

Potent Antiretroviral Effect of MK-0518, a Novel HIV-1 Integrase Inhibitor, in Patients with Triple-class Resistant Virus

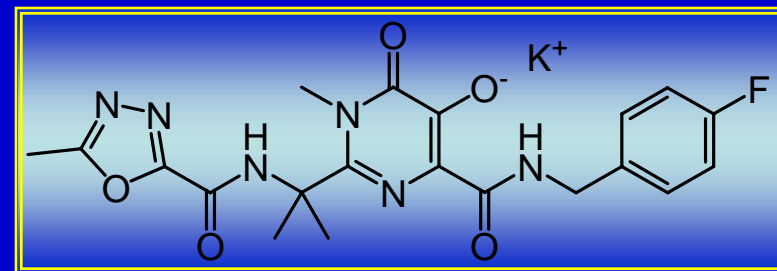
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MK-0518:

A Novel HIV-1 Integrase Inhibitor

- A new mechanism of action
- Potent *in vitro* activity
 - $IC_{95} = 33 \text{ nM} \pm 23 \text{ nM}$ in 50% human serum
 - Active against:
 - multi-drug resistant HIV-1
 - CCR5 and CXCR4 HIV-1
 - HIV resistant to MK-0518 remain sensitive to other ARTs
 - Synergistic *in vitro* with all ARTs
- Potent activity in combination therapy
 - in ART-naive patients at Week 24 (Markowitz et al, IAC 2006, Abst THLB0214)
 - 85 – 95% with HIV RNA < 50 copies/mL
 - In patients failing therapy with triple class resistant virus at Week 16 (Grinsztejn et al, CROI 2006, Abst 159LB)
 - 56 – 72% with HIV RNA < 50 copies/mL



Study Design (1)

- **Randomized, double-blind**
 - **200, or 400, or 600 mg MK-0518 b.i.d. p.o. vs Placebo**
 - All in combination with optimized background therapy (OBT)
 - **Baseline stratification**
 - Use of enfuvirtide (T-20) in OBT
 - Resistant to 1 PI or > 1 PI at entry
 - **To evaluate potential atazanavir (UGT1A1 inhibitor) effect**
 - Sub-study A (non-ATV containing OBT) (**hypothesis testing**)
 - Sub-study B (ATV containing OBT)
 - Similar treatment effect observed across Sub-Study A and B
 - ⇒ Data presented are combined from 2 sub-studies

Study Design (2)

- **Key Inclusion Criteria**
 - Documented genotypic/phenotypic resistance to ≥ 1 drug in each of 3 classes (NNRTI + NRTI + PI)
 - HIV RNA > 5000 copies/mL and CD4 > 50 cells/mm³
- **Endpoints at Week 24**
 - HIV RNA and CD4 counts
 - Adverse experiences

Baseline Patients Characteristics

	MK-0518*			Placebo*
	200 mg N=43	400 mg N=45	600 mg N=45	N=45
Median Age (yrs)	43	43	44	43
Male	84%	89%	91%	89%
Mean log₁₀ HIV RNA	4.6	4.8	4.7	4.7
Mean CD4 Count (/mm³)	245	221	220	274
Median Years of Prior ARTs	9	10	9	9
OBT: Median # of ARTs	4	4	4	4
PSS§: 0 to all ARTs	20 (47%)	26 (58%)	22 (49%)	19 (42%)
PSS§: 0 to PI	42 (98%)	42 (93%)	40 (89%)	39 (87%)
# pts with enfuvirtide as new OBT	12 (28%)	9 (20%)	11 (24%)	10 (22%)

* + OBT

§ PSS = Phenotypic sensitivity score by Phenosense GT

Enfuvirtide is not included in the PSS since there is no clinical cut-off.

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Patient Status at Week 24

Description	MK-0518*			Placebo*	Total
	200 mg n (%)	400 mg n (%)	600 mg n (%)	n (%)	n (%)
Total Enrolled	N = 44	N = 45	N = 45	N = 45	N = 179
Treated	43 (98)	45 (100)	45 (100)	45 (100)	178 (99)
Discontinued by Wk 24[§]	10 (23)	8 (18)	8 (18)	31 (69)	57 (32)
- due to lack of efficacy	8 (18)	8 (18)	7 (16)	30 (67)	53 (30)
- due to AE	2	0	1	1	4

