# A Phase I study of Savolitinib in Recurrent, Progressive, or Refractory Medulloblastoma, High-Grade Glioma, Diffuse Intrinsic Pontine Glioma, and CNS Tumors Harboring MET Aberrations

## Abstract and Schema

This is a multicenter Phase I trial for children with recurrent, progressive, or refractory primary central nervous system tumors.

Mesenchymal epithelial transition (MET) receptor, also known as c-MET, is an oncogene encoding for a trans-membrane tyrosine kinase receptor activated by the hepatocyte growth factor (HGF). MET has a normal function in organ development during embryogenesis and in tissue homeostasis during adult life.

Abnormal MET activation in cancer correlates with poor prognosis, where aberrantly active MET triggers tumor growth, formation of new blood vessels (angiogenesis) that supply the tumor with nutrients, and cancer spread to other organs (metastasis). Deregulation of HGF/MET signaling pathway is frequently observed in many cancer types of the kidney, liver, stomach, lung, breast, and brain, conferring invasive growth and tendency to progression. Thus, HGF and MET are therapeutic targets and anti HGF/MET agents may represent a potential antitumor strategy.

Savolitinib is a potent and selective small molecule inhibitor of c-MET kinase. It is found to inhibit c-MET kinase at the cellular and enzymatic levels with an $IC_{50}$ between 3–5 nM. In preclinical studies, it demonstrated strong *in vitro* and *in vivo* activity against c-MET kinases and its downstream signaling targets and significantly decrease tumor cell growth.

This is a dose escalation study of savolitinib administered orally once a day to patients with recurrent, progressive, or refractory central nervous system tumors. There are three stages in this study: a dose escalation cohort, PK expansion cohort, and an efficacy expansion cohort. The dose escalation cohort is designed to determine the maximum tolerated dose (MTD)/recommended Phase II dose (RP2D), to evaluate the pharmacokinetics, safety, and preliminary anti-tumor activity of savolitinib. Once the MTD/RP2D is determined, the enrollment for an efficacy expansion cohort will open for patients whose tumors harbor genetic MET activation as determined by testing performed in a CLIA-certified laboratory.

Savolitinib will be given once a day orally for 28 days. Twenty-eight (28) consecutive days will constitute one course. The starting dose will be 150 mg/m$^2$ (Dose Level 1). As of protocol Version 4.0, Dose Level 2 was re-instated and Dose Level 3 was added based on guidance from the drug company that the adult RP2D has been revised to 600 mg/day as the maximum dose. Dosing should be adjusted based on BSA calculated at the beginning of each course for Courses 1–39. Therapy may continue up to 39 courses (approximately 3 years) in the absence of disease progression or unacceptable toxicity.

As of protocol version 7.0 (version date October 6, 2022), the RP2D has been declared as Dose Level 3 (350 mg/m$^2$). In addition, patients may receive extended therapy with savolitinib beyond 39 courses if there is evidence of clinical benefit, in the absence of disease progression or

unacceptable toxicity. Provided that these extended therapy patients continue to meet study criteria, study treatment may continue until all other subjects meet off-treatment criteria.

| Dose Escalation Schedule | | |
|---|---|---|
| **Dose Level** | **Dose of savolitinib ($mg/m^2$ once a day)** | **BSA Requirements** |
| 0 | 75 $mg/m^2$ | $\geq 1.00\ m^2$ |
| 1* | 150 $mg/m^2$ | $\geq 0.55\ m^2$ |
| 2 | 240 $mg/m^2$ | $\geq 0.67\ m^2$ |
| 3 # | 350 $mg/m^2$ | $\geq 0.73\ m^2$ |

* Starting dose

# RP2D. With declaration of the RP2D at Dose Level 3, the upper BSA restriction used for enrollment at Dose Level 3 during the dose finding phase has been lifted. During the expansion phases (PK and efficacy), patients with BSA $\geq 2.10\ m^2$ will receive 600 mg flat dose once a day.

# 1 OBJECTIVES

## 1.1 Primary Objectives

1.1.1 To estimate the maximum tolerated dose (MTD) and recommend a Phase II dose of savolitinib administered orally daily in children with refractory, progressive, or recurrent primary CNS tumors.

