Pre-engraftment Initiation of Brincidofovir (CMX001) in Hematopoietic Cell Transplant (HCT) Recipients is Supported by Lack of Myeloid Toxicity

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Introduction: Currently available antivirals with anti-CMV activity have been associated with myeloid toxicity in HCT recipients, limiting treatment initiation until after engraftment, and reducing the potential benefits of CMV prevention by increasing risks of other infections. Brincidofovir (BCV), currently in Phase 3 development for prevention of CMV infection post-HCT, is a nucleotide analogue with broad-spectrum double-stranded DNA antiviral activity and a favorable safety profile.

Patients and methods: Absolute neutrophil counts (ANC) from HCT recipients enrolled in two placebo (PBO)-controlled (Studies 201 and 202) and one open-label clinical trial (Study 350) of BCV were reviewed. In 201 and 202, study drug was initiated a median of 24 and 55 days post-HCT, respectively. Subjects from 201 and 202 receiving a total weekly dose of 200mg BCV or PBO, who had baseline (BL) ANC <1500 cells/µL, and who did not receive concomitant valganciclovir (vGCV) or ganciclovir (GCV) were included in the analysis. Last and maximum on-treatment ANC values were compared to baseline. Clinically identified graft failure rates were also compared.

Results: In 201 and 202, 40 subjects were analyzed: 24 on BCV and 16 on PBO. Subjects received a mean 6.0 (PBO) to 6.5 weeks (BCV) treatment. On-treatment ANC recovery to >1500 cells/µL occurred in 83% (20/24) on BCV compared to 81% (13/16) on PBO. Numerically improved ANC (>BL) was noted in 92% (22/24) BCV subjects versus 94% (15/16) on PBO. Due to the clinical importance of early ANC recovery, similar analyses were performed for the first 4 weeks of treatment: 68% of subjects on BCV versus 75% on PBO achieved ANC >1500, while 83% BCV versus 81% PBO subjects had an ANC >BL at week 4. Observed ANC through the first 4 weeks revealed a maximum ANC >1500 in 79% of BCV subjects compared to 81% of PBO subjects; evidence of early neutrophil recovery

with a maximum ANC >BL was observed in 88% of BCV subjects compared to 94% of PBO subjects.

In Study 350, 41 post-HCT subjects had BL ANC <1500 cells/µL. Of these, prior vGCV or GCV use was reported in 41%, and 27% were enrolled due to concerns of cytopenia. Fourteen subjects were excluded due to concomitant vGCV or GCV use. The remaining 27 subjects received BCV for a median of 4 weeks; 19/27 (71%) had last on-treatment ANC >1500, and 21/27 (78%) had last on-treatment ANC >BL. Maximum on-treatment ANC was >1500 in 23/27 (85%), and >BL in 25/27 (93%).

In 201 and 202, graft failure was reported in 2/123 (1.6%) of the 200mg/week BCV subjects, versus 4/77 (5.2%) of the PBO subjects. In 350, graft failure was reported in 1 (4%) subject on BCV monotherapy, versus 3/14 (21%) on BCV plus GCV/vGCV.

Discussion: These data suggest BCV has no negative impact on neutrophil recovery, supporting initiation of BCV in the immediate post-transplant period prior to engraftment, as per the design of the current Phase 3 SUPPRESS trial. The hematologic safety profile of brincidofovir and earlier initiation of antiviral prophylaxis in the post-HCT period may not only provide improved efficacy in the prevention of CMV infection and disease, but may also reduce rates of invasive bacterial and fungal infections post-HCT.