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CMX001

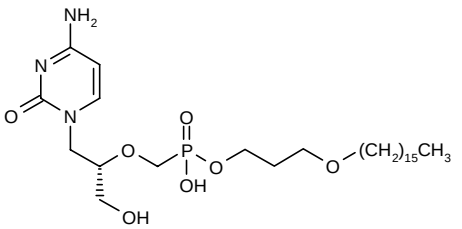
Anti-Smallpox Agent
Anti-Cytomegalovirus Agent
Viral Polymerase Inhibitor

HDP-CDV

1-*O*-Hexadecyloxypropyl-cidofovir

[2-(4-Amino-2-oxo-1,2-dihydropyrimidin-1-yl)-1(*S*)-(hydroxymethyl)ethoxy]methylphosphonic acid 3-(hexadecyloxy)-propyl monoester

InChI=1/C27H52N3O7P/c1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-19-35-20-16-21-37-38(33,34)24-36-25(23-31)22-30-18-17-26(28)29-27(30)32/h17-18,25,31H,2-16,19-24H2,1H3,(H,33,34)(H2,28,29,32)/t25-/m0/s1



$C_{27}H_{52}N_3O_7P$
Mol wt: 561.6914

CAS: 444805-28-1

EN: 317302

Abstract

CMX001 is a lipid (1-*O*-hexadecyloxypropyl) conjugate of the phosphonate nucleotide analogue cidofovir (CDV). CDV, which is approved by the FDA for the treatment of cytomegalovirus (CMV)-induced retinitis in AIDS patients, is active against all five families of double-stranded DNA (dsDNA) viruses that cause human morbidity and mortality. However, the clinical utility of the drug is limited by the need for administration by intravenous infusion and the possibility of acute nephrotoxicity. The formation of the lipid conjugate increases *in vitro* antiviral activity up to a thousand-fold, promotes high oral bioavailability and minimizes the potential for nephrotoxicity. CMX001 is currently in phase I single- and multiple-dose clinical trials for the prophylaxis and treatment of smallpox infection, and is entering development for use in prophylactic and pre-emptive therapy of dsDNA viral infections that can cause graft loss in transplant patients.

Synthesis

CMX001 is synthesized from cidofovir (CDV) (I) as previously described (Scheme 1) (1). CDV (I) is first converted to cyclic CDV and isolated as the dicyclohexylmorpholinocarboxamidine salt (II). Compound (II) is reacted with 1-bromo-3-hexadecyloxypropane (III) and the product (IV) is purified by flash chromatography. Compound (IV) is treated with 0.5 M sodium hydroxide and kept at room temperature for 90 min. The reaction is then neutralized with acetic acid and the final product, CMX001, is collected by vacuum filtration and purified by flash column chromatography.

Background

Smallpox, a viral disease caused by the variola virus (VARV), has been feared throughout history due to the high fatality rate (30%) and for frequently causing extreme disfigurement and blindness in survivors (2). In the late 1970s the disease was declared eradicated as a human health threat after completion of an intensive worldwide vaccination campaign sponsored by the World Health Organization (WHO). Vaccination of the general population was subsequently suspended due to the morbidity and mortality associated with the live virus vaccine used in the campaign, and was never resumed. As a result, the worldwide population currently lacks herd

