



Update on the Development of Brincidofovir (CMX001) for Smallpox and Other Indications

Lawrence C. Trost, Ph.D., DABT
Chimerix Inc.
Durham NC USA

Brincidofovir (CMX001) is a potent inhibitor of multiple dsDNA viruses including adenovirus, CMV and *Variola major*. The key attributes of brincidofovir compared with intravenously administered cidofovir (Vistide) are improved ease of use, oral bioavailability, increased potency and decreased nephrotoxicity. In addition, brincidofovir has demonstrated a favorable resistance profile and a low risk of significant drug-drug interactions. It has been administered to more than 900 human subjects, many with life-threatening illnesses caused by dsDNA viruses. It has also been studied in patients with renal and/or hepatic impairment and pediatric subjects as young as 1 month of age. A Phase 3 study for prevention of CMV in immunocompromised transplant patients is currently enrolling with doses that, scaling from efficacious doses in animal models, are also proposed for treatment of smallpox. The US FDA has agreed that the intradermal rabbitpox model in rabbits and the intranasal ectromelia model in mice are acceptable animal models to support development of brincidofovir for a therapeutic indication for treatment of smallpox. The activity of brincidofovir was recently demonstrated in a blinded efficacy study in the rabbitpox model in which a statistically significant survival benefit of two different regimens was observed when treatment was initiated after clinical signs of infection. In the first half of 2013, BARDA notified Chimerix of its intention to exercise an option to provide additional funds (Option Segment 1) to further advance the development of brincidofovir for treatment of smallpox. Supported by the work of BARDA's "Animal Model Development Program," Chimerix will initiate pharmacokinetic studies of brincidofovir in the rabbitpox and ectromelia models in the last quarter of 2013. These studies will support dose selection for pivotal efficacy studies. Brincidofovir is anticipated to be commercially available in tablet and liquid formulations. Manufacturing of brincidofovir has been validated at commercial scale and the drug is stable for multiple years. Taken together the smallpox animal model and human efficacy data against related viruses support the likely efficacy of brincidofovir for treatment of smallpox.

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