BACKGROUND: ACT001, an oral parthenolide derivative targeting STAT3 and NF-kB pathways, has shown activity in preclinical models of DMG. We evaluated safety, toxicity and activity of ACT001 in this recently completed, first-in-child study of DMG and other relapsed/refractory brain and solid tumors. METHODS: Eligible patients ≥ 1 and ≤ 21 years old were enrolled with dose escalation following a rolling 6 design and tumor lesions evaluated every 8 weeks per RANO/RECIST criteria. RESULTS: A total of 29 patients were enrolled across 3 cohorts, including 19 with DMG (13 with Diffuse Intrinsic Pontine Glioma (DIPG)). Median age was 11 years for the whole cohort and 7 years (3-17) for DMG patients. Safety was evaluated in escalating doses in 188, 533, 700, 875 and 1100 mg/m² BID cohorts. No DLT nor grade 3 and above TRAE was identified. One SUSAR was noted for a grade 1 pain in extremity event. Peak ACT001 concentration for each dose cohort were estimated based on limited PK sampling time (cycle 1 day 1 at pre-dose, 2 and 4 hours post dose; cycle 1 day 15 and cycle 2 day 1 both at pre-dose). ACT001 peak concentration plateaued at the highest dose levels, fluctuating in the range of 6360, 5430 and 5980 mg/m² for 700, 875 and 1100 mg/m² cohorts respectively. The half-life was approximately 3 hours. 8/14 DMG patients treated at ≥ 700 mg/m² exhibited objective response or stable disease (SD), including one patient with SD for 14 months, another patient with confirmed Partial Response who remained on study for 11-months before disease progression and five other patients with different degrees of tumor burden reduction. CONCLUSION: ACT001 was well tolerated and showed preliminary evidence of anti-tumor activity in DMG/DIPG patients dosed at the highest dose levels. A Phase 2 trial is planned using 875 mg/m² as the RP2D.