MCT (1, 5, and 25 mg/(kg day)) were compared when initiated 24–72 h post inoculation (hpi). Animals were evaluated for survival and symptoms of neonatal herpes infection. We had previously shown that high dose ACV (60 mg/(kg day)) is effective in this model, but only when treatment is initiated within 24 hpi. Therefore, in the first experiment, we evaluated therapy begun at 24 hpi. Both ACV and N-MCT significantly improved survival, but only 25 mg/(kg day) N-MCT significantly reduced the number of animals with symptoms. When therapy was begun at 48 hpi, N-MCT (25 mg/(kg day)) significantly increased survival to 91% compared to 27–30% for the untreated and ACV groups ($P < 0.01$). We next evaluated a lower dose of N-MCT (1 and 5 mg/(kg day)) begun at 48 hpi, as well as N-MCT (5 and 25 mg/(kg day)) begun at 72 hpi. In this study, 80–89% of animals treated with N-MCT at 48 hpi survived compared to 38% of untreated animals ($P < 0.01$). When therapy was initiated at 72 hpi, 80% of N-MCT (5 mg/(kg day)) and 100% of N-MCT (25 mg/(kg day)) treated animals survived. The number of animals with symptoms was also significantly reduced in the low dose treatment groups when therapy was initiated at both 48 and 72 hpi. In conclusion, N-MCT was highly effective and superior to high dose ACV therapy for the treatment of neonatal herpes in the guinea pig model.

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CMX001 Potentiates the Efficacy of Acyclovir in Herpes Simplex Virus Infections

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Although acyclovir (ACV), valacyclovir and famciclovir have proven to be effective in the therapy of certain herpes simplex virus (HSV) infections, there is a need for more effective therapies particularly for serious infections in neonates and immunocompromised individuals where resistance to these drugs can be problematic. CMX001 is an orally bioavailable lipid conjugate of cidofovir that is substantially less nephrotoxic than the parent drug and has excellent antiviral activity against all the human herpesviruses. Since this nucleotide analog does not require phosphorylation by the viral thymidine kinase it retains full antiviral activity against ACV-resistant clinical isolates. Further studies indicated that combinations of CMX001 and ACV synergistically inhibited the replication of both HSV-1 and HSV-2 in cell culture. Combined therapy with CMX001 and ACV was also highly effective in murine models of HSV infection and synergistically reduced mortality. These results suggest that CMX001 may be effective in the treatment of HSV infections and as an adjunct therapy in individuals with suboptimal responses to ACV.

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Safety and Human Pharmacokinetics of AIC316, a Potent Helicase-Primase Inhibitor of Herpes Simplex Virus (HSV)

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Background: AIC316 belongs to a novel class of anti-HSV compounds, the helicase-primase inhibitors, which have a mode of action that is distinct from that of nucleoside analogues currently in clinical use (e.g. acyclovir). AIC316 is in phase II clinical development and a comprehensive nonclinical and clinical program has been conducted. Here we report on the safety and pharmacokinetics (PK) of AIC316 in healthy volunteers within phase I clinical trials.

Methods: Safety and PK of AIC316 was investigated in two double-blinded, placebo controlled trials comprising single (trial A) and multiple (trial B) dose escalation as well as in an open-label food interaction cross-over trial (trial C). Single oral doses of 5–600 mg AIC316 in males and an oral dose of 80 mg AIC316 in females (to assess a potential gender effect) were administered in trial A. A single oral dose of 80 mg was administered in trial C with and without a high fat, high calorie breakfast. In trial B, subjects received once daily doses of 5 mg, 25 mg, and 100 mg for three weeks.

Results: In all three trials AIC316 was safe and well tolerated. No dose-dependent adverse events occurred, no effects on safety laboratory, vital signs and ECG parameters were detected. There was dose proportional increase in exposure after single doses of up to 400 mg (C_{max}) and 480 mg (AUC), respectively, and with daily doses up to 100 mg at steady state. Terminal elimination half-life varied between 52 and 85 h after single dose and at steady state resulting in about 5 times higher plasma concentrations at steady state compared to single dose administration. No clinically relevant gender-related difference in exposure was detected for the single dose of 80 mg. The rate of absorption was decreased by food intake, but both C_{max} and AUC showed a slight increase. Comparison of human exposures with the effective concentration of AIC316 in cell culture showed that plasma levels were maintained above the EC_{90} for 24 h after 40 mg single dose administration and at steady state with daily doses of 25 mg.

Conclusion: AIC316 was safe and well tolerated in healthy volunteers and has a favorable PK profile indicative of efficacy with once per day dose administration.

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