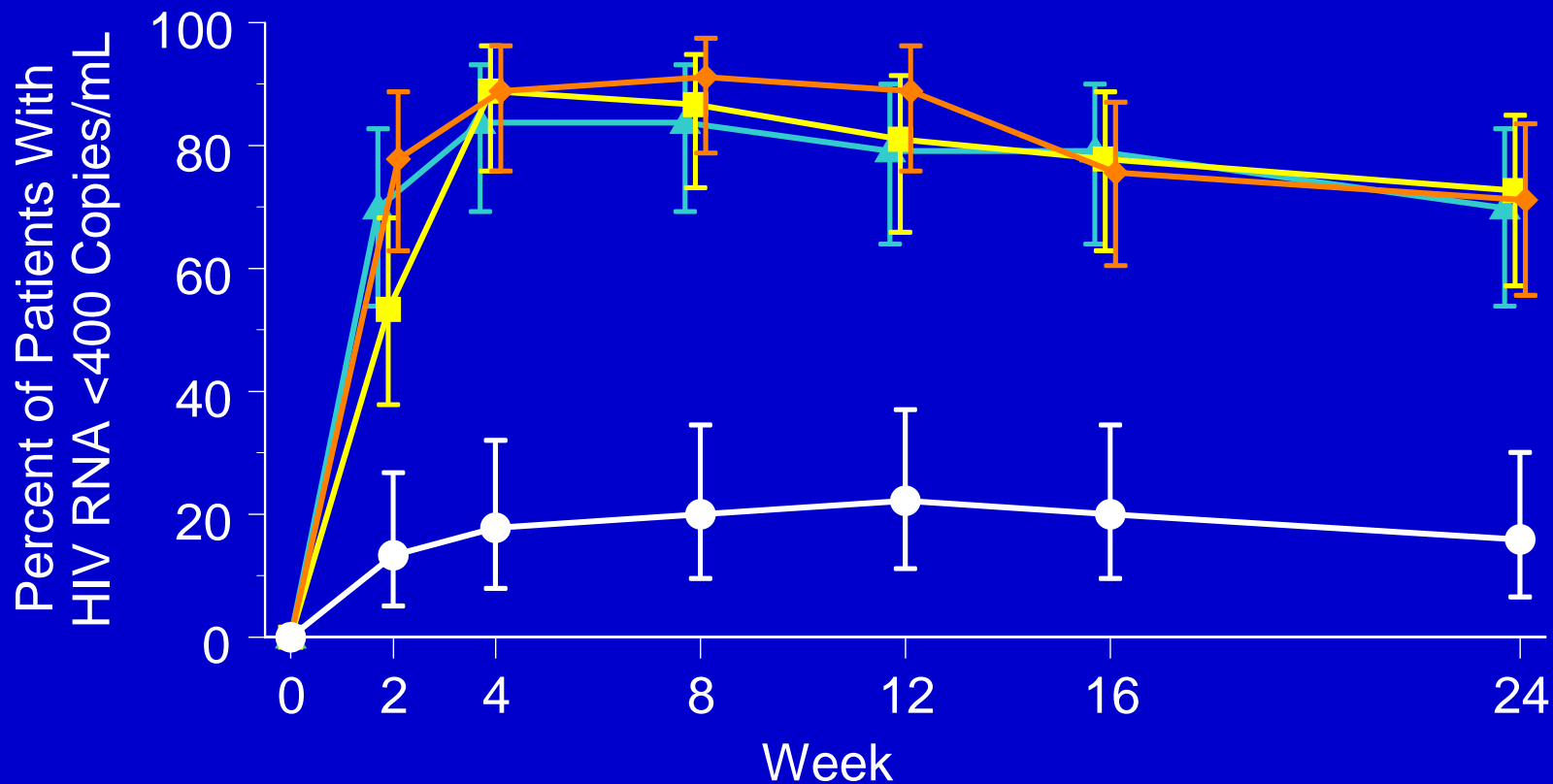
* + OBT

§ Most switched to open-label virologic failure treatment group

n = Number of patients in each category

N = Total number of pts enrolled in each group

