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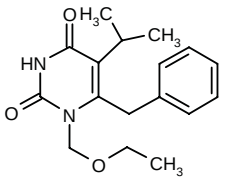
MKC-442

Non-Nucleoside Reverse Transcriptase Inhibitor

6-Benzyl-1-(ethoxymethyl)-5-isopropyluracil
6-Benzyl-1-(ethoxymethyl)-5-isopropylpyrimidine-2,4(1*H*,3*H*)-dione



$C_{17}H_{22}N_2O_3$ Mol wt: 302.37

CAS: 149950-60-7

EN: 201056

Introduction

Several new antiviral agents have recently been introduced to treat patients infected with the human immunodeficiency virus (HIV), the etiologic agent of acquired immune deficiency syndrome (AIDS). Three drug classes are now available for the treatment of infection with HIV-1: 1) nucleoside analogue inhibitors of the HIV reverse transcriptase (RT) (*e.g.*, zidovudine [AZT], didanosine [ddI], zalcitabine [ddC], stavudine [d4T] and lamivudine [3TC]); 2) aspartyl protease inhibitors (*e.g.*, saquinavir, ritonavir, indinavir and nelfinavir); and 3) nonnucleoside reverse transcriptase inhibitors (NNRTIs) (*e.g.*, nevirapine and delavirdine).

The availability of multiple anti-HIV-1 agents has reduced the morbidity and mortality associated with AIDS. However, the approved anti-HIV drugs have significant limitations, including toxicity, pharmacokinetic interactions with other agents and complex dosing regimens. Additionally, the appearance of resistant strains of virus is one of the most important limitations encountered with currently available therapy despite the development of combination, or "coactive", regimens designed to limit the incidence of viral resistance. Because of these obstacles, the search for new anti-HIV agents continues.

This report presents an overview of MKC-442, a new drug candidate that fulfills many of the criteria for an improved anti-HIV agent. Extensive preclinical data and preliminary clinical studies suggest that MKC-442 will be an excellent candidate for use in combination regimens for the treatment of HIV-1 infection.

Mechanism of Action

MKC-442 is a derivative of 1-[(2-hydroxyethoxy)-methyl]-6-(phenylthio)thymine (HEPT) (1), a compound that was described in 1989 as a novel inhibitor of the HIV-1 RT (2, 3). MKC-442 and other NNRTIs inhibit the HIV-1 RT through allosteric interactions. Although structurally similar to nucleoside analogue RT inhibitors, MKC-442 does not compete with nucleotide substrates (4) or interact with the RT catalytic site (5).

Examination of the crystal structure of the HIV-1 RT complexed with MKC-442 at a resolution of 2.55 Å revealed additional important features concerning the drug's mechanism of action. The site to which MKC-442 and other NNRTIs are bound is located approximately 10 Å from the catalytic site of the HIV-1 RT (5). Binding to this hydrophobic pocket appears to result in conformational changes similar to those observed in the inactive polymerase site in the RT p51 chain. However, NNRTI binding results in other RT conformational changes as well. Compared with other NNRTIs, the position and conformation of the MKC-442 binding site and the disposition of the drug within the binding site show that the MKC-442 binding configurations are unique. The uniqueness may account for the increased potency of MKC-442, compared with other NNRTIs.

In vitro enzyme assays provided evidence for the potency and specificity of MKC-442 to inhibit HIV RT. In experiments where thymidine 5'-triphosphate was used as a substrate and poly(rA)·(dT) as the template, the mean concentration of MKC-442 required for 50% inhibition of RT activity (IC_{50}) was 0.21 μmol, a value approximately 10-fold more potent than that of nevirapine (4). The activity of MKC-442 was also highly selective for HIV RT. The IC_{50} values of MKC-442 for other enzymes, including HIV-1 RNase H, calf DNA polymerase α and the avian myeloblastosis virus and Moloney murine leukemia virus RTs, were > 1000 μmol (4).

Antiviral Activity

In vitro *activity*

Studies of a range of host-cell/virus systems indicate that MKC-442 is a potent inhibitor of HIV-1 but does not

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Table I: Inhibition of HIV-1 replication in clinical isolates (6, 8).