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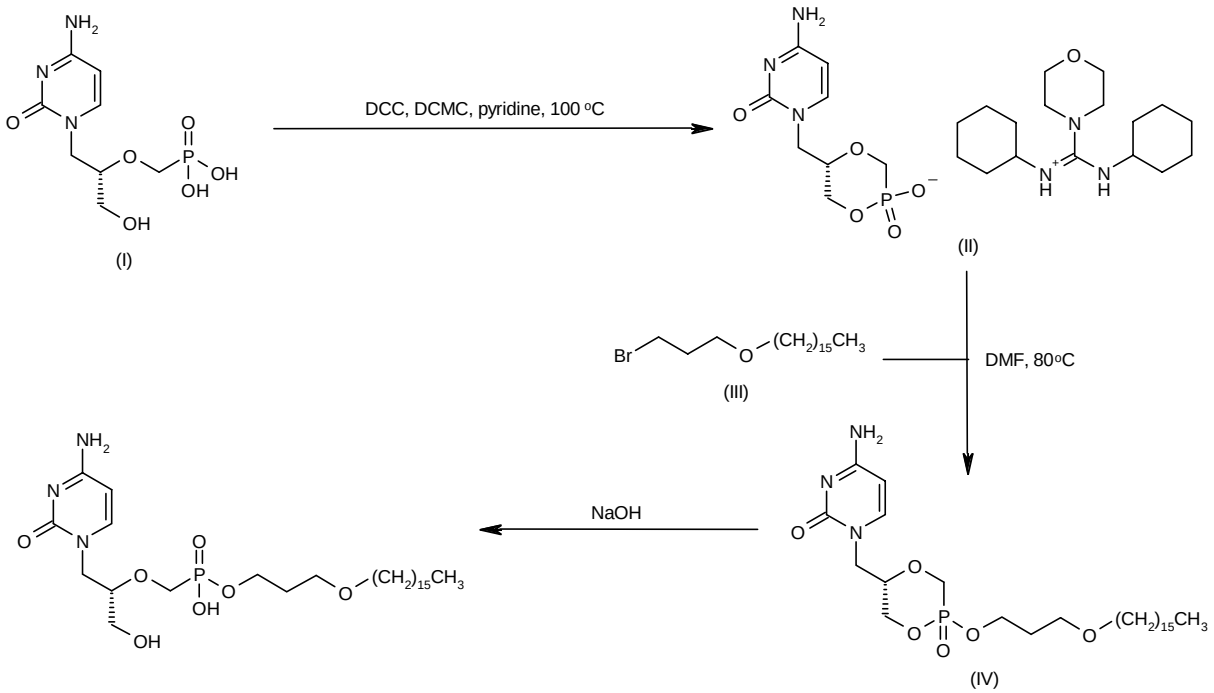
Scheme 1: Synthesis of CMX001



immunity and is highly susceptible to infection. This vulnerability is of substantial concern because weaponized smallpox virus may be in the hands of groups who could use it as a biological weapon. In addition, the closely related monkeypox virus (MPXV) causes a similar disease in humans and its incidence is on the rise (3). If VARV was reintroduced into the general population, vaccination could potentially provide protection for the majority of the unexposed population. The vaccine, however, must be administered 4-8 days prior to exposure to elicit a protective immune response, and consequently would not be effective for those infected during the initial release of the virus. There are also tens of millions of people who are not good candidates for vaccination because they have severely weakened immune systems (from infections such as HIV, immunosuppressive drug therapy for organ transplantation or cancer chemo- and radiation therapy), or skin conditions such as eczema and atopic dermatitis. A safe, orally active antiviral drug is needed to provide an alternative means of protection, as well as a means of treatment.

Human cytomegalovirus (CMV) infection typically causes mild or subclinical disease, but can cause severe localized or systemic disease in immunocompromised individuals (4). Manifestations of organ involvement in CMV disease include hepatitis, pneumonitis, pancreatitis, colitis, erosive gastrointestinal bleeding, meningoencephalitis, myocarditis and chorioretinitis. In the past, CMV-induced disease was most frequently observed in HIV/AIDS patients, but with the advent of HAART (highly active antiretroviral therapy) the incidence of CMV disease in this population has dropped dramatically. However, CMV is still a common opportunistic pathogen following immunosuppressive therapy for organ transplantation and is a significant cause of morbidity and mortality (5). Although several drugs are available for treating CMV infection and are used both on- and off-label for protecting against and treating CMV-induced graft disease, more drugs are needed due to limitations resulting from toxicity and the development of drug resistance. In addition, posttransplant infection with other dsDNA viruses (including BK polyoma virus, Epstein-Barr and adenovirus) causes morbidity and graft loss. Coinfection with these dsDNA viruses may enhance CMV pathogenicity and lead to more severe cumulative immunosuppression in the host (6). Consequently, a drug with potent anti-CMV activity that is also broadly active against dsDNA viruses would be extremely important for prophylaxis in the pre- and posttransplant setting.

