4.4.2.1 CMX001 Animal Efficacy

The *in vivo* activity of CMX001 has been evaluated in multiple animal models of poxvirus disease. CMX001, administered by oral gavage, protected mice from lethal intranasal challenge with VACV, CPXV and ECTV.[84,85] CMX001 administered by oral gavage protected A/Ncr mice infected with a lethal challenge dose of ECTV (5×10^4 PFU). This amount of virus is 10 000-fold above the LD_{50} delivered by intranasal inoculation or directly to the respiratory tract *via* aerosolized droplets. Moreover, CMX001 protected mice even when the compound was delivered 5 days post-infection.[86] Oral delivery of CMX001 protected rabbits infected with rabbitpox virus when administered prophylactically or at symptom onset.[44,87] These studies were conducted as randomized, double-blind, placebo-controlled trials, providing robust data sets that can be used to establish PK–PD relationships. These data demonstrate that CMX001 is well tolerated in multiple animal species and can protect animals from lethal poxvirus challenge.

Despite showing dramatic antiviral activity in numerous animal species against poxviruses and other DNA-containing viruses, CMX001 was not active in NHPs infected with monkeypox virus when delivered orally. This result was unexpected since CMX001 has been shown to be active against monkeypox virus in cell culture.[50] Moreover, CMX001 was active in a mouse model of monkey pox virus infection established in STAT1-deficient knockout mice.[88] The lack of antiviral activity was likely caused by compound metabolism, since PK assessment following oral administration of CMX001 to NHPs showed low systemic exposure of the parent compound. Intramuscular administration improved systemic exposure but did not protect animals from lethal infection. Whereas CDV and CMX001 produce the same active metabolite (CDVpp) and CDV was effective at protecting NHP from lethal MPX infection when administered by intravenous injection, CDVpp levels were much lower in PBMCs from animals treated with CMX001 compared with intravenous CDV administration. This is consistent with CMX001 being poorly metabolized to CDV in monkeys.[50]

Non-human primate models of OPV infection are considered by some as essential for evaluating antiviral efficacy of smallpox therapeutics. Since CMX001 is not efficiently metabolized in this species, alternative models need to be considered in order to develop PK–PD relationships to establish the human dose. Since CMX001 has broad antiviral activity against DNA viruses, it is possible to establish dosing regimens in humans against other naturally occurring viral infections once the safety and tolerability of CMX001 have been assessed.

4.4.2.2 CMX001 Clinical Studies

CMX001 was evaluated for safety and pharmacokinetics in single and multiple ascending-dose human trials.[89] The compound was found to be well tolerated in humans at all dose levels. Oral administration of single doses of CMX001 of 0.25–2 mg kg^{-1} and multiple doses ranging from 0.1 to 1.0 mg kg^{-1} were well