Cell type and HIV-1 isolate	EC_{50} (nM) MKC-442	Nevirapine	AZT	ddC	ddI
PBMC					
HIV-1_{cc2}	10	22	4	18	520
HIV-1_{cc3}	40	70	1.9	15	35
HIV-2_{cc4}	2.2	15	18	32	28
MT-4					
HIV-1 (HE)	16	73	6	ND	ND

EC_{50} = 50% effective concentration based on reduction in p24 antigen (PBMCs) or the inhibition of HIV-1-induced cytopathic effect (MT-4 cells); PBMC = peripheral blood mononuclear cells; ND = not determined.

affect the replication of HIV-2 (6-8). These *in vitro* studies utilized established cell lines and laboratory strains of virus as well as human peripheral blood lymphocytes (PBLs) or monocyte/macrophages (M/Ms) infected with HIV-1 clinical isolates. The 50% effective concentration (EC_{50}) values were assessed by HIV-induced cytopathicity (MT-4 and MOLT-4 cells) or the reduction of p24 antigen levels (PBLs and M/Ms). In these *in vitro* systems, the EC_{50} values of MKC-442 for HIV-1 ranged from 3-40 nM, while EC_{90} values ranged from 8-98 nM (6-8).

The ability of MKC-442 to inhibit the replication of clinical HIV-1 isolates *in vitro* compares well with that of other antiretroviral agents (Table I) (6). The EC_{50} values for MKC-442 were approximately 2- to 7-fold lower than those observed for nevirapine and generally comparable to the values for AZT, ddC and ddI, although some variation in the sensitivity of different clinical isolates to the antiviral activity of MKC-442 was observed.

In vitro *synergism*

Drug synergism not only has the potential to improve the antiviral effect of a multidrug regimen but also may allow a significant reduction in the dose required for each drug, thus decreasing drug-related toxicity. *In vitro*, MKC-442 acts synergistically with several agents commonly used in HIV therapy (Table II). In these assays, the effect of the drug combination on HIV-1-induced cytopathicity in MT-4 cells was determined by calculating the combination index (CI). CI values < 1 indicate synergism; the lower the CI value, the greater the synergism. CI values of 1 indicate an additive drug effect, while CI values > 1 indicate antagonism.

In two-drug combination assays, marked synergism was observed between MKC-442 and AZT (6, 7, 9), MKC-442 and ddI (6, 7) and MKC-442 and 3TC (9). One study also observed significant synergism between MKC-442 and ddC (7), although another study demonstrated only moderate synergistic effects (6). Combinations of MKC-442 and either nevirapine or saquinavir produced weakly synergistic additive effects (6). Synergistic responses were also observed when MKC-442 was combined with the protease inhibitors nelfinavir, indinavir, ritonavir, saquinavir, DMP-450 and 141W94, with the nucleoside analogues dioxolane guanosine, FTC and 1592U, and with the NNRTIs nevirapine and delavirdine (19).

Table II: Synergism of MKC-442 in two- and three-drug combination assays.

Drug combination	Reference	Ratio (range)	CI (range)
MKC-442 and AZT	6	1:0.2 to 1:19	0.40 to 0.56
	7	2:1 to 8:1	0.47 to 0.52
	9	4:1 to 10:1	0.48 to 0.75
MKC-442 and ddI	6	1:86 to 1:1562	0.62 to 0.74
	7	1:1000 to 1:4000	0.43 to 0.48
MKC-442 and ddC	6	1:1.1 to 1:32	0.83 to 0.84
	7	1:16 to 1:64	0.54 to 0.58
MKC-442 and 3TC	9	1:5 to 1:25	0.5 to 0.64
MKC-442 and nevirapine	6	1:0.03 to 1:22	0.86 to 0.99
MKC-442 and saquinavir	7	1:0.007 to 1:0.4	0.86 to 0.93
MKC-442, saquinavir and AZT	6	1:0.02:0.2 to 1:5:3	0.44 to 0.78
MKC-442, 3TC and AZT	9	4:100:1 to 10:100:1	0.41 to 0.64

CI = combination index at which 50% of the cells were protected from HIV-1-induced cytopathicity in MT-4 cells. CI values of < 1, 1 and >1 indicate synergism, additive effect and antagonism, respectively.

