Single doses as low as 0.5 mg of the novel NRTTI MK-8591 suppress HIV for at least seven days

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Background

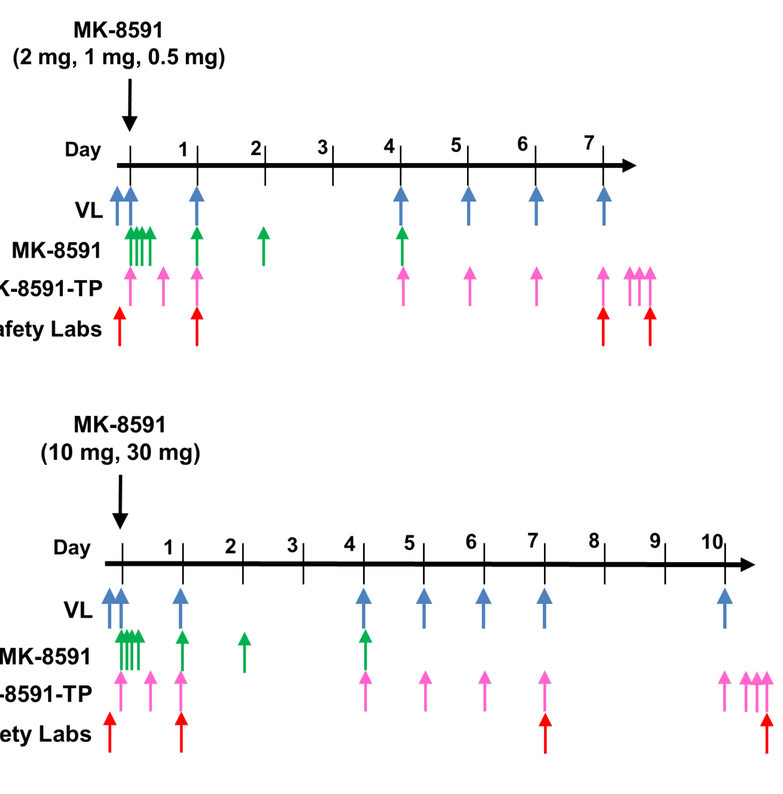
- MK-8591 is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) with a novel mechanism of action.
- MK-8591 demonstrates high potency and a high barrier to resistance *in vitro.*
- MK-8591 demonstrates a long half-life in preclinical species and in healthy human subjects.
- MK-8591 has been generally well tolerated in healthy human subjects to date.

Study design

- Open-label, single-dose, multiple panel study.
- Treatment-naïve HIV-1-infected adult subjects.
- Doses administered: 30 mg, 10 mg, 2 mg, 1 mg, 0.5 mg.
- Subjects strongly encouraged to initiate standard of care therapy after 10 days (30 mg, 10 mg) or 7 days (2 mg, 1 mg, 0.5 mg).
- Frequent assessment of pharmacokinetics (PK) and safety markers (vital signs, ECGs, laboratory studies.)

Study objectives

- Assess preliminary safety and tolerability of MK-8591 in HIV-1-infected subjects.
- Assess PK of MK-8591, as parent in plasma and as triphosphate (MK-8591-TP) in peripheral blood mononuclear cells (PBMCs) in HIV-1-infected individuals.
- Determine the degree of viral load suppression at 7 or 10 days post treatment
  - *Determine the lowest dose at which the true mean VL decline is at least 0.5 log_{10} from placebo-corrected baseline.*
- Determine the PK/PD relationship between MK-8591-TP and viral load decline.



