tolerated, with no severe adverse events reported. Moreover, no clinically significant drug-related changes in blood chemistry, hematology, renal function or intraocular pressure were observed. Systemic exposure was dose proportional with no significant accumulation of compound after administration of multiple doses. Importantly, the concentration of CDV in the plasma remained low, indicating that CMX001 was not readily metabolized outside the cell. Hence the lipid prodrug moiety effectively eliminated the dose-limiting toxicity caused by systemic administration of CDV. At doses above $1\,mg\,kg^{-1}$, the plasma concentration at C_{max} was in the range expected to provide antiviral activity against herpes virus, adenovirus and variola virus.[89]

CMX001 was used in several of compassionate use cases for the treatment of disease caused by adenovirus or polyomavirus. The cases provided human data that demonstrated safety and efficacy of CMX001 in the treatment of viral disease.

CMX001 was used to treat a severely immunocompromised pediatric stem cell transplant recipient infected with adenovirus. In normal healthy adults, adenovirus causes a self-limiting infection of the respiratory tract leading to flu-like symptoms that resolve in several days. In severely immunocompromised patients, adenovirus spreads systemically, producing high levels of circulating virus and severe disease, with high levels of associated mortality. In this case, the patient failed to respond to intravenous CDV treatment and CMX001 was administered at $2\,mg\,kg^{-1}$ twice per week. Upon administration of CMX001, viral titers in the blood dropped below the limit of detection after the fifth dose and the clinical outcome significantly improved. These data demonstrate that CMX001 can be used to treat severe infections caused by adenovirus in immunocompromised patients.[90]

The antiviral activity of CMX001 in humans was further demonstrated in a multicenter cohort of 13 severely immunocompromised patients infected with adenovirus who failed CDV therapy. In this study, CMX001, administered at $2\,mg\,kg^{-1}$ per week, reduced the viral load in all patients and significantly improved the clinical outcome. Although the patient population was too small to determine the statistical significance of the data, the results suggest that CMX001 had an antiviral effect in severely immunocompromised humans. Hence CMX001 is safe and well tolerated in severely ill patients.[91]

The utility of CMX001 was further established against polyomaviruses (BK and JC) that are clinically significant DNA viruses associated with distinct human disease (reviewed by Bennett *et al.*[92] and Berger[93]). BK virus infection is a major cause of allograft failure in renal transplant recipients. BK virus is associated with nephropathy and urethral stenosis and in hematopoietic stem-cell transplant recipients with hemorrhagic cystitis. JC virus causes a demyelinating disease of the brain called progressive multifocal leukoencephalopathy, which can be fatal.

In vitro, CMX001 inhibited BK virus in primary human proximal renal tubular cells. CMX001 was shown to inhibit both intracellular and extracellular virus as measured by Q-PCR of viral genomic DNA and Western blotting and immunofluorescence detection of viral proteins.[94] Likewise, CMX001 inhibited