Consistent with results from two-drug combinations, strong synergistic responses were observed in three-drug assays consisting of MKC-442, AZT and saquinavir (6) or MKC-442, AZT and 3TC (9). For the latter combination, the concentrations required of each drug were 3- to 20-fold lower than the doses needed to attain the same extent of viral inhibition when each drug was used alone (9).

Viral suppression

The ability of HIV-1 to rapidly acquire mutations that confer drug resistance presents a significant clinical challenge. However, the emergence of these mutations requires active viral replication. Complete suppression of viral replication can thus delay or prevent the emergence of resistant isolates and may improve therapeutic outcome.

Both alone and in combination with other drugs, MKC-442 efficiently suppresses viral breakthrough in long-term cultures, an assay system that may provide insights into the efficacy of extended clinical therapy. In long-term culture experiments, 0.5 μM MKC-442 was found to prevent viral breakthrough for a period of 40 days, as assessed by p24 antigen assays (9). As suggested by the *in vitro* synergism data, complete viral suppression could be achieved at even lower doses of MKC-442 when combined with other agents. The combination of MKC-442 at 0.02 or 0.04 μg/mL plus 3TC at 0.05 or 0.1 μg/mL prevented viral breakthrough during a 52-day culture (10). The combination of MKC-442 and AZT also mediated complete viral suppression for at least 40 days at concentrations of 0.14 μM MKC-442 and 0.01 μM AZT (9), and for at least 52 days at concentrations of 0.2 μM MKC-442 and 0.005 μM AZT (11). In contrast, combinations of AZT and either of two other NNRTIs tested, loviride and nevirapine, were unable to achieve complete inhibition of viral breakthrough for the duration of the 52-day incubation period (11). The three-drug combination of MKC-442 (0.09 μM), AZT (0.009 μM) and 3TC (0.9 μM) also completely prevented viral breakthrough for at least 40 days (9).

In addition to examining viral suppression in the presence of antiviral agents, continued viral suppression when the agents are removed was also investigated. Single-agent studies reported that when MKC-442 was removed from the culture medium after 20 days, p24 antigen did not appear during the remaining 20 days of culture (9). Similarly, when the combination of MKC-442 and 3TC was removed after 52 days, the cell cultures remained p24-negative for at least an additional 12 passages (10). The ability of MKC-442 to mediate long-term suppression of HIV-1 after the removal of drug from the culture medium has been confirmed with an even more sensitive test for the presence of virus, the polymerase chain reaction assay for HIV-1 proviral DNA. In studies in which the combination of MKC-442 plus AZT was removed from the culture medium after 52 days of incubation, both p24 antigen and HIV-1 proviral DNA remained undetectable in these cultures throughout the 16-day drug-free incubation period (11). These studies suggest that MKC-442 in combination with other agents *in vitro* suppresses viral replication to undetectable levels.

Drug Resistance

Emergence of MKC-442 resistance

For all classes of anti-HIV agents, drug resistance is a significant problem. However, it is of particular concern for the NNRTIs because of the rapidity with which resistance has been shown to develop to drugs in this class, such as nevirapine (12). Compared with nevirapine, for example, MKC-442 treatment is associated with a delayed emergence of resistance *in vitro* (8). In these studies, MT-4 cells were infected with a clinical isolate of HIV-1 and passaged in medium containing either MKC-442 or nevirapine. As shown in Figure 1, virus grown in the presence of nevirapine rapidly developed a high level of drug resistance; by 6 passages, the EC_{50} had increased from 0.099 μM to > 20 μM. However, after 6 passages in the presence of MKC-442, HIV-1 remained moderately sensitive to the drug (EC_{50} = 2.1 μM) and did not become highly resistant until after passage 9 (EC_{50} = 80 μM).

