

Brincidofovir for Prevention of Cytomegalovirus (CMV) after Allogeneic Hematopoietic Cell Transplantation (HCT) in CMV-Seropositive Patients: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trial

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Background: CMV is the most common viral infection after HCT. Due to hematologic and renal toxicities, current antivirals are used preemptively after evidence of CMV replication; no drug is approved for CMV prophylaxis post-HCT. Brincidofovir (BCV, CMX001) is an orally bioavailable lipid conjugate of cidofovir with *in vitro* activity against common transplant-related human dsDNA viruses. In a Phase 2 trial, BCV 100 mg twice weekly (BIW) prevented CMV reactivation and was generally well tolerated.

Methods: The Phase 3 SUPPRESS trial (NCT01769170) compared BCV prophylaxis versus placebo through the first 14 weeks (100 days) post-HCT. Adult CMV-seropositive HCT recipients without CMV viremia at screening were randomized 2:1 to receive BCV 100 mg BIW or placebo as soon as they could swallow tablets. Randomization was stratified by center and patient risk for clinically significant CMV reactivation. Patients were assessed weekly until Week 15 post-HCT (and every 3 weeks thereafter) for CMV viremia (Roche Cobas® PCR Assay), CMV disease, GVHD, and other adverse events. Patients who developed CMV reactivation based on pre-defined, risk-based thresholds discontinued study drug and received institutional standard of care CMV therapy. The primary endpoint of the study, assessed at Week 24 post-HCT, is the intention-to-treat incidence of CMV disease or CMV reactivation requiring preemptive therapy. CMV disease and GVHD were adjudicated by blinded committees.

Results: From Aug 2013 until Jun 2015, 458 patients from 37 centers in the US, Canada, and Europe were randomized: 58% were males, 83% were white, and median age was 56 years (range, 18-77). Patients began study drug at a median of 15 days (range, 2-33) post-HCT. The indication for transplant was AML in 42% and MDS in 16%; 55% underwent myeloablative conditioning, 78% received PBSCs, 14% received BM, and 12% received cord blood or haploidentical grafts. 46% of donors were HLA-matched unrelated, 21% of donors were HLA-mismatched and 53% of donors were CMV-seropositive. *Ex vivo* T-cell depletion was used in 12% of patients, 29% of patients received ATG and 9% received alemtuzumab during conditioning. Thirty-eight percent of patients had ANC < 500/L at the time of first dose. In addition to CMV seropositivity, 73% had factors (T-cell depletion, cord or haplo; steroids >1mg/kg) that confer high risk for progression to CMV disease. The last study visit is expected in November 2015.

Conclusion: Most patients in the SUPPRESS trial had baseline factors that place them at high risk for reactivation of CMV and progression to clinically significant disease caused by CMV and other dsDNA viruses. The SUPPRESS trial was designed to evaluate the safety and extent to which brincidofovir prophylaxis may prevent the reactivation of CMV and other prevalent dsDNA viruses that affect morbidity and mortality in HCT recipients. Final study results will be presented at the meeting.