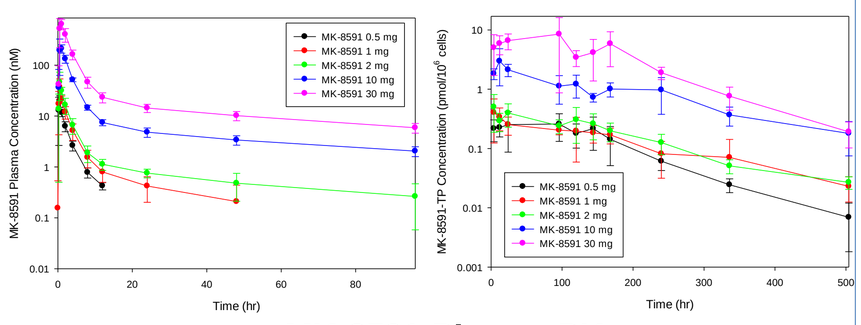
MK-8591 Safety

Subjects (#)	SAEs	AEs (#)	TEAEs (#) [ab]	Most common MK-8591 TEAEs [c]	MK-8591 Related TEAEs[d]	Vital Signs	ECG Parameter Value Changes	Lab Safety Findings
30	None	63 (29 subjects)	60 (27 subjects)	Headache (n=10) Common cold (n=4) Diarrhea (n=3) Vomiting (n=3)	Headache (n=9) Diarrhea (n=2) Eczema (n=2)	NCS	NCS	NCS

TEAE: Treatment-emergent adverse event
NCS: Not clinically significant
[a]All adverse events were mild to moderate in intensity and resolved by study completion.
[b]TEAEs do not include AEs that occurred prior to dosing.
[c]TEAEs reported by more than 2 subjects following treatment.
[d]MK-8591 related TEAEs reported by more than one subject.

- MK-8591 was generally well-tolerated in 30 HIV-1-infected adult subjects.
- AEs were seen in 29/30 subjects, and treatment-emergent (after dosing) AEs were seen in 27/30 subjects.
- There was no relationship between dose and frequency or severity of AEs.
- There were no SAEs and no discontinuations due to an AE. All AEs were mild or moderate in severity.
- The most common AEs were headache, common cold, diarrhea and vomiting.
- The most common AEs assigned as related were headache, diarrhea, and eczema.
- There were no clinically significant changes in vital signs, ECG parameter values, or laboratory safety findings.

MK-8591 Pharmacokinetics



MK-8591 Plasma PK

Dose (mg)	Geometric Mean (%GCV)					
	AUC0-∞ (hr*nM)	Cmax (nM)	Tmax† (hr)	Apparent Terminal t1/2 (hr)	CL/F (L/hr)	Vz/F (L)
0.5	38.2 (23.6)	20.3 (36.4)	0.5 (0.25 - 0.5)	2.31 (16.7)	44.6 (23.6)	149 (16.4)
1	88.7 (35.1)	38.8 (31.3)	0.5 (0.5 - 1)	10.4 (144)	38.5 (35.1)	575 (102)
2	157 (41.1)	43.8 (51.2)	0.5 (0.5 - 1)	47.4 (74.6)	43.4 (41.1)	2960 (38.8)
10	1100 (17.4)	235 (32.1)	1 (0.5 - 1)	59.7 (15.4)	31 (17.4)	2670 (20.7)
30	3220 (24.7)	678 (29.6)	0.75 (0.5 - 1)	56.8 (11.2)	31.8 (24.7)	2600 (25.5)

N = 6 for all Panels . %GCV: The geometric mean percent coefficient of variation. †Median (Min-Max)