Characterization of MKC-442-resistant mutants

Determination of the RT nucleotide sequence in MKC-442-resistant isolates has revealed key amino acid changes that significantly affect viral sensitivity to this agent (8, 10). The greatest loss of sensitivity to MKC-442 was seen in viral isolates with a $Tyr^{188}Leu$ change; this mutation also affected sensitivity to nevirapine (Table III)

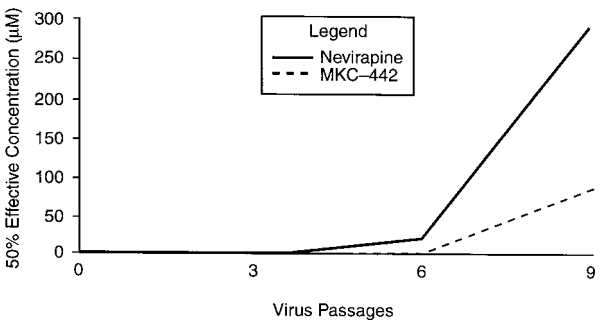

Fig. 1. The emergence of HIV-1 resistance to MKC-442 and nevirapine. EC_{50} concentrations were based on the inhibition of HIV-1-induced cytopathic effect in MT-4 cells. The EC_{50} values of nevirapine for virus recovered after the sixth passage were estimated as >20 μM for the sixth passage and >281 μM for the ninth passage (8).

Table III: Sensitivity of HIV-1 RT mutants to MKC-442 and nevirapine (13).

	EC_{50} (μM)	
Virus genotype	MKC-442	Nevirapine
WT	<0.001	0.02
$Tyr^{181}Cys/Lys^{103}Asn$	5	>100
$Tyr^{181}Cys/Val^{108}Ile$	0.4	19
$Tyr^{188}Leu$	20	>100
$Gly^{190}Ala$	0.48	46

EC_{50} = 50% effective concentration. Studies were performed in the laboratory of D. Richman at the University of California, San Diego, with the HeLa/$CD4^+$ focus-forming assay (18).

Table IV: Pharmacokinetic parameters of MKC-442 in plasma after oral administration to male rats, monkeys or dogs (14).

	Species (dose)		
Parameter	Rat (50 mg/kg p.o.)	Monkey (50 mg/kg p.o.)	Dog (10 mg/kg p.o.)
C_{max} (ng/mL)	3090	60	54
T_{max} (h)	0.25	1.0	1.0
AUC (ng.h/mL)	5064*	935*	109^+

*$AUC_{0-\infty}$. $^+AUC_{0-8\ h}$. C_{max} = maximum plasma concentration; T_{max} = time to maximum plasma concentration; AUC = area under the time-concentration curve.

(13). Additionally, viruses containing a $Gly^{190}Ala$ change, a combination of $Tyr^{181}Cys$ and $Lys^{103}Asn$ or a combination of $Tyr^{181}Cys$ and $Val^{108}Ile$ mutations had reduced sensitivity to MKC-442. These same mutations resulted in a high degree of resistance to nevirapine. To date in the clinical trials, the predominant mutation that has emerged is $Lys^{103}Asn$.

Cross-resistance

Viral cross-resistance to multiple agents is a growing concern in the evaluation of new anti-HIV-1 agents because it severely restricts the options available to patients who no longer respond to a given therapy. Cross-resistance patterns may also limit the agents that are suitable for use in combination regimens.

To date, no cross-resistance between MKC-442 and nucleoside RT inhibitors has been detected. Viruses resistant to AZT or 3TC retain full sensitivity to MKC-442, and strains with reduced sensitivity to MKC-442 are still fully sensitive to AZT and 3TC (7-9).

Cross-resistance patterns between MKC-442 and other NNRTIs vary depending on the precise nature of the RT amino acid substitution. Although some HIV-1 mutant strains selected *in vitro* for resistance to other NNRTIs were resistant to MKC-442, others remained sensitive (8, 10). In particular, MKC-442 could still inhibit the replication of two nevirapine-resistant viral isolates, although at higher concentrations than required to inhibit wild-type virus (8). HIV-1 isolates resistant to MKC-442 typically showed decreased susceptibility to other NNRTIs (8, 10).

Preclinical Pharmacology

Absorption, metabolism and elimination

The pharmacokinetics of MKC-442 have been investigated in rats, monkeys and dogs. As shown in Table IV, MKC-442 rapidly achieves high plasma concentrations after oral administration in all three species (14).

The absorption of MKC-442 was assessed in rats given MKC-442 by oral gavage, intrarectal infusion, intravenous infusion or intraportal vein infusion by measuring the area under the time-concentration curve (AUC). The oral absorption (AUC_{PO}/AUC_{IPV}) was 67.6%, but the oral bioavailability (AUC_{PO}/AUC_{IV}) was determined to be much lower at 18.4% (14). These data suggested that MKC-442 was subject to first-pass hepatic metabolism.

