Patients ***http://www.natap.org/2014/IAC/IAC_108.htm***

Conclusions

This 48-week study demonstrated equivalent virologic and immunologic efficacy of ART regimens including Elpida or EFV in ART-naive HIV-1 infected patients. Elpida was significantly safer than EFV-based therapy offering a better tolerated alternative to EFV-based ART. Based on these findings and the pharmacokinetic properties of Elpida, future studies will examine parenteral and oral administration at less frequent dosing intervals.

Background

Elpida® / Elsulfavirine (VM1500) is the prodrug of VM1500A, a new potent non-nucleoside reverse transcriptase inhibitor with unique pharmacokinetic properties ($T_{1/2}$ is ~8 days). A 20 mg once daily dosing was chosen for further study based on 12-week efficacy, pharmacology and safety data. The objective of this study was to compare the efficacy and safety of an ART regimen including Elpida or Efavirenz (EFV) plus tenofovir/emtracitabine (TDF/FTC).

Methods

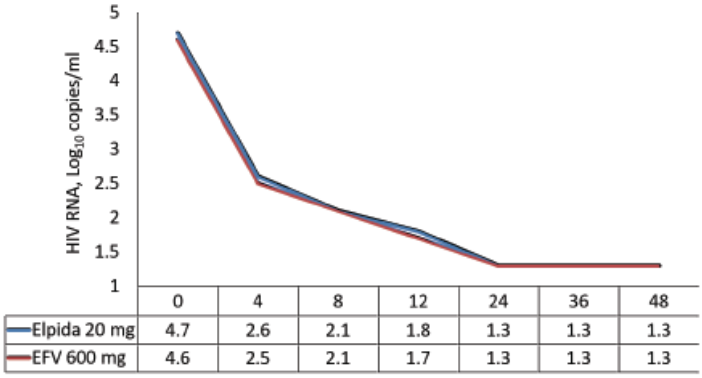
Phase IIb randomized, placebo-controlled, double-blind, multicenter study in ART-naïve HIV-1-infected patients treated for 48 weeks. Patients were randomized 1:1 to receive; 1) Elpida 20 mg QD, or 2) EFV 600 mg QD. All patients were treated with TDF/FTC.

Results

120 patients enrolled, 60 Elpida/60 EFV. Baseline plasma HIV RNA median was 4.7-4.8 $\log_{10}$ copies/ml; median CD4+ T lymphocyte count was 349 and 379 cells/mm^3 for Elpida and EFV, respectively. A total of 55/60 (91.7%) Elpida and 47/60 (78.3%) EFV (p=0.041) completed treatment. At Week 48 of therapy 45/55 (81%) of Elpida and 35/47 (73.7%) of EFV patients had HIV-1 RNA values < 400 copies/ml (MITT). Patients with baseline HIV-I RNA > 100 000 copies/ml, 14/18 (77.7%) and 15/22 (68.2%) had HIV RNA <400 copies/ml, respectively. CD4+ T lymphocyte counts increased at Week 48 by 179 and 182 cells/mm^3 respectively. Median CD4/CD8 ratio increased in both groups from 0.41 to 0.78 and from 0.34 to 0.63 respectively. Study drug-associated adverse events were observed in 22/60 (36.7%) of Elpida patients and 45/58 (77.6%) of EFV patients (p<0.0001). AEs of special interest (CNS disorders, skin disorders) with a frequency > 5% occurred in 31.7% and 62.1% of patients respectively (p = 0.008). The most frequent were headache (15% and 24.1%), dizziness (6.7% and 27.6%), sleep disorders (5% and 20.7%). Only EFV patients had abnormal dreams (17.2%), skin rash (17.2%), and pruritus (5.2%). Only 5 patient discontinued Elpida (2 AE [1 pregnancy], 1 lack of adherence, 1 LTFU, 1 withdrew consent), and 13 patients discontinued EFV (7 AE, 5 LTFU, 1 withdrew consent).

Results

Fig.1.Serum HIV RNA levels (PP-analysis)



	0	4	8	12	24	36	48
Elpida 20 mg	4.7	2.6	2.1	1.8	1.3	1.3	1.3
EFV 600 mg	4.6	2.5	2.1	1.7	1.3	1.3	1.3

Fig.2. Patients with HIV RNA < 50 copies/ml at week 48(MITT analysis)

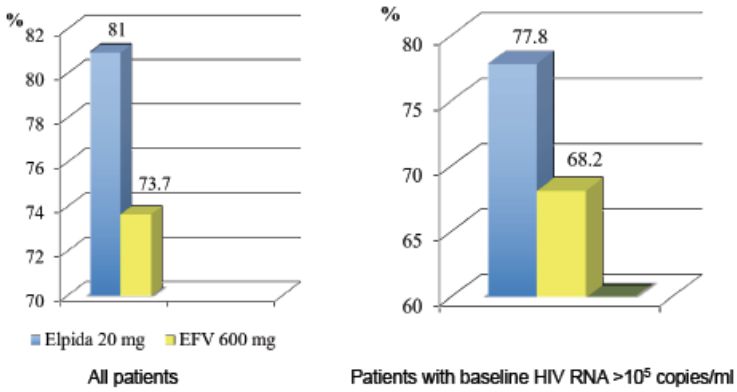


Fig. 3. Median CD3/CD4+ cell count (PP-analysis)