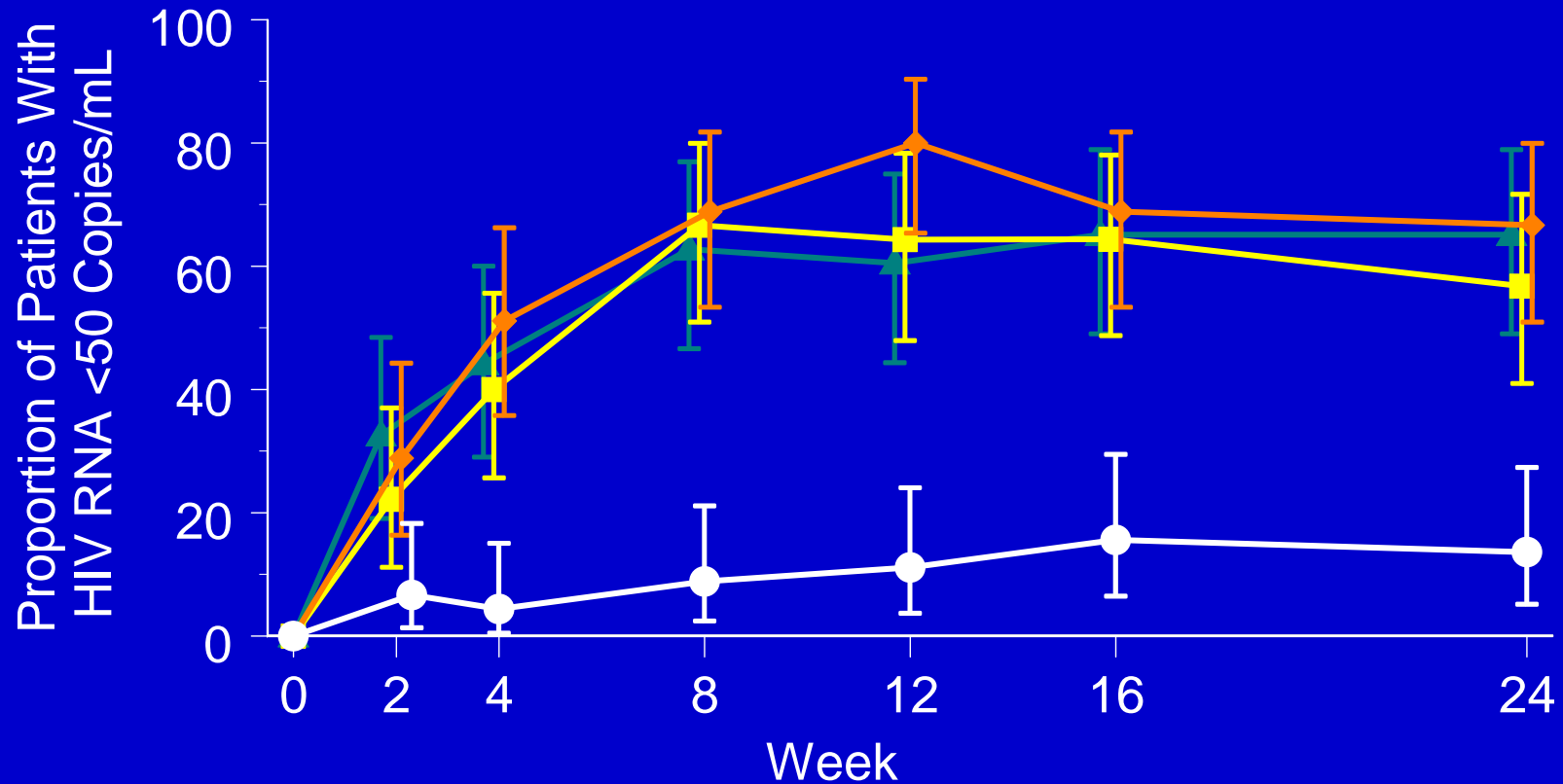
% Patients (95% CI) with HIV RNA <400 copies/mL (NC = F)



▲	MK-0518 200 mg	43	43	43	43	43	43
■	MK-0518 400 mg	45	45	45	42	45	44
◆	MK-0518 600 mg	45	45	45	45	45	45
●	OBT alone	45	45	45	45	45	44