To examine further the role of hepatic metabolism, liver microsomes from rats, cynomolgus monkeys or humans were incubated with MKC-442. MKC-442 metabolism by human liver microsomes was found to be minimal compared with the other species; microsomes from human liver formed only about 25% of the total metabolites formed by microsomes from rats or monkeys. Inhibition studies with nifedipine and troleandomycin showed that in human liver microsomes, MKC-442 was metabolized by cytochrome P450 CYP3A4 and CYP3A5, with CYP3A5 accounting for the preponderance of metabolism. Hepatic microsomes from rats, cynomolgus monkeys and humans produce the same three putative metabolites, but in differing proportions (14).

In rats, the overall pathways of elimination were examined by administering a single oral dose of 10 mg/kg [^{14}C]-MKC-442. Greater than 98% of the radioactivity was recovered in the urine and feces. Approximately one-third (37.9%) of the radioactivity was excreted in the urine, with the remainder in the feces. The fecal recovery likely represented both biliary excretion and unabsorbed drug.

Tissue distribution

The central nervous system is a site of HIV infection and may serve as a viral reservoir in some patients (15). Unfortunately, however, most antiviral chemotherapeutic agents do not cross the blood-brain barrier. In rats given 10 mg/kg [^{14}C]-MKC-442 by gavage, autoradiography determined that MKC-442 was widely distributed to tissues, including brain and spinal cord, and had a mean residence time of 26 h. Further studies in rats were conducted specifically to investigate the ability of MKC-442 to cross the blood-brain barrier. Concentrations of MKC-442

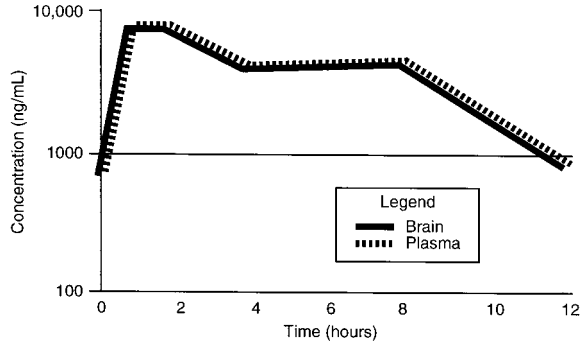

Fig. 2. MKC-442 concentrations in the brain and plasma of rats given an oral 250 mg/kg dose (14).

in brains from rats given 250 mg/kg MKC-442 by gavage were measured by high-performance liquid chromatography (HPLC). Over the postdose interval, from 30 min to 12 h, concentrations of MKC-442 in brain were the same as those in plasma (Fig. 2) (14).

Serum protein binding

Binding to serum proteins has been shown to significantly affect drug activity. Higher protein binding can result in improved plasma concentrations *in vivo* but may also reduce the ability of the molecules to penetrate cells. The serum binding capacity and *in vitro* activity of a chemotherapeutic agent in the presence of human serum may thus provide insights into clinical efficacy.

MKC-442 was found to be highly bound to human serum proteins; the extent of binding ranged from 78.2-95.5% at serum concentrations of 10-100% (16). However, the addition of human serum and 1 mg/ml α_1-acid glycoprotein to anti-HIV-1 assays had only a minimal effect on the antiviral activity of MKC-442. Human serum concentrations of 30% and 50% resulted in a 2- and 5-fold reduction in MKC-442 activity, respectively (16).

Toxicity

Cytotoxicity

The clinical utility of many anti-HIV drugs can be limited by their toxicity. The cytotoxicity of MKC-442 has been evaluated in several *in vitro* systems by assessing the reduction in viability of mock-infected cells. In the human cell lines MT-4 and MOLT-4, the concentration of MKC-442 required to inhibit cell viability by 50% (CC_{50}) was > 100 μM (7, 8, 11). MKC-442 also demonstrated low toxicity in monocyte/macrophages and peripheral blood mononuclear cells (PBMCs), particularly in comparison to other anti-HIV agents. For instance, MKC-442 was found to have a CC_{50} of 95 μM in HIV-1-infected PBMCs, while the CC_{50} for AZT was 12 μM (7).

