days. The results showed that ST-246 protected animals from lethal infection and reduced lesion formation and viral DNA levels in the blood. A compilation of the efficacy data from NHP studies conducted with ST-246 showed a strong correlation between viral DNA levels in the blood, lesion formation and mortality.[103] In all studies, ST-246 protected NHPs from lethal infection with monkeypox virus and reduced lesion formation and viral DNA levels in blood even when compound was administered as late as 5 days post-inoculation. These results demonstrate that ST-246 provides therapeutic efficacy against lethal monkeypox virus infection of NHP.

ST-246 was also shown to be effective at reducing disease in NHP infected with variola virus.[48] A randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy of ST-246 in cynomolgous macaques infected with variola virus *via* intravenous injection. Treatment was initiated at lesion onset (between days 3 and 4 post-infection). The results showed that ST-246 reduced lesion numbers compared with placebo-treated animals.[103] Moreover, the rate of increase in viral DNA levels in the blood were significantly different between ST-246-treated and placebo-treated animals. The effects of ST-246 on mortality rates could not be evaluated since all of the animals survived the challenge. Taken together, these results suggest that ST-246 administered at lesion onset at $10\,mg\,kg^{-1}$ can protect monkeys from lethal infection with monkeypox virus and reduce variola virus-induced disease.

4.4.3.2 ST-246 Clinical Studies

Single and multiple ascending dose studies in healthy human volunteers established that ST-246 was safe and well tolerated, with plasma drug exposures in the range predicted to be sufficient for inhibiting OPV replication.[110,111] No severe adverse events (SAEs) were observed and no subject was withdrawn due to ST-246. The most commonly reported drug-related adverse effect was neutropenia, which was found, upon further analysis, not to be treatment related. ST-246 was readily absorbed following oral administration with mean times to maximum concentration in plasma of 3–4 h. Absorption was greater in non-fasting than fasting volunteers.

The robust antiviral activity across multiple animal species provided a means to estimate the efficacious human dose. Data from non-human primate models of OPV infection were used as the most relevant model of human smallpox. Using survival as an endpoint, an oral dose of $\sim 3\,mg\,kg^{-1}$ in non-fasted non-human primates confers 100% protection from death following intravenous injection of monkeypox virus. Pharmacological assessment in non-human primates found that a dose of $10\,mg\,kg^{-1}$ results in blood exposure levels comparable to levels attained in humans administered a 400 mg dose in the fed state. Given the variability in exposure levels in monkeys and humans in the fed and fasted states, it was predicted that human doses of 400 mg in the fed state will encompass plasma drug exposure levels comparable to those that provide protective efficacy in the non-human primate model of orthopoxvirus disease.[103]