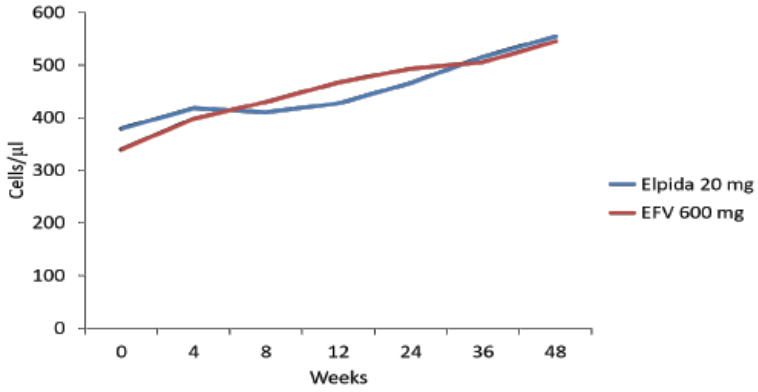


Fig.4. Median CD3/CD8+ cell count (PP-analysis)

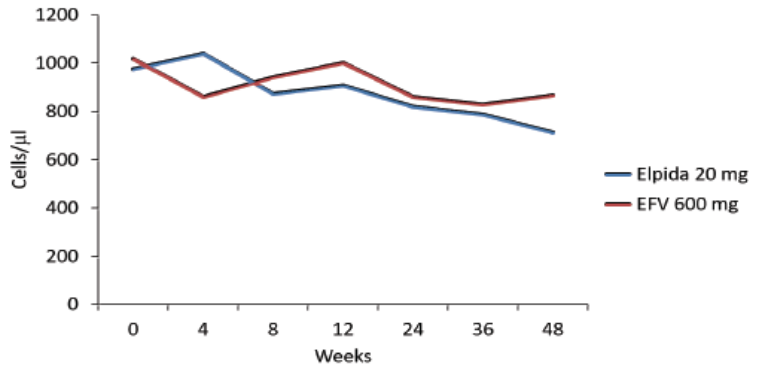


Fig.5. CD4/CD8+ cell count ratio (PP-analysis)

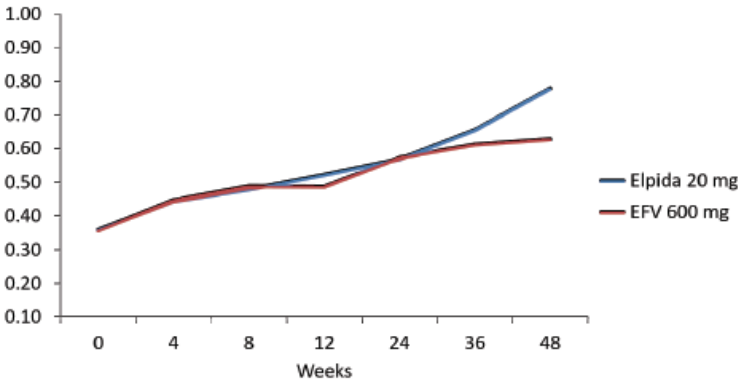


Table 1. Adverse events by frequency, severity and relation to treatment

Adverse Events (AEs)	Elpida 20 mg	EFV 600 mg
	N=60	N=58
	N(%)/total #events	n (%)/total #events
All	47 (78.3%)/288	50 (86.2%)/521
Grades 1-2	6 (10.0%)/285	10 (17.2%)/513
Grades 3-4 (SAE)	3 (5.0%)/3 All not drug-related	7 (12.1%)/8 3 not drug-related 5 probably drug-related
Probably- and possibly drug-related	22 (**36.7%**)/124**	45 (**77.6%**)/402**
AE-related treatment discontinuation (%)	1 (1.7%)	7 (**12.1%**)

- - p=0.008; ** - p<0.0001
- N – number of patients
- % - fraction of patients with at least one AE
- Special interest: CNS events

Table 2. CNS adverse events (>5%) CNS AEs

CNS AEs	Elpida 20 mg N=60 n (%)Y	EFV 600 mg N=58 n (%)Y
All	16 (**26.7%**)/42*	15 (**50.0%**)/164*
Unusual dreams	2 (3.3%)/5	10 (17.2%)/15
Dizziness	4 (6.7%)/5	16 (27.6%)/25
Headache	9 (15.0%)/20	14 (24.1%)/56
Insomnia	1 (1.7%)/1	5 (8.6%)/10
Memory loss	1 (1.7%)/2	3 (5.2%)/6
Sleepiness	2 (3.3%)/1	9 (15.5%)/21
Apathy	1 (1.7%)/1	3 (5.2%)/5
Depression	2 (3.3%)/2	7 (12.1%)/17

* - p=0.002
n - number of patients with at least one AE
% - fraction of patients with at least one AE Y
Y - total number of AEs

Table 3. Other AEs (>5%) AEs Elpida 20 mg N=60

AEs	Elpida 20 mg N=60 n (%)Y	EFV 600 mg N=58 n (%)Y
Skin rash	0 (**0.0%**)/0	13 (**22.4%**)/16
Diarrhea	4 (6.7%)/8	3 (5.2%)/7
Nausea	3 (5.0%)/5	6 (10.3%)/7
Fatigue	2 (3.3%)/2	5 (8.6%)/12

n – number of patients with at least one AE
% - fraction of patients with at least one AE
Y – total number of AEs