the compound is co-administered with food. The absolute measure of bioavailability in mice and non-human primates was ~40% when administered to animals in the fed state as an oral suspension. The increase in bioavailability was non-linear at high compound concentrations, likely due to decreased absorption. ST-246 is metabolically stable and is widely distributed in tissues. Studies using the radiolabeled compound showed that 72% of the radioactivity is eliminated in the feces and 24% in the urine as intact ST-246 by 96 h post-compound administration. ST-246 was well tolerated in mice and non-human primates in 28 day repeat-dose toxicity studies with a no observable adverse effect level (NOAEL) of 2000 mg kg^{-1} for mice and 300 mg kg^{-1} for non-human primates. Hence ST-246 is well tolerated with very little observable toxicity at doses that far exceed the proposed human dose required for the antiviral activity.[103]

4.4.3.1 ST-246 Animal Efficacy

ST-246 was evaluated in a variety of animals, including mice, rabbits, ground squirrels, prairie dogs and non-human primates.[48,51,104–107] In the mouse model, ST-246 protected animals from lethal OPV infection established by a variety of routes, including intranasal, intravenous, intradermal, subcutaneous and aerosol delivery of vaccinia, cowpox and ectromelia viruses.[104,108] ST-246 treatment has been demonstrated to inhibit poxvirus dissemination, virus shedding and systemic disease in mice.[108] Data from these studies were used to establish the optimal dosing regimen for protective efficacy. These studies demonstrated that once per day oral dosing in mice at 100 mg kg^{-1} for a period of >7 days was optimal for protective efficacy. Treatment can be initiated as late as 72 h post-infection for full protection. Moreover, mice that survive lethal infection due to ST-246 treatment are resistant to subsequent challenge with lethal doses of vaccinia virus due to acquisition of protective immunity during the initial infection.[51] ST-246 has also been shown to protect mice that are deficient in either CD4+ or CD8+ T cells from lethal infection, but not both, regardless of the presence or absence of B-cell deficiency.[109] ST-246 treatment in combination with smallpox vaccination does not appear to diminish the immune response, raising the possibility that ST-246 could be co-administered with the smallpox vaccine to reduce vaccine-related side effects and protect individuals from infection prior to acquisition of protective immunity.[109]

In non-human primates infected with monkeypox virus, ST-246 reduced viral load and lesion formation and protected animals from lethal infection.[47,48] The minimum effective dose was 3 mg kg^{-1}, which produced plasma drug levels below the proposed human dose of 400 mg in the fed state. A randomized, double blind, placebo-controlled study was conducted to evaluate the efficacy of ST-246 in cynomolgous macaques inoculated with a lethal dose of monkeypox virus *via* intravenous injection.[103] Treatment was initiated at 3 and 4 days post-infection at the onset of lesions and ST-246 delivered at 10 mg kg^{-1} or placebo was administered by oral gavage once per day for 14 consecutive