MK-8591 Potency and PK Provide High Inhibitory Quotients at Low Doses QD and QW

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Abstract

Background: MK-8591, a nucleoside reverse transcriptase translocation inhibitor (NRTTI), has demonstrated HIV-1 suppression for ≥7 days with single doses as low as 0.5 mg. It is currently in a Phase 2 clinical trial (NCT03272347) for the treatment of HIV-1 infection with once-daily (QD) administration of 0.25 mg, 0.75 mg, or 2.25 mg in combination with doravirine. Inhibitory quotients (IQ) for nucleoside inhibitors, based on the ratio of intracellular phosphorylated drug concentrations at trough ($C_{trough,IC}$) and the intracellular concentrations required for efficacy ($IC_{50,IC}$), predict virologic response. We evaluated the IQ of MK-8591-triphosphate (MK-8591-TP) in relation to other NRTIs for WT and NRTI-resistant HIV-1 to assess the likelihood of virologic response and barrier to resistance at clinically relevant doses.

Methods: MK-8591-TP, TFV-DP, 3TC-TP, and FTC-TP $IC_{50,IC}$ levels were determined in activated, uninfected human peripheral blood mononuclear cells (hPBMC) after 24 hr incubation with varying concentrations of MK-8591, TDF, 3TC, or FTC, followed by lysis and analysis by LC-MS/MS. MK-8591 IQs for wild-type (WT) HIV-1 were calculated as the ratio of steady-state $C_{trough,IC}$, as observed with QD or weekly (QW) dosing in Phase 1 clinical studies, to the $IC_{50,IC}$ in hPBMCs. TDF, TAF, 3TC, and FTC IQs were calculated using their corresponding $C_{trough,IC}$s, as determined after dosing in humans at clinical dose levels, and hPBMC $IC_{50,IC}$s. IQs for NRTI-resistant HIV-1 were calculated using fold-shifts for NRTI-resistant clinical isolates.

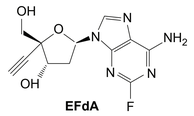
Results: The MK-8591-TP $IC_{50,IC}$ for WT HIV-1 is >4-fold lower than any marketed NRTI. MK-8591 IQs at steady state with 0.25 mg QD and 10 mg QW dosing are 85.3 and 101, respectively, and proportionately greater for higher dose levels. Common NRTI mutations, including M184I/V, thymidine analog mutations, K65R, and K70E, confer low fold-shifts in antiviral potency, and MK-8591 retains greater IQs against these NRTI-resistant viruses than those of TDF, TAF, and 3TC with WT virus.

Conclusion: The IQs of MK-8591 for both WT and NRTI-resistant HIV-1 at low QD and QW doses are substantially higher than those of any NRTIs approved for HIV treatment. Coupled with the long intracellular half-life of MK-8591-TP, these IQs suggest the opportunity for multiple low dosing options with the potential for a high barrier to the development of resistance.

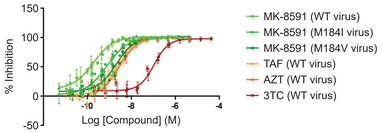
BACKGROUND

MK-8591: A Novel Nucleoside With a Unique Mechanism of Action

- MK-8591 (4′-ethynyl-2-fluoro-2′-deoxyadenosine; EFdA), licensed from Yamasa
- First-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI)
  - Inhibits HIV replication through multiple mechanisms
- Potency, pharmacokinetics, and physical properties amenable to once-daily, once-weekly, and long-acting parenteral administration
- Currently being investigated in a Phase 2 clinical trial (NCT03272347) for the treatment of HIV-1 infection with once-daily (QD) administration of 0.25 mg, 0.75 mg, or 2.25 mg in combination with doravirine



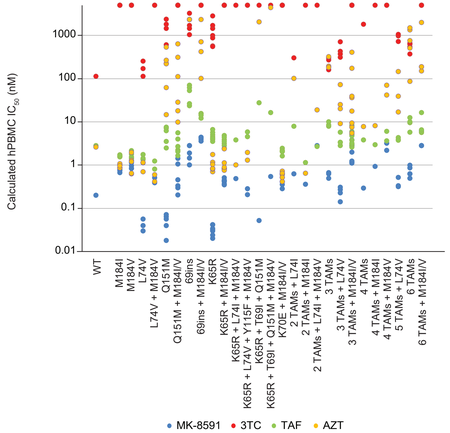
MK-8591 Exhibits Potent Antiviral Activity Against Wild-Type and NRTI-Resistant HIV-1



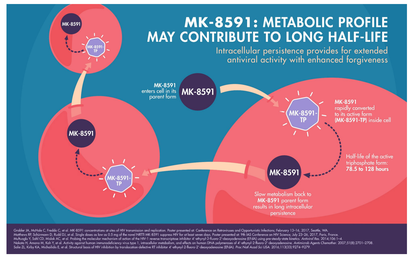
Compound	Virus	IC_{50} (nM)	
		$HIV_{NL4-3-GFP}$[a]	HIV_{IIIB}[b]
MK-8591	WT	0.2 ± 0.1 (n=68)	0.2 ± 0.1 (n=6)
	M184I	1.0 ± 0.4 (n=9)	ND
	M184V	1.6 ± 0.3 (n=10)	ND
TAF	WT	2.8 ± 0.8 (n=22)	ND
AZT	WT	2.6 ± 0.3 (n=5)	10.1 ± 3.9 (n=4)
TDF	WT	73.3 ± 37.1 (n=20)	48.0 ± 29.5 (n=4)
3TC	WT	112.3 ± 19.9 (n=10)	144 ± 68 (n=4)

Results are geometric means ± standard deviations, with number of replicates displayed in parentheses.
[a]IC_{50}s were determined by quantification of GFP-positive PBMCs infected with an HIV reporter virus in the presence of increasing compound concentrations and 10% normal human serum.
[b]IC_{50}s were determined by monitoring p24 production from infected PBMCs in the presence of increasing compound concentration and 10% fetal bovine serum.