CDV, which is approved by the FDA for the treatment of CMV-induced retinitis in AIDS patients, is active against all five families of dsDNA viruses that cause human morbidity and mortality, but its clinical utility is limited by the need for administration by i.v. infusion and the risk of dose-limiting acute nephrotoxicity (7). Conjugation of a lipid to CDV to form a mimic of the natural lipid lysolecithin results in high oral availability, a 200-fold drop in EC_{50} values compared to cidofovir for VARV strain major (smallpox) and CMV, and minimization of the potential for nephrotoxicity. Given this favorable antiviral

activity, pharmacokinetic and toxicological profile, CMX001 is being developed for the treatment of smallpox infection and for the prophylaxis and treatment of CMV and other dsDNA viral infections associated with organ transplantation. CMX001 is currently in phase I clinical development for the treatment of smallpox infection.

Preclinical Pharmacology

CMX001 is active against members of all five families of dsDNA viruses that cause human morbidity and mortality (8). Its *in vitro* and *in vivo* activity against members of the poxvirus family (Poxviridae), which includes smallpox and monkeypox, and against CMV, a member of the herpesvirus family (Herpesviridae), will be described in detail below. Examples of *in vitro* activity against viruses of the three other families, expressed as EC_{50} values, include adenovirus serotype 5 (Ad5, Adenoviridae; EC_{50} = 0.02 μM) (9), human papillomavirus 18 (HPV18, Papillomaviridae; EC_{50} = 0.42 μM) (10) and BK virus (Polyomaviridae; EC_{50} = 0.13 μM) (11). For comparison, the EC_{50} values for CDV against Ad5, HPV18 and BK viruses are 1.3, 516 and 115.1 μM, respectively. No activity has been detected against retroviruses (HIV-1 or HIV-2), RNA viruses (hepatitis C virus) or hepadnaviruses (hepatitis B virus) at concentrations up to 100 μM.

CMX001 has *in vitro* activity against a broad range of *Orthopoxvirus* strains. The EC_{50} value determined in a neutral red cytopathic effect (CPE) inhibition assay against VARV strain major (Bangladesh) and MPXV (Zaire) ranged from 0.04 to 0.10 μM and from 0.013 to 0.07 μM, respectively, depending on whether VERO 76 or LLC-MK_2 cells were used in the assay (12). Using a plaque reduction assay, similar EC_{50} values were obtained against wild-type ectromelia virus (ECTV) strain Moscow (EC_{50} = 0.5 μM), the causative agent of mousepox, and a recombinant ectromelia virus expressing murine IL-4 that breaks through vaccine immunity (EC_{50} = 0.2 μM) (13). EC_{50} values against cowpox virus (CPXV; strain Brighton) and vaccinia virus (VACV) determined using a plaque reduction assay were 0.6 and 0.2-1.2 μM, respectively (1). The range in apparent EC_{50} values observed for VACV was the result of using different cell types and virus strains in the assay. The presence of the lipid moiety on CMX001 results in significant decreases in apparent EC_{50} values against *Orthopoxvirus* strains relative to the parent drug CDV: 250-fold for VARV strain major (12), up to 400-fold for MPXV (12), 20-fold for ECTV (13), up to 60-fold for VACV (1) and 80-fold for CPXV (1).

In vitro experiments to generate *Orthopoxvirus* strains resistant to CMX001 have not been conducted; however, serial passages of camelpox, cowpox, monkeypox and vaccinia viruses with CDV have generated resistant strains (14). The extent of viral resistance is reported to be on the same order as that observed for CDV-resistant forms of herpes simplex virus and CMV (10-27-fold). Resistant strains of VACV (strain WR) generated after 20-30 passages in the presence of increasing concentrations of CDV have been shown to be crossresistant to CMX001 (15). Mutations conferring this resistance are located in the virally encoded DNA polymerase**.** Additionally, the development of resistance to CDV and CMX001 in VACV leads to a significant attenuation of virulence in mice (16), suggesting that any mutations that might derive from drug pressure during treatment of smallpox could be less virulent.