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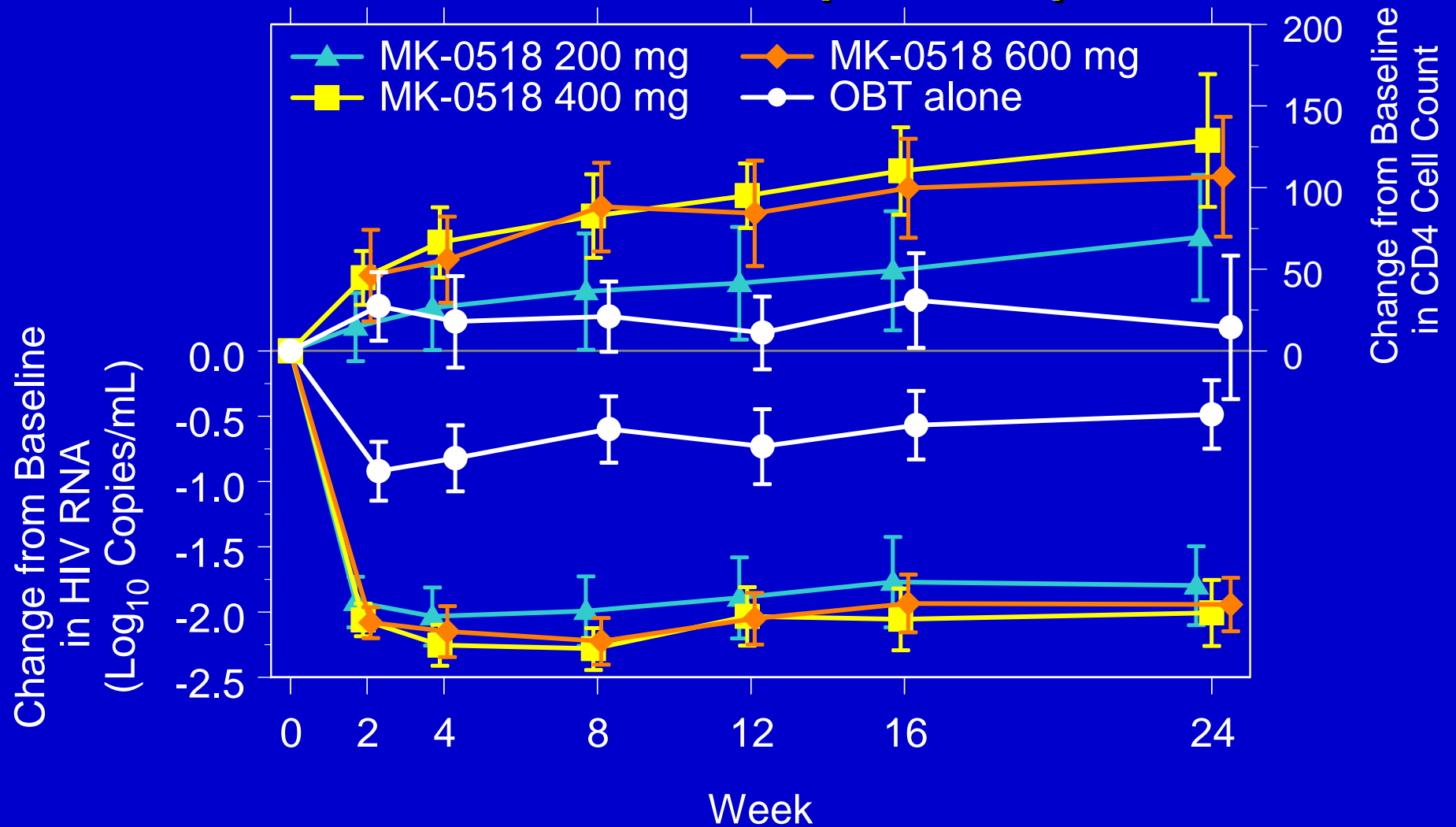
% Patients (95% CI) with HIV RNA <50 copies/mL (NC = F)



▲	MK-0518 200 mg	43	43	43	43	43	43
■	MK-0518 400 mg	45	45	45	42	45	44
◆	MK-0518 600 mg	45	45	45	45	45	45
●	OBT alone	45	45	45	45	45	44

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Change from Baseline in CD4 cell counts and HIV RNA (95% CI)