1.1.2 To define and describe the toxicities of savolitinib in children with refractory, progressive, or recurrent primary CNS tumors.

1.1.3 To characterize the pharmacokinetics of savolitinib in children with refractory, progressive, or recurrent primary CNS tumors.

## 1.2 Secondary Objectives

1.2.1 To preliminarily define the antitumor activity of savolitinib within the confines of a Phase I study.

1.2.2 To perform a genomic analysis within the confines of a Phase I study to investigate correlation between response to treatment (as measured by objective response or PFS) and the presence of specific genomic alterations (e.g., *MET* or *HGF* amplification, *MET* mutations, or *MET fusion*) and/or specific subgroups of disease.

# 3 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 3 weeks prior to enrollment. All other clinical evaluations to establish eligibility must be done within 7 days prior to enrollment.

## 3.1 Eligibility Criteria for Enrollment

### 3.1.1 Diagnosis

- Patients with a histologically confirmed diagnosis of a primary CNS tumor (medulloblastoma, high-grade glioma, or DIPG) that is recurrent, refractory, or progressive. All tumors must have histologic verification at either the time of diagnosis or recurrence except patients with diffuse intrinsic brain stem tumors. These patients must have radiographic or clinical evidence of progression.

  Patients with a recurrent, progressive, or refractory primary CNS tumor with evidence of genetic activation of the MET pathway, regardless of histology, are also eligible to the Phase I component of this study. Refer to the efficacy expansion cohort section below for MET pathway activation definition and testing information.

  Note: Refractory disease is defined as the presence of persistent abnormality on conventional MRI imaging that is further distinguished by histology (biopsy or sample of lesion) or advanced imaging, OR as determined by the treating physician and discussed with the primary investigator prior to enrollment.

- Efficacy Expansion Cohort
  Patients must have a recurrent, progressive, or refractory primary CNS tumor with evidence of genetic activation of the MET pathway, regardless of histology. Specimens can be from diagnosis or recurrence and there is no time limit from when the specimen was obtained prior to enrollment onto the efficacy expansion cohort. Results from a CLIA-certified laboratory will be accepted for this eligibility criterion. Sites must provide a redacted copy of the local CLIA-certified sequencing laboratory report to the Study Chair via email prior to enrollment. See Section 4.4.2 for details.

  MET pathway activation is defined as:
  - *MET* mutations

  *OR*
  - *MET* or *HGF* amplification

  *OR*
  - *MET* fusion

  Acceptable *MET* mutations are listed in Appendix 15.4.

#### 3.1.2 Available Pre-trial Tumor Tissue

Recurrent or refractory primary malignant CNS tumor patients must have adequate pre-trial frozen or FFPE tumor material available for the required correlative studies (Section 9.1.4 and 9.1.5). If target amounts of tissue or number of slides are not available, the site must obtain Study Chair/Co-Chair approval for adequacy of submitted tumor samples and prioritization of studies to be performed, prior to patient enrollment.

Patients with DIPG who have pre-trial tumor tissue available are requested to submit tissue; however, this is not required for eligibility.

#### 3.1.3 Disease Status

Patients must have evaluable disease to be eligible. Evaluable disease is defined as the presence of at least one lesion that can be measured accurately in at least 2 (two) dimensions.

#### 3.1.4 Age

Patients must be > 5 years and ≤ 21 years of age at the time of study enrollment.

#### 3.1.5 BSA

- Patients enrolled on 75 mg/m$^2$/day (Dose Level 0) must have a BSA ≥ 1.00 m$^2$.
- Patients enrolled on 150 mg/m$^2$/day (Dose Level 1) must have a BSA ≥ 0.55 m$^2$.
- Patients enrolled on 240 mg/m$^2$/day (Dose Level 2) must have a BSA ≥ 0.67 m$^2$.
  Patients enrolled on 350 mg/m$^2$/day (Dose Level 3) must have a BSA ≥ 0.73 m$^2$

#### 3.1.6 Prior Therapy

Patients must have failed prior standard therapy for their tumor. Patients with medulloblastoma must have received radiation therapy in addition to platinum and alkylator-based chemotherapy. Patients with HGG and DIPG must have at least received radiation therapy.

