The First Interventional Trial for Adenovirus (AdV): Brincidofovir (CMX001) for AdV in HCT

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Background: Disseminated AdV has a high mortality rate in hematopoietic cell transplant (HCT) recipients and no approved therapy. The broad-spectrum nucleotide analog brincidofovir (BCV, CMX001) has demonstrated *in vitro* potency against all major AdV species.
Methods: Incidence and progression rates of AdV disease/viremia are unknown. This exploratory Phase 2 study screened allogeneic HCT recipients for AdV viremia: pts with asymptomatic AdV PCR $\geq$ 100 c/mL were randomized to placebo (pbo), BCV 200 mg once weekly (QW), or BCV 100 mg twice weekly (BIW). The composite primary endpoint was progression of AdV disease or a $\geq$ 1 $\log_{10}$ increase in AdV viremia.
Results: 735 adult and pediatric HCT recipients at 29 centers were screened for AdV viremia over 18 months; 48 subjects were randomized. Baseline demographics were similar across groups. No subject discontinued for diarrhea; there was no lab evidence of hematologic, renal, or hepatic toxicity. Subjects receiving BCV BIW had a mean 0.9 $\log_{10}$ c/mL decline in AdV viremia at wk 1 vs 0.3 $\log_{10}$ c/mL on pbo (p=0.075). Three of 14 (21%) BCV BIW and six of 18 (33%) pbo subjects met the primary AdV progression endpoint (p=0.45); all-cause mortality on BCV was 14% (2 of 14) vs pbo 39% (7 of 18, p=0.16). Neither death on BCV BIW was attributed to AdV and both occurred >24d after the last dose. Among subjects at high risk of rapid progression to disseminated AdV, 20% (2 of 10) BCV BIW reached the AdV endpoint vs pbo 50% (4 of 8, p=0.32). All-cause mortality in high-risk BCV BIW subjects was 20% (2 of 10) vs pbo 75% (6 of 8, p=0.054).
Conclusions: BCV 100 mg BIW as preemptive therapy decreased AdV viremia and showed potential benefit in reduced progression to AdV disease and all-cause mortality. Although statistical significance was not established in this exploratory study, ITT and subset analyses of disease progression and all-cause mortality were consistent in trends favoring the

BCV BIW regimen over placebo or BCV QW. These data support the continued development of BCV as prevention for dsDNA viral infections including AdV and CMV.