BACKGROUND: Histone deacetylase inhibitors have been found preclinically to be among the most active agents against Diffuse Midline Gliomas (DMGs), however, they are clinically ineffective with systemic delivery due to low blood brain barrier penetration and systemic toxicity. Using an implantable subcutaneous pump connected with a catheter directly implanted into the pons we have conducted a phase I, 3+3 dose escalation study to investigate the safety and feasibility of repeated infusions of MTX110 (Biodex Ltd), a water-soluble formulation of panobinostat, via CED. METHODS: Eligible patients were between 3 and 18 years of age with newly diagnosed DMG following radiation therapy, without evidence of hemorrhage or cyst in the tumor, and having normal organ function. First, patients underwent tumor biopsy and device implantation, then received two 48-hour-infusion pulses 7 days apart. Three dose levels of MTX110 infusions (30, 60, 90 mcM) were studied. The infusion pump was prefilled with MTX110 (and gadolinium for co-infusion as a contrast agent), which was then administered using the wireless N’Vision clinical programmer at a rate of 0.2 mL/hr. RESULTS: Nine patients were treated in the study (30 mcM group, n=3; 60 mcM group, n=4; 90 mcM group, n=2). All patients had an H3K27M mutated tumor. All but one patient had adequate tumor coverage with the infusate. One patient suffered a severe adverse event related to the infusion and tumor anatomy. Four patients had Grade 2 transient neurological deficits related to biopsy (n=1) or infusion (n=3). We observed one objective response. Median PFS was 10 months from diagnosis (range 8 to 20 months) while median OS was 16.5 months (range 12 to 35 months). CONCLUSIONS: The study has demonstrated safety and feasibility of repeated infusions of MTX110 via CED in DMG patients with a favorable trend in overall survival warranting further trials with higher number of infusion pulses.