Title: Safety and Pharmacological Assessment of BXQ-350, a novel biologic Sphingolipid Metabolism Modulator, Combined with Radiotherapy, for Pediatric Diffuse Intrinsic Pontine Glioma and Diffuse Midline Glioma

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Background: Diffuse intrinsic pontine glioma (DIPG) and diffuse midline glioma (DMG) represent aggressive brain tumors in children, leading to a uniformly poor prognosis, as median survival rates seldom surpass two years, even with conventional radiotherapy.

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BXQ-350 is a nanovesicle formulation of Saposin C that induces apoptosis of cancer cells and an anti-tumoral immune response by lowering Sphingosine-1-Phosphate and increasing ceramides concentrations. Saposin C is a human protein encoded by the *Psap* gene and is an allosteric activator of enzymes involved in sphingolipid metabolism. The significance of sphingolipid metabolism in brain cancers has been demonstrated and enzymes involved in sphingolipid metabolism are being investigated as novel therapeutic targets for adult and pediatric brain cancers.

Preliminary studies of BXQ-350 have shown meaningful anti-tumor effects and a favorable safety profile, which supports the need for further clinical investigation, especially in pediatric patients who are at high risk.

Methods: This open label multi-center Phase 1 trial studied concomitant intravenous BXQ-350 and radiotherapy followed by adjuvant BXQ-350 in children and young adults aged 1 to 30 years recently diagnosed with DIPG or DMG. The dose-escalation phase successfully enrolled 11 patients.

Results: The initial results reveal that BXQ-350 is generally well-tolerated at doses reaching 3.2 mg/kg, which is the RP2D. There were a few instances of infusion related reactions that were appropriately managed with standard pre-medications. Comprehensive results, including safety profiles, PK/PD correlations, and response evaluations per RANO criteria, will be shared.

In conclusion, BXQ-350 shows a positive safety profile and holds potential therapeutic promise when used alongside radiotherapy for patients recently diagnosed with DIPG and DMG. These results encourage further research aimed at refining dosing strategies and assessing the long-term effectiveness in this vulnerable group of pediatric patients.