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 0 . 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 measurable 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		

PATIENT SELECTION

All subjects must meet the following inclusion and exclusion criteria. No exceptions will be given. Imaging studies to establish eligibility must be done within three weeks prior to enrollment. All other clinical evaluations to establish eligibility must be done within 7 days prior to enrollment.

Screening Criteria

Tumor

Patient must have a diagnosis of medulloblastoma that is recurrent or progressive. All tumors must have histologic verification either at the time of diagnosis or recurrence.

Adequate Pre-trial Tumor Tissue

Patient must have adequate pre-trial tumor material available for subgrouping.

Prior Therapy

Patient must have received and failed standard therapy for medulloblastoma that included radiation therapy.

Screening Consent
Participant is willing to sign a screening consent. The screening consent is for subgroup testing for all participants and for bone age determination in subjects ≤ 18 years. The screening consent is to be obtained according to institutional guidelines. Assent, when appropriate, will be obtained according to institutional guidelines.

Eligibility Criteria for Enrollment

Phase I Skeletally-Immature
Skeletal maturity
Patient must be skeletally-immature at the time of study enrollment, defined as females with a bone age < 14 years and males with a bone age < 16 years.

Disease Status
Patients who participate in the expansion cohort must have bi-dimensionally measurable disease, defined as at least one lesion that can be accurately measured in at least two dimensions Section 12.2.2. Patients with measurable extraneural disease only are also eligible.

Age
Patient must be ≥ 3 and ≤ 18 years of age at the time of enrollment.

BSA
Patients enrolled on the Phase 1 study must have a BSA as noted below:

Dose level	Minimum	Maximum
0 (400 mg/m^2 BID)	0.84m^2	2.25m^2
1 (600 mg/m^2 BID)	0.60m^2	2.00m^2
2 (800 mg/m^2 BID)	0.63m^2	2.00m^2

Phase II Skeletally-mature
Skeletal Maturity
Patients must be skeletally-mature at the time of study enrollment, defined as females with a bone age ≥ 14 years and males with a bone age ≥ 16 years OR have a chronologic age > 18 years.

Disease Status
Patients must have bi-dimensionally measurable disease, defined as at least one lesion that can be accurately measured in at least two dimensions (Section 12.2.2). Patients with measurable extraneural disease only are also eligible.

Surgical Study
Disease Status
Surgical resection of CNS disease must be clinically indicated.

Age
Patient must be ≥ 3 at the time of enrollment.

Therapy Prior to Resection
Patients must be amenable to receiving CX-4945 for 5-7 days prior to their resection.

Inclusion Criteria – All Phases
Tumor
Patient must have a diagnosis of SHH medulloblastoma that is recurrent or progressive, confirmed histologically and by CLIA-certified methylation-based subgroup testing at Cincinnati Children's Hospital Medical Center (CCHMC); see Section 5.2.1.

Prior Therapy
Patients must have received prior disease directed therapy which included radiation therapy and must have recovered from the acute treatment related toxicities (defined as ≤grade 1 if not otherwise defined in eligibility criteria) prior to entering this study.

Chemotherapy
Patients must have received their last dose of known myelosuppressive anticancer therapy at least 21 days prior to enrollment or at least 42 days if nitrosourea.

Investigational/Biologic Agent
Biologic or investigational agent (anti-neoplastic):
Patient must have recovered from any acute toxicity potentially related to the agent and received their last dose of the investigational or biologic agent ≥ 7 days prior to study enrollment.

- For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.
- Monoclonal Antibodies and agents with known prolonged half-lives: Patient must have recovered from any acute toxicity potentially related to the agent and received their last dose of the agent ≥ 28 days prior to study enrollment.

Radiation
Patients must have had their last fraction of:

- Craniospinal irradiation or total body irradiation or radiation to ≥ 50% of pelvis > 3 months prior to enrollment.
- Focal irradiation > 4 weeks prior to enrollment

Stem Cell Transplant
Patient must be:

- ≥ 6 months since allogeneic stem cell transplant prior to enrollment with no evidence of active graft vs. host disease
- ≥ 3 months since autologous stem cell transplant prior to enrollment

Growth Factors
Patients must be off all colony- forming growth factor(s) for at least 1 week prior to enrollment (e.g. filgrastim, sargramostim or erythropoietin). 2 weeks must have elapsed if patients received long-acting formulations.

Neurologic Status
Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to enrollment, documented by a detailed neurological exam.
Patients with seizure disorders may be enrolled if seizures are well controlled.

Performance Status
Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within two weeks of enrollment must be ≥ 50. Patients who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

Organ Function
Patients must have adequate organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1.0 x 10^9 cells/ L
- Platelets ≥100 x 10^9 cells/ L (unsupported, defined as no platelet transfusion within 7 days)
- Hemoglobin ≥8g/dl (may receive transfusions)
- Total bilirubin ≤1.5 times institutional upper limit of normal (ULN)
- ALT(SGPT) ≤3 x institutional upper limit of normal (ULN)
- AST(SGOT) ≤3 x institutional upper limit of normal (ULN)
- Albumin ≥2 g/dl
- Serum electrolytes (Sodium, Potassium, Chloride) within institutional limits of normal (patients can be on enteral supplementation)
- Serum creatinine based on age/gender as noted below. Patients that do not meet the criteria in but have a 24 hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 mL/min/1.73 m^2 are eligible.

Serum Creatinine for age/gender

Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
3 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4
The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.		

Corticosteroids
Patients who are receiving dexamethasone must be on a stable or decreasing dose for at least 1 week prior to enrollment.

Pregnancy Status
Female patients of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Pregnancy Prevention
Patients of childbearing or child fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study and for 3 months after drug cessation.

Informed Consent
The patient or parent/guardian is able to understand the consent and is willing to sign a written informed consent document according to institutional guidelines.

Exclusion Criteria – All Phases
Breast-feeding
Nursing mothers are excluded from this study. There is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with CX-4945.

Concurrent Illness
- Patients with a history of any other malignancy, except patients with a secondary brain tumor if the patient's prior malignancy has been in remission for at least 5 years from the end of treatment.
- Patients with any of the following gastrointestinal disorders:
  - Difficulty with swallowing or active malabsorption (e.g., short gut) syndrome
  - Uncontrolled diarrhea (excess of 2-3 stools/day above normal frequency)
  - Gastritis, ulcerative colitis, Crohn's disease, or hemorrhagic coloproctitis
  - History of gastric or small bowel surgery involving any extent of gastric or small bowel resection

Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that in the opinion of the investigator would compromise the patient's ability to tolerate protocol therapy, put them at additional risk for toxicity or would interfere with the study procedures or results.

Cardiac
Corrected QT (QTc) interval is >480ms

Concomitant Medications
- Patients who are receiving any other anti-cancer or investigational drug therapy are ineligible.
- Patients on warfarin
- Patients on statins

Prisoners
Prisoners will be excluded from this study.

Inability to participate

Patients who in the opinion of the investigator are unwilling or unable to return for required follow-up visits or obtain follow-up studies required to assess toxicity to therapy or to adhere to drug administration plan, other study procedures, and study restrictions.