The *in vivo* anti-*Orthopoxvirus* activity of CMX001 has been extensively characterized in mice infected with CPXV, VACV and ECTV viruses, and in rabbits infected with rabbitpox virus (RPXV, a strain of VACV). In the CPXV model, oral administration of 5 mg/kg of CMX001 daily for 5 consecutive days was 100% protective in mice infected by either the aerosol or intranasal route when dosing was initiated 4 h postinfection (17). A larger single oral dose of 12.5 mg/kg was 80% protective when given as early as 5 days before exposure and 87% protective when given as late as 3 days postexposure. Against VACV infections in BALB/c mice, oral administration of CMX001 at 5 mg/kg for 5 days beginning 4 h postinfection was 100% protective (17). CMX001 therapy showed significant protection (86%) against lethal VACV infection when initiated as late as 24 h postinfection. A large number of dosing regimens have been studied in ECTV-infected A/NCR mice. In this model, a 2.5 mg/kg dose of CMX001 given once daily for 5 days starting 4 h postinfection provided complete protection against a lethal intranasal challenge (18). When treatment was started as late as 5 days postinfection (3-4 days prior to the death of untreated controls), animals were completely protected from mortality with a loading dose of 10 mg/kg followed by a maintenance dose of 2.5 mg/kg every other day for 14 days. A single 20 mg/kg oral dose of CMX001 given as late as 4 days postinfection provided 100% protection against lethal ECTV infection. In a study in New Zealand white rabbits infected intradermally with a lethal inoculum of RPXV, a total daily dose of 2 mg/kg CMX001 for 5 days provided a 100% survival benefit (19). Treatment experiments in rabbits have also shown that CMX001 can be given late into the infection cycle after signs of disease are apparent (fever and lesions) and still prevent mortality.

The *in vitro* activity of CMX001 against CMV has been determined using a plaque reduction assay in human foreskin fibroblast (HFF) cells infected with selected laboratory strains and clinical isolates of CMV, including CDV- and ganciclovir (GCV)-resistant isolates (Table I) (20). In all cases, CMX001 was considerably more potent than CDV or GCV.

Treatment of CMV infections in immunocompromised patients with drugs that target the virally encoded DNA polymerase has led to multiple mutations in the conserved regions of two viral genes, *UL97* (protein kinase) and *UL54* (DNA polymerase), and the development of drug resistance (21). While mutations in *UL97* can lead to resistance to GCV, these mutations are not crossresistant to CDV or CMX001 (see isolates C8914-6 and C8805/37-1-1 in Table I). In contrast, mutations in the *UL54* gene can confer resistance to GCV, CDV and CMX001 (see

Table I: Activity of CMX001, cidofovir (CDV) and ganciclovir (GCV) against human CMV laboratory strains (AD169 and Towne) and representative clinical isolates, including CDV- (GDGP53, 759D100) and GCV- (8914-6, C8805/37-1-1, GDGP53, 759D100) resistant isolates, in HFF cells.

Isolate/strain	EC_{50} ± SD (μM)		
	CMX001	CDV	GCV
AD169	0.0009 ± 0.0001	0.30	2.75 ± 1.6
Towne	0.0009	0.4 ± 0.11	4.3
C8914-6	0.0003	0.99 ± 0.6	13.5 ± 2
C8805/37-1-1	0.00095 ± 0.00007	0.84 ± 0.2	47.4 ± 1.1
GDGP53	0.020 ± 0.009	15.7 ± 14.1	54.6 ± 2.3
759D100	0.0065 ± 0.0007	2.0 ± 0.56	177 ± 28.2

isolates GDGP53 and 759D100 in Table I). The EC_{50} values of the CMX001-resistant strains shown in Table I are significantly below achievable plasma concentrations in humans (see below), suggesting that CMX001 could block the breakthrough of GCV- and CDV-resistant virus in the clinic.