Patients must have recovered from the acute treatment related toxicities (defined as ≤ Grade 1 if not defined in eligibility criteria) of all prior chemotherapy, immunotherapy, radiotherapy, or any other treatment modality prior to entering this study.

##### 3.1.6.1 *Myelosuppressive 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 it included nitrosourea.

##### 3.1.6.2 *Investigational/Biologic Agent*

- Biologic or investigational agent (anti-neoplastic):

Patients 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 antibody treatment and agents with known prolonged half-lives:

Patients 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.

3.1.6.3 *Radiation*

Patients must have had their last fraction of:

- Craniospinal irradiation or total body irradiation or radiation to ≥ 50% of pelvis > 12 weeks prior to enrollment.
- Focal irradiation > 4 weeks prior to enrollment

3.1.6.4 *Stem Cell Transplant*

Patients must be:

- ≥ 24 weeks since allogeneic stem cell transplant prior to enrollment with no evidence of active graft vs. host disease
- ≥ 12 weeks since autologous stem cell transplant prior to enrollment

### 3.1.7 Neurologic Status

- Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to enrollment. A baseline detailed neurological exam should clearly document the neurological status of the patient at the time of enrollment on the study.
- Patients with seizure disorders may be enrolled if seizures are well controlled.
- Patients must be able to swallow whole tablets to be eligible for study enrollment.

### 3.1.8 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.

### 3.1.9 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 prior to enrollment)
- Hemoglobin ≥ 8 g/dL (hemoglobin should be unsupported, i.e., red blood cell transfusions are not allowed within 14 days prior to enrollment)
- Adequate liver function defined as:
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x the upper limit of normal (ULN) with Total Bilirubin ≤ 1x ULN
  OR
  - Total Bilirubin > ULN – ≤ 1.5 x ULN with ALT and AST ≤ 1 x ULN
- Albumin ≥ 2 g/dL

- Serum creatinine based on age/gender as noted in Table 1. Patients that do not meet the criteria in Table 1 but have a 24 hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 mL/min/1.73 $m^2$ are eligible.

**Table 1.**

| Serum Creatinine for age/gender | | |
|---|---|---|
| **Age** | **Maximum Serum Creatinine (mg/dL)** | |
| | **Male** | **Female** |
| 2 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. | | |

- Coagulation parameters: INR < 1.5 x ULN and aPTT < 1.5 x ULN unless patients are receiving therapeutic anti-coagulation which affects these parameters.
- Patients with known tumor thrombus or deep vein thrombosis are eligible if clinically stable on low molecular weight heparin for ≥ 2 weeks.
- Cardiac Function:
  - Mean resting corrected QT interval (QTc Bazett) ≤ 450 msec on screening obtained from 3 electrocardiograms (EKGs)
- Pulmonary Function
  - Oxygen saturation as measured by pulse oximetry is > 93% on room air

#### 3.1.10 Corticosteroids

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

#### 3.1.11 Growth Factors

Patients must be off all colony-stimulating factor(s) (e.g., filgrastim, sargramostim, or erythropoietin) for at least 1 week prior to enrollment. Two (2) weeks must have elapsed if patients received PEG formulations.

#### 3.1.12 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.
- Women of child-bearing potential should use effective contraception from the time of enrollment until 4 weeks after discontinuing study treatment.

- Male study participants should use a condom with female partners of child-bearing potential during the study and for 24 weeks after discontinuing study treatment.
- If the female partner of a male study participant is not using effective contraception, men must use a condom during the study and for 24 weeks after discontinuing study treatment.
- Male study participants should avoid fathering a child and refrain from sperm donation from study start to 24 weeks after discontinuing study treatment.

#### 3.1.13 Informed Consent

Ability to understand and willingness to sign a written informed consent document. Legally authorized representatives may sign and give informed consent on behalf of study participants.