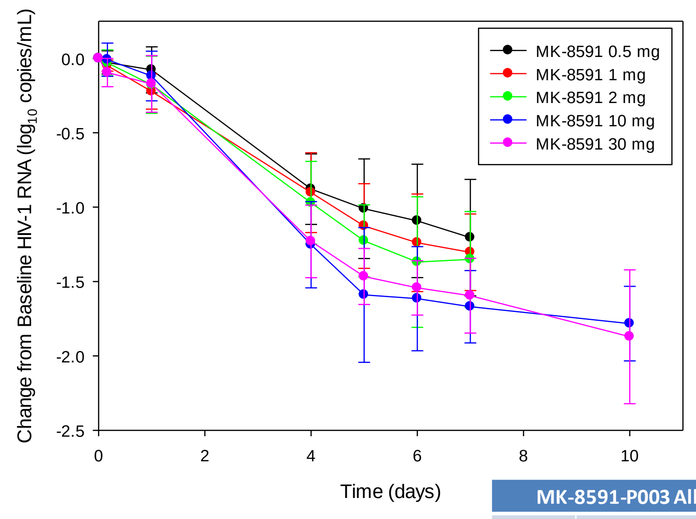
MK-8591-TP PBMC PK

Dose (mg)	Geometric Mean (%GCV)						
	AUC0-∞ (hr*pmol/10^6 cells)	AUC0-168hr (hr*pmol/10^6 cells)	Cmax (pmol/10^6 cells)	C336hr (pmol/10^6 cells)	C168hr (pmol/10^6 cells)	Tmax† (hr)	Apparent Terminal t1/2 (hr)
10	445‡ (31.9)	227 (33.3)	2.81 (49.9)	0.35 (36.4)	0.983 (26)	12 (12 - 240)	128‡ (42.2)
2	76.2 (33.0)	46.9 (38.1)	0.495 (62.9)	0.049 (29.9)	0.188 (39.2)	8 (4 - 144)	120 (14.7)
30	1380 (40.3)	926 (47.7)	8.9 (60.3)	0.703 (49.7)	4.83 (85.9)	24 (4 - 96)	78.5 (31.4)
1	60.0 (33.9)	35.9 (27.6)	0.408 (49.3)	0.041 (186)	0.164 (31.4)	8 (4 - 24)	118 (16.1)
0.5	35.3 (68.3)	23.1 (83.0)	0.263 (54.5)	0.02 (34.6)	0.116 (85.6)	12 (4 - 24)	95.3 (38.2)

N=6 for all panels; PBMC: Peripheral Blood Mononuclear Cells; %GCV: The geometric mean percent coefficient of variation.
†Median (Min-Max); ‡N = 5;

- MK-8591 parent plasma PK and MK-8591-TP PBMC PK were dose proportional.
- MK-8591 parent half-life ranged from 2.3-56.8 hr, MK-8591-TP half-life from 78.5-128 hr.
- PK parameter values generally similar between healthy subjects and HIV-1-infected subjects.

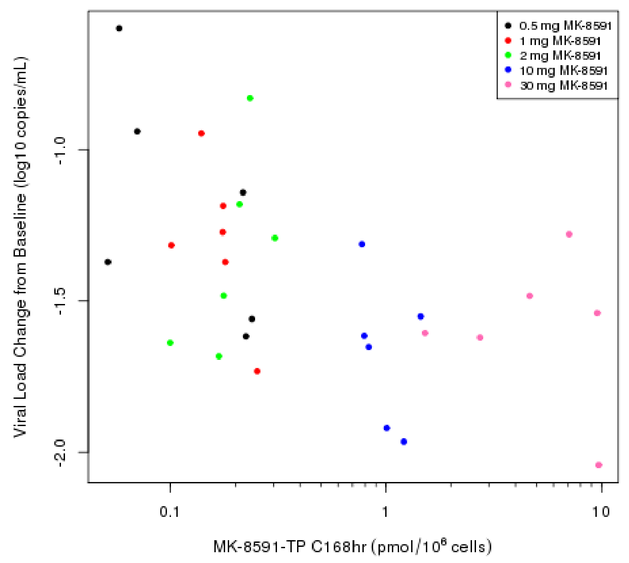
MK-8591 Pharmacodynamics



- **One-time treatment of MK-8591 in treatment-naïve HIV-1-infected subjects leads to >1.0 log_{10} VL decline from baseline at all doses tested (>99% posterior probability).**

MK-8591-P003 All Panels	
Dose	Posterior Mean of PBO Corrected VL Change from Baseline
30	-1.57
10	-1.64
2	-1.32
1	-1.28
0.5	-1.18

- Mutant screening in post-treatment samples were negative in all subjects with sufficient VL for testing (17).



- PK/PD analysis performed comparing VL decline and MK-8591-TP levels at 168 hr (C168hr)
- Lower doses lead to lower C168hr levels, which generally correlate with a lower magnitude of VL decline (R^2=0.228, p=0.005).

Conclusions

- MK-8591 is generally well-tolerated when administered as a one-time dose (0.5-30 mg) to HIV-1-infected adult subjects.
- MK-8591-TP demonstrates a half-life in PBMCs from HIV-1-infected subjects of 78.5-128 hr, which is compatible with a variety of potential dosing regimens.
- One-time treatment with MK-8591 at doses as low as 0.5 mg leads to robust VL decline in treatment-naïve HIV-1-infected subjects.

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