SCHEMA

This is a multicenter, Phase I, Phase II, and Surgical study of the CX-4945 drug (silmitasertib sodium) for patients with recurrent SHH (Sonic hedgehog) medulloblastoma.

Brain tumors are the most common solid tumor in the pediatric population and the second leading cause of cancer-related death in children. Of these, medulloblastoma (MB) is one of the most common malignant tumors. Around 20% of MBs are driven by over activity of the Hedgehog (Hh) signaling pathway. Typically, children with SHH medulloblastoma undergo surgical resection followed by craniospinal irradiation and intense multi-agent chemotherapy. While many SHH MBs will respond to current therapies, around 30% will recur, often while still undergoing primary therapy. There are no standard options for tumor recurrence and these patients have a dismal prognosis with <5% long-term survival.

CX-4945 is a tetracyclic synthetically derived small molecule carboxylate acid salt that exhibits potent and highly selective inhibition of Casein Kinase 2 (CK2). The biological activity of CX-4945 has been evaluated in both *in vitro* and *in vivo* studies. Key attributes of CX-4945 include potent inhibition of CK2 enzymatic activity and a highly selective kinase profile. The mode of action of CX-4945 is intracellular inhibition of the CK2 enzyme but no other kinases. Evaluation of CX-4945 in cell viability assays revealed broad spectrum anti-proliferative activity in cancer cell lines and direct suppression of DNA repair pathways.

We have previously shown that treating SHH MBs with CX-4945 results in a dose-dependent loss in tumor cell viability in multiple human MB cell lines. These included cell lines with *TP53* mutations, MYC amplification and chromosomal instability, which represent some of the most aggressive forms of MBs. Furthermore, mice harboring flank allografts of vismodegib-resistant MBs had near-complete cessation of tumor growth when treated with CK2 inhibitors. Finally, 43% of mice with cerebellar SHH MB had long-term tumor regression following 30 days of treatment with CX-4945. Therefore, we propose the following studies:

Phase I
The primary objectives of the Phase I part of the study are to find the maximum tolerated dose, recommend a Phase II dose for skeletally-immature children, study the toxicities associated with doses of this drug, define dose limiting toxicities, and characterize the pharmacokinetics in skeletally-immature children.

Skeletally-immature children with refractory or recurrent medulloblastoma of SHH subgroup will be enrolled on the Phase I component of this trial once it is initiated after a safety cohort of 3 subjects are treated on the skeletally-mature cohort. CX-4945 will be administered twice a day on a continuous basis to skeletally-immature children with refractory or recurrent medulloblastoma of the SHH subgroup. Each course will be 28 days (4 weeks) in duration and the first course will be used as the Dose Limiting Toxicity (DLT) observation period. CX-4945 is available in 200 mg capsules. The starting dose will be dose level 1, 600 mg/m^2 BID which corresponds approximately to the BSA-adjusted adult recommended phase 2 dose (RP2D) of 1000 mg. Dose level 0 is provided in case the adult RP2D is not well tolerated in skeletally-immature children.

The CX-4945 dose will be increased in an approximately 30% increment to dose level 2 in the subsequent cohort if dose level 1 is well tolerated. No intrapatient dose escalation will be permitted on the protocol. Only DLTs observed during the dose-finding period of therapy will be used to guide dose escalation. Dose escalation will be governed by the statistical design as described in section 9 of the protocol.

Once the MTD is established, an expansion cohort for pediatric skeletally-immature patients will be opened to better describe the safety, PK and preliminary efficacy of the maximum tolerated dose (MTD) of CX-4945 in this cohort as described on the Statistical Section.

Phase I Dose Escalation Schedule		
Dose Level	**Dose of CX-4945**	**Eligible BSA Range**
Level 0	400 mg/m^2 twice a day	$\geq 0.84 m^2$ - $\leq 2.25 m^2$
Level 1*	600 mg/m^2 twice a day	$\geq 0.60 m^2$ - $\leq 2.00 m^2$
Level 2	800 mg/m^2 twice a day	$\geq 0.63 m^2$ - $\leq 2.00 m^2$
*Starting Dose		

Surgical Study
The primary objective of the surgical part of the study is to characterize the concentrations of CX-4945 in tumor tissue after treatment with CX-4945. The surgical study will be initiated after the first 3 patients in the skeletally-mature cohort are treated for initial assessment of safety. The surgical component will be initiated if no more than 1/3 subjects experience a DLT.

Patients will receive CX-4945 at the established pediatric MTD/adult RP2D for 5-7 days before surgical resection of their tumor, at which time tumor samples will be taken for pharmacokinetic analysis. Skeletally-mature patients with SHH medulloblastoma will be eligible for enrollment as soon as accrual to the surgical study is initiated, and will receive the drug at 1000 mg BID or its BSA adjusted equivalent depending on age and BSA criteria as per Section 6.3

Skeletally-immature children will only be eligible to enroll on the surgical study once the MTD/RP2D is defined in the Phase I part of the study and will receive drug at the established MTD/RP2D dose for this cohort. Following recovery from surgery (no earlier than 2 weeks and no later than 4 weeks), patients will resume CX-4945 for up to 26 cycles if they meet laboratory parameters as defined in Section 3.2.4.10 . Patients who meet the criteria for initiation of treatment for the Phase I expansion cohort or Phase II part of the study post-surgery will contribute to the accrual goals of those components. The only exception to this rule are the phase II and phase I expansion subjects without measureable disease post-surgery, who will still be treated but will not be counted towards the accrual goals since they won't be assessable for objective response. They will however contribute to all other objectives of the study including the primary toxicity objectives.

Phase II
The primary objectives of the Phase II part of the study are to establish the safety and characterize the toxicity of 1000mg BID or its BSA adjusted equivalent of CX-4945 given

continuously in skeletally-mature patients with recurrent SHH medulloblastoma, and to estimate the objective response rate associated with CX-4945 in skeletally-mature patients with recurrent SHH medulloblastoma.

Skeletally-mature children and adults with SHH medulloblastoma will enroll on the Phase II component of this trial. CX-4945 will be administered twice a day at the adult RP2D, 1000 mg BID or at its BSA adjusted equivalent; however, the dose will be given continuously throughout 28-day courses. The patient will remain on CX-4945 for up to 26 cycles. Accrual to this component will be staggered to ensure that the planned continuous dosing as well as the new formulation is safe in this population. More specifically up to 3 patients will be enrolled initially at dose level 1 and will be observed during the first course for any dose limiting toxicities. If no more than 1 patient experiences a DLT then 3 additional patients will be enrolled at dose level 1 and if no more than 1/6 patients experience a DLT then accrual will follow the Phase II design. If more than 1/6 patients experience a DLT during the first course, the dose of CX-4945 will be reduced to 800mg BID or at its BSA adjusted equivalent given on a continuous basis.

Phase II Dose Schedule – Skeletally-Mature Patients		
Dose Level	**Dose of CX-4945**	
	Dosing for patients ≤18 years and BSA ≤ 1.74m^2	**Dosing for patients >18 years or BSA >1.74m^2**
Level 0	400 mg/m^2 twice a day	800 mg twice a day
	Dosing for patients ≤18 years and BSA ≤ 1.50m^2	**Dosing for patients >18 years or BSA> 1.50m^2**
Level 1*	600 mg/m^2 twice a day	1000 mg twice a day
* Starting Dose		