MK-8591 Is More Potent Against Most Resistant Mutants Than Approved NRTIs

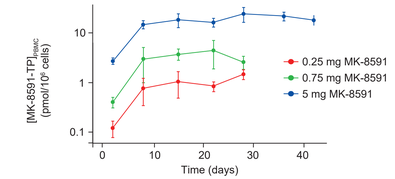


Antiviral Activity of MK-8591 and NRTIs Requires Intracellular Phosphorylation to Their Active Anabolites

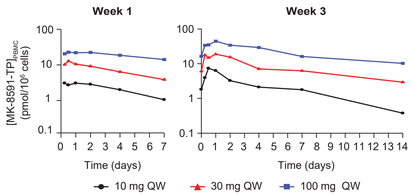


MK-8591-TP Accumulates to High Levels at Low Doses in Humans and Exhibits a Long Intracellular $t_{1/2}$

MK-8591-TP Concentration-Time Profile with QD Dosing



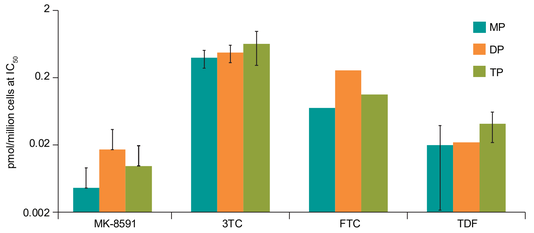
MK-8591-TP Concentration-Time Profile with QW Dosing



Matthews, CROI 2018
Grobler et al., CROI 2016

RESULTS

Intracellular MK-8591-TP and NRTI-TP Concentrations at IC_{50}



Drug	Dose Levels	Active Form	IC_{50} (fmol/10^6 hPBMCs) Mean ± SD	Steady-State C_{trough} (fmol/10^6 hPBMCs) Mean (CV%)	N	IQ (90% CI)
MK-8591	0.25 mg QD	MK-8591-TP	9.74 ± 4.06[3]	831 (28.5)	9	85.3 (44.8-126)
	0.75 mg QD			3320 (23.6)	9	341 (221-460)
	10 mg QW			983 (26)	6	101 (53.1-149)
3TC	150 mg BID/ 300 mg QD	3TC-TP	635 ± 331[2]	2620 (112)[4,5,6]	68	4.13 (1.47-6.79)
FTC	200 mg QD	FTC-TP	113[1]	4160 (63.7)[7,8,9]	64	36.9 (32.1-41.7)
TAF	25 mg QD	TFV-DP	41.5 ± 19.7[2]	311 (19.8)[11,12]	160	7.48 (3.37-11.6)
TDF	300 mg QD	TFV-DP	41.5 ± 19.7[2]	95.0 (59.7)[7,8,10]	63	2.29 (1.00-3.58)

[1]N=1, [2]N=2, [3]N=4
[4]Moore KH, et al. *AIDS.* 1999;13(16):2239-2250.
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[9]Wang LH, et al. *AIDS Res Hum Retroviruses.* 2004;20(11):1173-1182.
[10]Pruvost A, et al. *Antimicrob Agents Chemother.* 2009;53(5):1937-1943.
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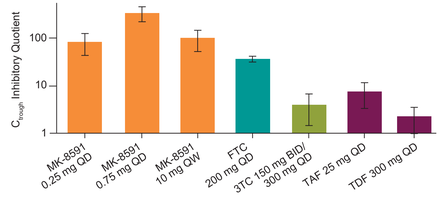
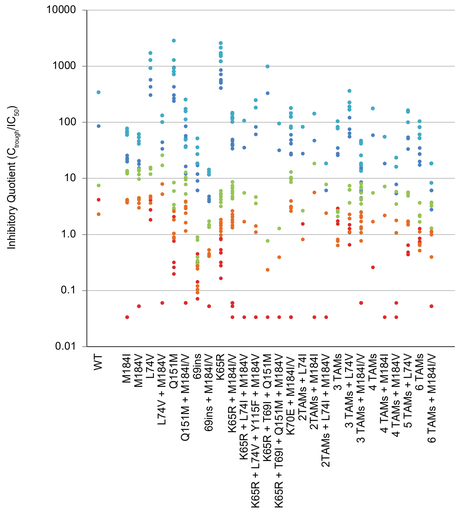
[12]Ruane PJ, et al. *J Acquir Immune Defic Syndr.* 2013;63(4):449-455.

MK-8591 Administered at Low Doses Exhibits Substantially Higher Inhibitory Quotients Than Marketed NRTIs



Inhibitory Quotients of MK-8591 and NRTIs Against Wild-Type and NRTI-Resistant HIV-1



SUMMARY AND CONCLUSIONS

- The MK-8591-TP $IC_{50,IC}$ for WT HIV-1 is >4-fold lower than any marketed NRTI
- MK-8591 IQs at steady state with 0.25 mg QD and 10 mg QW dosing are 85.3 and 101, respectively, and proportionately greater for higher dose levels
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Presented at CROI: Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA; March 4-7, 2019.

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