In another assessment of cytotoxicity, MKC-442 was found to result in only minimal effects on the mitogen-induced replication of human cells *in vitro*. After exposure to the mitogen concanavalin A, the proliferation of human PBMCs was examined in the presence of different concentrations of MKC-442. In this system, the concentration of drug required to inhibit replication by 50% (as determined by incorporation of [^{3}H]-thymidine into cellular DNA) was 52.5 μM for MKC-442, 4.4 μM for AZT and 13.3 μM for saquinavir when used as single agents (6).

Combination therapies can result in great therapeutic benefits, but the addition of new agents may also increase the toxicity of the treatment regimen. It is thus notable that the CC_{50} values of AZT and saquinavir were not altered by the addition of MKC-442 at concentrations up to 10 μM. Perhaps most significantly, the three-drug combination of 1 μM MKC-442, 1 μM AZT and 1 μM saquinavir showed no effects on PBMC replication compared with untreated cells (6).

Additional studies support these observations concerning the minimal cytotoxicity of MKC-442 and further indicate that MKC-442 is not toxic to human bone marrow progenitor cells or to mitochondria (14), two key targets of nucleoside analogue-associated cytotoxicity. For human bone marrow progenitor cells, only the highest concentration of MKC-442 tested (100 μM) showed marked effects on cell survival (Fig. 3). The concentration of MKC-442 required to inhibit the formation of granulocyte-

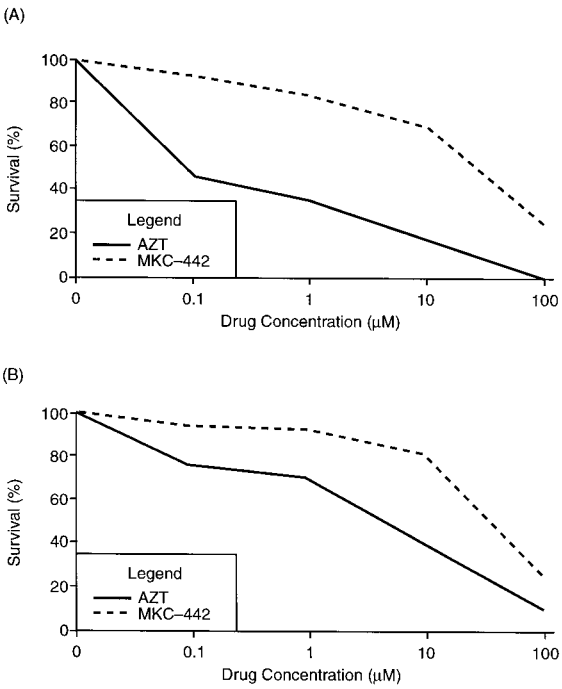

Fig. 3. Survival of bone marrow progenitor cells treated with MKC-442 or AZT, showing erythroid colony formation (A) and granulocyte-macrophage colony formation (B). Values for each data point were obtained from 3 separate experiments (14).

macrophage colonies by 50% (IC_{50}) was 60 μM compared with 8.5 μM for AZT. Similar results were obtained with erythroid progenitor cells: the IC_{50} for erythroid colony formation was 45 μM for MKC-442 and 0.1 μM for AZT (14). These data suggest that MKC-442 is unlikely to cause significant myelosuppression in HIV-infected patients.

The inhibition of DNA polymerase gamma by some nucleoside analogues inhibits mitochondrial DNA synthesis and is believed to result in myopathy. The effect of MKC-442 on mitochondrial function in HepG2 cells was evaluated by measuring three parameters: the concentration of lactic acid in extracellular medium, mitochondrial DNA content and structural effects (lipid droplet formation and mitochondrial morphology) as determined by electron microscopy. MKC-442 did not affect any of these parameters of mitochondrial function at concentrations up to 10 μM (14).

Preclinical toxicology

The preclinical toxicology profile of MKC-442 is extremely favorable. Neither the parent compound nor its major metabolite, 6-benzyl-5-isopropyl uracil (BIU), is associated with significant toxicity. In rats, the approximate lethal dose of a single oral dose of MKC-442 was ≥ 3 g/kg for males and 2.5 g/kg for females. BIU did not produce death in rats given a single oral dose of 3 g/kg (14).