The *in vivo* activity of CMX001 against CMV was tested in 4-8-week-old SCID mice with human fetal thymus or liver implanted under their kidney capsules (22). Implants were allowed to develop for 12-16 weeks before inoculation with 7,000 plaque-forming units (pfu) of CMV (Toledo strain). Daily drug treatment was introduced 24 h after inoculation and continued for 35 days with orally administered CMX001 at either 5 or 10 mg/kg, or with 20 mg/kg of CDV administered by i.p. injection. On days 14, 21, 28 and 35 postinoculation, implants were biopsied and infectious virus quantitated by plaque assay on HFF cells. Daily oral treatment of mice for 35 days with 5 or 10 mg/kg CMX001 or by i.p. injection with 20 mg/kg of CDV significantly reduced CMV replication in the implanted tissue. At day 28 after infection, the mean viral titer in vehicle-treated mice was 5.7 $\log_{10}$ pfu/g, while viral titers in implant tissue from animals treated with either 5 or 10 mg/kg CMX001 were below detectable limits. Viral titers in implant tissue from the CDV-treated animals were 3.3 $\log_{10}$ pfu/g, intermediate between vehicle-treated and CMX001-treated animals. Similar results have been reported using the SCID mouse–human retinal implant model (23).

The antiviral mechanism of action of CMX001 has been extensively studied in MRC-5 cells. These studies have shown that the conjugate is rapidly transported across the plasma membrane by passive diffusion and possibly membrane flippase activity (24). Once CMX001 has reached the endoface of the target cell membrane or is within the cytoplasmic compartment, the lipid phosphonate ester linkage is cleaved by the hydrolytic action of phospholipase C to yield free CDV. The phosphorylation of CDV to form CDV-PP (cidofovir diphosphate), the antiviral agent, occurs in two steps (25). The synthesis of CDV-MP (cidofovir monophosphate) from CDV is catalyzed by cytidylate kinase (EC 2.7.4.14). CDV, with a K_m value of 2.10 ± 0.18 mM and a V_{max} of 0.10 ± 0.05 μM/min/mg, is utilized much less efficiently as a substrate by cytidylate kinase than the natural substrates CMP, UMP and dCMP. Pyruvate kinase (EC 2.7.1.40), creatine kinase (EC 2.7.2.3) and nucleoside-diphosphate kinase (EC 2.7.4.6) can all catalyze the synthesis of CDV-PP from CDV-MP. Based on efficiency values (K_m/V_{max}) determined using enzymes purified from human tissues, the most efficient phosphorylation of CDV-MP to CDV-PP is catalyzed by pyruvate kinase.

CDV-PP is a potent alternative substrate inhibitor of DNA synthesis catalyzed by herpesvirus- and *Orthopoxvirus*-encoded DNA polymerases (26). It is efficiently incorporated into nascent chain DNA by these polymerases, resulting in significant reductions in the overall rate of viral DNA synthesis. The incorporation of a single molecule of CDV into a synthetic DNA primer by CMV DNA polymerase causes DNA synthesis to slow down by 31%. The incorporation of two consecutive CDV molecules stops any further DNA elongation. Incorporation of two CDV molecules separated by either one or two natural deoxynucleoside monophosphates (dAMP, dGMP or TMP) also drastically decreases the rate of DNA chain elongation by CMV DNA polymerase (27). The activity of CDV-PP has also been studied against purified vaccinia virus DNA polymerase (28). CDV is incorporated into nascent chain DNA opposite dG in the template. The result of incorporation is chain termination at the next nucleotide (n + 1) position.

The reported K_i values of CDV-PP for human DNA polymerases α, β and γ are 51, 520 and 299 μM, respectively (29). Based on the K_i reported for CMV DNA polymerase (6.6 ± 0.8 μM), CDV-PP appears to selectively inhibit viral polymerases encoded by dsDNA viruses. Additionally, the K_i/K_m (CDV-PP/dCTP) values for human polymerases α, β and γ (10.8, 121 and 1,424, respectively) indicate that CDV-PP is a poor inhibitor of these enzymes. Selectivity for *Orthopoxvirus*-encoded polymerases cannot be specifically established since no K_i values are currently available for an *Orthopoxvirus*-encoded DNA polymerase.