## 3.2 Exclusion Criteria

#### 3.2.1 Pregnancy or Breast-feeding Women

Pregnant women or nursing mothers are excluded from this study. Female patients of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to enrollment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Pregnant women are excluded from this study because there are unknown but potential risks to an unborn baby from savolitinib. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with savolitinib, breastfeeding should be discontinued if the mother is treated with savolitinib.

#### 3.2.2 Concurrent Illness

- Patients with a known serious active infection including, but not limited to human immunodeficiency virus, and tuberculosis.
- Patients with a known active or resolved viral hepatitis infection.
- Patients with any clinically significant unrelated systemic illness 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.
- Patients with uncontrolled hypertension (i.e., a blood pressure (BP) > 95$^{th}$ percentile for age, height, and gender, patients with values above these levels must have their blood pressure controlled with medication prior to starting study drug)
    - The normal blood pressure by height, age, and gender can be assessed by using the NIH Guidelines on the PBTC Member's website (*Protocols* → *Generic Forms and Templates* → *Normal Blood Pressure by Height and Age*)
- Patients with any of the following cardiac diseases
    - Congestive heart failure (New York Heart Association ≥ Grade 2) (see Appendix 15.2)
    - Clinically significant cardiac arrhythmia
    - Mean resting corrected QT interval (QTc Bazett) > 450 msec on screening obtained from 3 electrocardiograms (EKGs) or

- Factors that may increase the risk of QTc prolongation such as chronic hypokalemia not correctable with supplements, congenital or familial long QT syndrome, or
- Family history of unexplained sudden death under 40 years of age in first-degree relatives or
- Any concomitant medication known to prolong the QT interval and cause Torsade de Pointes. Refer to Appendix 15.3 for a partial list of medications that are associated with QTc prolongation and Torsade de Pointes. These drugs must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table 5 of Appendix 15.3.
- Any clinically important abnormalities in rhythm, conduction, or morphology of resting EKG, e.g., complete left bundle branch block, third degree heart block, second degree heart block, PR interval > 250 msec.

- Patients with history of liver cirrhosis of any origin and clinical stage; or history of other serious liver disease or chronic disease with relevant liver involvement, with or without normal LFTs, including but not limited to:
  - Hemochromatosis
  - Alpha -1 Antitrypsin deficiency
  - Autoimmune hepatitis (AIH)
  - Primary sclerosing cholangitis (PSC)
  - Primary biliary cirrhosis (PBC)
  - Biopsy-confirmed Non-Alcoholic Steatohepatitis (NASH) with advanced fibrosis
  - Biopsy-confirmed Alcoholic Steatohepatitis with advanced fibrosis
  - Wilson's disease
  - Hepatocellular carcinoma

* Patients with liver metastases are eligible, provided they meet other eligibility criteria, including liver biochemistry criteria.

- Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen for this trial.

#### 3.2.3 Concurrent Therapy

- Patients who are receiving any other anticancer or investigational drug therapy.

- Patients receiving strong inducers of CYP3A4, strong inhibitors of CYP3A4 or CYP1A2 or CYP3A4 substrates with a narrow therapeutic index within 2 weeks of the first dose of savolitinib (3 weeks for St John's Wort). Strong inducers of CYP3A4 and CYP3A4 substrates which have a narrow therapeutic range or CYP3A4 sensitive substrates should not be used during the trial or used with caution. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. Appendix 15.6 (Patient Drug Information Handout and Wallet Card) should be provided to patients.
- Prior or current treatment with a MET inhibitor (e.g., foretinib, crizotinib, cabozantinib, or onartuzumab).

#### 3.2.4 Herbal preparations/medicines

Patient is currently receiving any of the following herbal preparations or medications and cannot be discontinued 1 week (7 days) prior to enrollment (3 weeks for St. John's wort). These herbal medications include, but are not limited to: Cannabis products, St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

#### 3.2.5 Surgical procedures

Patient has undergone major surgical procedure ≤ 28 days prior to beginning study drug or a minor surgical procedure ≤ 7 days prior to beginning study drug. No waiting is required following port-a-cath placement.

#### 3.2.6 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.

#### 3.2.7 Allergy

Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition.

#### 3.2.8 Prisoners

Prisoners will be excluded from this study.