In a 1-month study in rats, 50 mg/kg/d was identified as a no-effect dose (14). At the next higher dosage level, 150 mg/kg/d, effects on body weight, kidney and liver were observed. The 1-month study in monkeys identified a no-effect dose of 40 mg/kg/d. Inconsistent emesis and mild diarrhea, increased blood urea nitrogen, minimal vacuoles in kidney tubules, increased values for the liver enzyme alanine aminotransferase and hepatocellular hypertrophy were observed at the next highest dose, 200 mg/kg/d. Adverse effects involving the liver and kidney were dose-related and reversible.

A key observation in our studies was that MKC-442 does not appear to be associated with chronic or cumulative toxicity in animals. The results of the 3-month and the chronic toxicology studies were very similar to those from the 1-month studies. No additional toxicities developed with long-term drug exposure.

Fertility studies in rats indicated that MKC-442 has no identifiable effects on fertility. In developmental toxicology studies performed in rats and rabbits, the only adverse effects observed were minimal decreases in maternal and fetal body weights; these occurred only in animals receiving the highest dose of MKC-442 (140 mg/kg/d). Finally, there was no indication of genotoxicity in the Ames test, the Chinese hamster ovary chromosomal aberration assay or the rat micronucleus assay (14).

Clinical Studies

Safety and pharmacokinetic data from early clinical studies of MKC-442 provide futher evidence for the potential therapeutic utility of MKC-442 (17). In a randomized, double-blind, placebo-controlled phase I trial, escalating single oral doses of 100-1000 mg MKC-442 were given to 32 HIV-infected male patients. The maximum plasma concentration (C_{max}) at the lowest dose tested, 100 mg, was 152 ng/mL; this level was well above the concentration required for 90% HIV-1 inhibition *in vitro* (EC_{90} = 19.8 ng/mL). C_{max} values for higher doses were dose proportional, with the 1000-mg dose resulting in a C_{max} of 1575 ng/mL. Food intake in patients receiving the 500-mg dose produced a moderate (< 25%) increase in AUC but had no effect on C_{max}. It thus appears likely that MKC-442 can be administered with or without meals. The plasma half-life for MKC-442 was determined to be approximately 7 h, suggesting that at appropriate doses, a twice-daily dosing regimen may be sufficient to maintain trough MKC-442 plasma concentrations above the EC_{90} required for inhibition of HIV-1 *in vitro*. MKC-442 was well tolerated by patients. No serious adverse events were reported at any of the doses tested, and no adverse events of any type were experienced at doses of 100 or 300 mg (17).

Conclusions

The arsenal of agents for combating HIV-1 has expanded greatly in recent years. However, problems with drug-related toxicity, pharmacokinetic interactions with other drugs and complex dosing regimens continue to be challenging issues in the treatment of AIDS. In addition, the ease and speed with which HIV-1 acquires resistance to therapeutic agents necessitate the continued search for new, more effective antiviral drugs.

In preclinical assessments, MKC-442 has demonstrated many favorable characteristics that suggest it may be a valuable addition to current HIV-1 treatment regimens. MKC-442 has potent *in vitro* activity against HIV-1 and acts synergistically with many of the mainstays of HIV-1 therapy, including AZT, d4T and 3TC. Alone or in two- or three-drug combinations, MKC-442 mediates the complete suppression of viral replication in long-term cultures, even after it has been removed from the culture medium. No cross-resistance between MKC-442 and nucleoside RT inhibitors has been demonstrated. In addition to its potent antiviral effect, comprehensive preclinical safety assessments indicate that MKC-442 has a favorable safety profile, even after prolonged exposure. Together, these data suggest that the addition of MKC-442 to combination therapies may add to the potency of such regimens without increasing their toxicity.

Although only limited clinical data are currently available for this drug, results from the completed phase I clinical trial have confirmed the favorable safety profile of MKC-442 revealed in preclinical testing. Data from larger

clinical studies are warranted to establish the role of MKC-442 in combination with other antiviral agents for the long-term treatment of HIV-1 infection.

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Manufacturer

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