SECTION 2: EXECUTIVE SUMMARY

We propose a phase I/limited efficacy clinical trial investigating repeated administration of MTX110, a soluble form of panobinostat, given via convection-enhanced delivery (CED) to pediatric patients with newly diagnosed diffuse intrinsic pontine glioma (DIPG). We hypothesize this therapy will be safe and well-tolerated and will be efficacious and prolong survival compared to historical controls.

The survival outcomes for pediatric DIPG are dismal. Despite decades of clinical trials and multi-modal therapy, there are essentially no survivors of this devastating disease. The location of DIPG within the central nervous system (CNS) and, more specifically, within the brainstem present unique treatment challenges. The presence of the blood brain barrier limits systemic delivery of therapy from reaching therapeutic levels in the tumor. Further, location within the brainstem prevents surgical resection. Because of this, delivery of drug to DIPG tumors via novel strategies is both warranted and likely necessary to improve outcomes. MTX110 given via CED offers such a strategy. CED uses a catheter system implanted within the tumor that delivers drug directly to the tumor along a pressure gradient. This direct tumor delivery strategy offers drug distribution throughout the tumor and avoids the toxic side effects often seen with oral or intravenous systemic drug delivery.

Panobinostat is a pan-histone deacetylase inhibitor currently approved for treatment of multiple myeloma and having shown pre-clinical efficacy in DIPG cell lines and animal models, regardless of histone status. MTX110 is a novel, soluble formulation of panobinostat that can be given intratumorally to DIPG tumors via CED. Our collaborators have shown in small as well as large animal studies (pig) that CED of MTX110 is feasible and safe. At UCSF, we have treated one patient under compassionate use with 2 CED treatments of MTX110 with no safety concerns. In the UK, several subjects have been treated with MTX110 via CED; one subject has continued on this regimen for several months.

In this study, we aim to investigate the safety and early efficacy of repeated administrations of MTX110 given via CED to children with newly diagnosed DIPG that have completed standard-of-care focal radiotherapy. To complete this investigation, we will carry out a phase I/limited efficacy clinical trial at a minimum of two institutions: University of California, San Francisco (UCSF) and Memorial Sloan Kettering (MSK). The trial will follow an accelerated titration design (ATD) that allows for intra-patient dose escalation and potentially decreases the number of patients treated at sub-efficacious dose levels. The trial includes 5 doses levels, each with increasing volume of drug and therefore, total drug dose. The ATD allows for transition to a standard 3+3 design within each dose level, should toxicity occur. Once the phase I dose escalation is complete and the recommended phase II dose determined, the trial will move into an expansion cohort to assess efficacy based on overall survival at 12 month (OS12). The primary aim of our investigation is to determine safety and toxicity of repeated administration of MTX110 delivered via CED to our target population. This aim will be assessed by monitoring adverse events, laboratory assessments, and physical examinations for each subject that receives at least 1 dose of drug. Descriptive statistics will be used to summarize the toxicity data. The secondary aim will investigate the efficacy of this approach by assessing OS12 and compare to historical controls using Kaplan-Meier survival analyses. The null hypothesis is OS12 of 40%, the alternative hypothesis is OS12 of 60%. An exploratory aim will also use quality of life assessments to evaluate the impact of this treatment approach on the quality of life for our patient population. Descriptive statistics will be used to summarize all quality of life data.

By completing the trial at multiple institutions, our study will increase patient catchment, leverage significant expertise with this novel delivery strategy and avoid barriers in meeting the anticipated accrual goal of 24 patients. The clinical trial will be executed by the Pacific Pediatric Neuro-Oncology Consortium (PNOC). PNOC has extensive experience executing multi-institutional clinical trials and offers the appropriate infrastructure to conduct multi-site studies including a secure HIPAA protected database and central monitoring by the UCSF Cancer Center's data and safety committee. The industry partner, Midatech Pharma, is committed to completing this trial alongside our group and will provide study drug for free.