treated with preemptive CDV, the authors concluded that CDV could be used as first-line therapy, especially in patients with low HCMV DNA concentrations in plasma. Early administration of CDV was not complicated by renal toxicity, and the relatively infrequent dosing required with CDV (weekly or every other week) allowed many of the patients to be treated in an outpatient setting (Bosi *et al.*, 2002). A similar observation was reported by Platzbecker *et al.* (2001); a moderate toxicity rate was reported, mostly renal, but always reversible.

Taken together, the data from these studies suggest that the role of CDV for patients with bone marrow and stem cell transplants developing HCMV infections should probably be defined on the basis of additional, larger studies. However, these are unlikely to be funded by the manufacturer, given the imminent expiry of the CDV patents; CDV analogs (e.g. CMX001) may replace CDV for these indications (Beadle *et al.*, 2002; Bidanset *et al.*, 2004).

BrinCDV has been evaluated for its safety and anti-HCMV activity in patients who had undergone allogeneic hematopoietic-cell transplantation (Marty *et al.*, 2013). In this study a total of 230 adult HCMV-seropositive transplant recipients from 27 centers were enrolled and randomly assigned to oral administration of BrinCDV or placebo. The patients were randomized to evaluate the study drug in five sequential dose-escalating placebo-controlled cohorts and were given BrinCDV after engraftment for 9–11 weeks, until week 13 posttransplantation. Analysis of HCMV DNA in plasma was performed weekly by polymerase chain reaction (PCR); patients in whom HCMV DNA was detected at a level that required treatment discontinued BrinCDV and received preemptive treatment against HCMV infection. The primary end point was a HCMV event (defined as HCMV disease or a plasma HCMV DNA level > 200 copies/ml when the study drug was discontinued). Approximately 42% of patients in the placebo arm had positive HCMV DNA during treatment administration; for the patients receiving BrinCDV, the percentages by dosage were 40% on 40 mg/week, 22% on 100 mg/ week, 18% on 200 mg/week, 7% on 200 mg twice weekly, and 8% on 100 mg twice weekly. The incidence of HCMV events was significantly lower among patients who received BrinCDV 100 mg twice weekly than those who received placebo; and this dose was well tolerated. The most common adverse event in patients receiving BrinCDV at doses of 200 mg weekly or higher was diarrhea, making the dose limit 200 mg twice weekly. It is important to note that myelosuppression and nephrotoxicity were not observed. Notably, in this study, mutations known to be associated with drug resistance were not detected in BrinCDV-treated subjects. The identified substitutions the HCMV DNA polymerase did not alter the sensitivity to HCMV antivirals *in vitro*, indicating that these changes are linked to interstrain variability unrelated to BrinCDV resistance.

The results of a phase III randomized double-blind placebo-controlled, parallel-group, multicenter study of the safety, tolerability, and efficacy of BrinCDV for the prevention of HCMV in seropositive hematopoietic stem cell transplant recipients, called SUPPRESS, were reported by Chimerix last year (clinical trial NCT01769170). The primary end point for SUPPRESS (i.e. prevention of clinical CMV infection through the first 24 weeks posttransplant) was not achieved. A clear antiviral effect was seen at the end of the on-treatment period at week 14 after transplantation, consistent with the antiviral effect of BrinCDV observed in the phase II study. However, at week 24 pottransplantation, the proportion of patients with clinically significant HCMV infection was similar in the BrinCDV (51%) and placebo (51%) groups. The failure of the SUPPRESS study to achieve the primary end point could be explained by the higher number of confirmed cases of graft-versus-host-disease (GvHD) in the BrinCDV group, which meant the higher use of corticosteroids than in the placebo arm. The use of corticosteroids and other immunosuppressive therapies for management of GvHD increases the risk of infection, including HCMV infections.

In light of the unexpected negative results obtained in the SUPPRESS clinical trial, Chimerix paused enrollment for two other phase III trials of BrinCDV for the prevention of HCMV in kidney transplant patients, SUSTAIN (clinical trial NCT02439970) and SURPASS (clinical trial NCT02439957), for which enrollment was initiated in October 2015. In the SUSTAIN trial, 750 patients who are HCMV seronegative (R−) who received a HCMV positive (D+) kidney were planned to be evaluated. The SURPASS trial was designed to evaluate 520 HCMV seropositive (R+) kidney transplant recipients. The goals of these studies was to demonstrate the ability of BrinCDV to preventing HCMV disease *versus* the current standard of care and to show a potential positive impact of the drug on improved graft function.

7c. Herpes simplex virus infections

CDV was initially described as a topical drug for the treatment of severe, mucocutaneous, antiviral drug-resistant HSV infections in two immunocompromised patients (Snoeck *et al.*, 1993; Snoeck *et al.*, 1994a). The first patient had an aciclovir-resistant HSV-2 infection and the second, an HSV-1 infection resistant to both aciclovir and foscarnet. Lesions of both patients responded completely to local applications of 1% CDV cream, but recurrences with wild-type virus were observed after treatment. In both patients the wild-type viruses were successfully treated with aciclovir but in the patient presenting with mucocutaneous HSV-2, anogenital infection relapsed with an aciclovir-resistant HSV that was successfully treated with CDV. CDV-resistant virus was never detected. Similar cases successfully treated with intravenous CDV have been reported (Kopp *et al.*, 2002; Lalezari *et al.*, 1994). The lesions responded to the therapy, and any relapses seen after treatment interruption responded to retreatment with CDV.

Two studies evaluated the CDV susceptibility of HSV isolates recovered from allogeneic stem cell transplant patients (Chakrabarti *et al.*, 2000; Chen *et al.*, 2000). In these two studies, none of the clinical strains isolated (including isolates resistant to aciclovir and/or foscarnet) were resistant *in vitro* to CDV, even those isolated from patients without a complete clinical response to CDV therapy (only three out of seven patients achieved complete response) (Chen *et al.*,