Week 24 Efficacy by Baseline PSS *

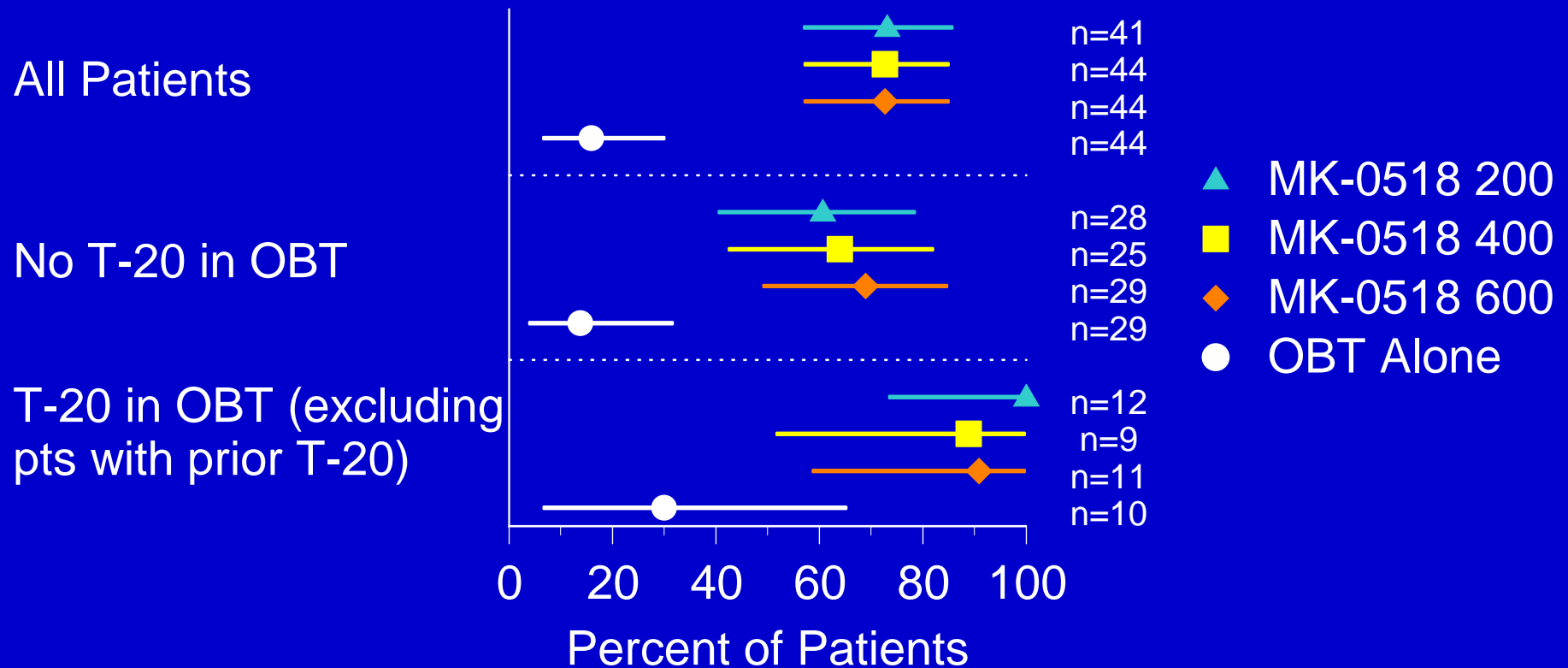
	% HIV RNA <400 copies/mL (95% CI)			
	N	PSS = 0	N	PSS = 1-2
MK-0518 200 bid**	13	54 (25, 81)	25	84 (64, 95)
MK-0518 400 bid**	13	69 (39, 91)	26	77 (56, 91)
MK-0518 600 bid**	13	62 (32, 86)	28	75 (55, 89)
OBT alone	11	0 (0, 28)	27	19 (6, 38)

* PSS = Phenotypic Sensitivity Score; enfuvirtide was counted as active drug.

** + OBT

Efficacy by Enfuvirtide Use in OBT

% < 400 copies/mL at Week 24 (95% CI)



Protocol 005 Safety (1)

- Total N = 178 patients in 4 groups
 - 4 Discontinuations due to clinical or laboratory AE
 - 4 drug-related SAEs
 - Acute Pancreatitis after 2 doses, considered 2° to OBT (200 mg)
 - Lacunar infarction by CT (placebo)
 - Lipoatrophy (blinded)
 - Metabolic acidosis; renal insufficiency; death (blinded)
- MK-0518 (all doses) safety profile similar to placebo
- Most clinical adverse experiences (AE): mild to moderate
- Grade 3 / 4 lab abnormalities uncommon and similar between treatment groups

Protocol 005 Safety (2)

**Most Common Drug-Related Clinical AE
(Incidence \geq 5% in at least one treatment group)**

	MK-0518*			Placebo*
	200 mg N = 43	400 mg N = 45	600 mg N = 45	N = 45
Diarrhea	4 (9%)	1 (2%)	0 (0%)	7 (16%)
Nausea	3 (7%)	2 (4%)	5 (11%)	5 (11%)
Fatigue	4 (9%)	0 (0%)	2 (4%)	1 (2%)
Injection site reaction	1 (2%)	3 (7%)	5 (11%)	3 (7%)
Headache	4 (9%)	0 (0%)	2 (4%)	3 (7%)
Pruritus	1 (2%)	2 (4%)	3 (7%)	0 (0%)

* Given bid with OBT

Conclusions

- MK-0518 is a promising new HIV integrase inhibitor
- In patients with advanced HIV infection, failing ARTs with triple-class resistant virus, and with limited active ARTs in OBT, MK-0518 at all doses studied
 - was generally well tolerated
 - had potent antiretroviral activity with or without enfuvirtide
 - » overall 70-73 % with HIV RNA < 400 copies/mL at Wk 24
 - » overall 57-67% with HIV RNA < 50 copies/mL at Wk 24

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