The cytotoxicity of CMX001 has been determined in HFF and MRC-5 cells (1). In HFF cells the CC_{50} (50% cytotoxic concentration) was calculated to be 31 μM using neutral red uptake as a measure of cell viability. The CC_{50} in MRC-5 cells ranged between 74.8 ± 18 μM (n = 5) and

93.3 ± 4.2 μM (n = 5), depending on the length of time the cells were exposed to drug and on the cell density in the test wells. The viability of the MRC-5 cells was quantified by measuring reduction of the soluble tetrazolium reagent WST-1 over a 2-h period. Based on these CC_{50} values, the selectivity index (SI) of CMX001 for CMV (AD169) is 34,400 in HFF cells, and ranges between 74,800 and 93,300 in MRC-5 cells. The SI for VARV strain major calculated using the EC_{50} determined in LLC-MK_2 cells (0.04 μM) and the CC_{50} values for MRC-5 cells ranges between 1,870 and 2,700.

CMX001 was also evaluated for its ability to inhibit the growth of normal human bone marrow progenitor cells. The IC_{50} for inhibition of the formation of two types of progenitor colonies, CFU-GM (colony-forming unit-granulocyte macrophage) and BFU-E (burst-forming unit-erythroid), was determined by comparison with PBS controls. Fresh human bone marrow cells from three different donors were used in these assays. The IC_{50} of CMX001 for CFU-GM colonies was 0.81 ± 0.6 μM (n = 3) and the IC_{50} for BFU-E colonies was 0.59 ± 0.36 μM (n = 3). In the same study the positive control zidovudine (AZT) had IC_{50} values of 1.25 ± 0.64 and 1.4 ± 0.1 μM for CFU-GM and BFU-E colonies, respectively.

Safety

Toxicology studies of CMX001 were conducted in mice, rats and monkeys. In a study of single oral doses in rats, gastrointestinal (GI) toxicity was observed at all doses (30, 100, 300 and 1000 mg/kg). Histological findings in all treated rats showed dose-dependent enteritis, particularly in the ileum. At the lowest dose (30 mg/kg), minimal enteritis observed on day 2 after dosing had fully reversed by day 15. A subsequent study in rats was conducted to define the chronology of the development and resolution of GI toxicity after a single oral dose. Decreased body weight and food consumption were the first signs of toxicity after a single dose of 100 mg/kg, appearing 2-3 days after dosing. Clinical observations including anorexia, nonformed/liquid/absent feces and other signs of malaise began 6-8 days after dosing. Histopathological changes in the GI tract were present 24 h after dosing, most severe about 6-7 days after dosing, and fully resolved by 14 days after dosing. In a 14-day oral study in mice given 0, 4, 20 or 100 mg/kg/day CMX001, the NOAEL (no adverse effect level) was 4 mg/kg/day. In a 14-day study in cynomolgus monkeys given 0, 4, 10 or 25 mg/kg/day CMX001 by the oral route, gastropathy was observed in all treated monkeys, and enteropathy, localized to the posterior portion of the small intestine and the large intestine, was observed only in monkeys given doses of 10 or 25 mg/kg/day. At the conclusion of a 6-week reversibility period, monkeys in all dose groups had normal clinical pathology values and body weights that exceeded their pretreatment values. Reversibility of the CMX001-related enteropathy was confirmed by histopathology. A second 14-day toxicology study in cynomolgus monkeys defined the NOAEL as 4 mg/kg/day for males and 1.5 mg/kg/day for females. Thus, reversible gastrointestinal toxicity is expected to be the dose-limiting toxicity of CMX001.

Pharmacokinetics and Metabolism

S9 fractions of pooled liver homogenates from mice, cynomolgus monkeys and humans were incubated with 1 and 10 μM CMX001 to assess the metabolic stability of CMX001. Metabolic stability, as evidenced by the rate of disappearance of the parent drug, was greatest in the mouse, followed by humans. Metabolism was particularly efficient in the monkey liver S9 fraction, with only 1-2% of CMX001 remaining after 60 min compared with 35-99% of CMX001 remaining in the mouse and human liver S9 incubations.

The metabolic stability of CMX001 was also examined in cryopreserved primary human, mouse, rat, rabbit and cynomolgus and rhesus monkey hepatocytes incubated with either 1 or 10 μM CMX001 for 4 h. Based on the results from this study, animals can be classified as either fast (monkeys and rats) or slow metabolizers of CMX001 (mice, rabbits and humans). In the fast metabolizing group, approximately 90% of the CMX001 is gone after 4 h, while in the slow metabolizing group < 50% of CMX001 is gone after 4 h. Four metabolites, two major and two minor, were consistently identified in extracts of incubation media hepatocytes from all species examined. The two major metabolites are an oxidative catabolite (CMX064) in which the lipid chain has been shortened by 12 carbons and free CDV (CMX021), and the two minor metabolites are hydroxylated and glucuronidated CMX001.

A three-part study was conducted to examine the interaction between CMX001 and cytochrome P-450 (CYP) enzymes. In part 1 of the study, there was no evidence of induction of CYP1A2, 2C9 or 3A4 activity by CMX001 in primary cultured human hepatocytes. Similarly, in part 2, CMX001 did not cause significant inhibition of CYP1A2, 2C9, 2C19, 2D6 or 3A4 enzyme activities in human liver microsomes. In part 3, the involvement of CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2E3 and 3A4 in the metabolism of CMX001 in human liver microsomes was examined. Only 3A4 was found to contribute to CMX001 metabolism.

Oral dosing of mice, rabbits and monkeys results in significant systemic exposure to CMX001, as indicated by C_{max} and $AUC_{0-\infty}$ (Table II). The highest exposure was in rabbits, followed by mice and then monkeys. The drug levels achieved at the 10 and 4.5 mg/kg doses in mice and rabbits are highly efficacious in mouse models of *Orthopoxvirus* and CMV infection, and in rabbit models of vaccinia virus infection. Oxidative catabolism to form CMX064 appears to result from CYP enzyme activity in the liver and small intestine. Levels of CMX064 are highest in monkeys, as would be predicted from *in vitro* metabolism data collected using S9 fractions of pooled liver homogenates and cryopreserved primary hepatocytes (see above).

Table II: Pharmacokinetic parameters for single oral doses of CMX001 and CMX064 in mice, rabbits, monkeys and humans (cohorts 3-6 of the phase I clinical study CMX001-102).

Species	Dose (mg/kg)	CMX001		CMX064	
		C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng.h/ml)
Mouse	10	69.20	103.5	96.53	785.5
Rabbit	4.5	75.23	460.6	305.00	2549.6
Monkey	4	12.92	31.7	569.67	4665.2
Human	0.1	10.62	132.8	2.85	ND
	0.2	24.48	225.5	4.55	39.7
	0.4	68.13	526.4	23.03	203.0
	0.6	114.73	728.8	24.86	187.0

ND, not determined.

Clinical Studies

A placebo-controlled, dose-escalating phase I safety and pharmacokinetic study of CMX001 (CMX001-102) in healthy volunteers is under way. The first phase of the study, which included 6 cohorts each containing 6 subjects is complete. Subjects in each cohort were randomized 4:2 to receive a single oral dose of study drug or placebo. Dose escalations from the starting dose of 25 μg/kg (1.875 mg in a 70-kg subject) were 50 μg/kg (cohort 2), 100 μg/kg (cohort 3), 200 μg/kg (cohort 4), 400 μg/kg (cohort 5) and 600 μg/kg (cohort 6). The pharmacokinetic profile of CMX001 determined using model-independent analysis was dose-proportional. C_{max} ranged from 2.36 ng/ml at the lowest dose to 114.73 ng/ml at the highest dose, while $AUC_{0-\infty}$ ranged from 18.51 ng.h/ml to 728.8 ng.h/ml. C_{max} and $AUC_{0-\infty}$ values for cohorts 3-6 are shown in Table II. The degree of oxidative catabolism observed in humans, as evidenced by CMX064 levels in plasma, was significantly lower than that seen in any of the animals studied to date, particularly monkeys. No serious adverse events have been observed.

Acknowledgements

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Source

Chimerix, Inc. (US).

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