# DISCLOSURE

## REDACTED PROTOCOL AMENDMENT 3

## CC-4047-BRN-001

## A PHASE 2 CLINICAL STUDY OF POMALIDOMIDE (CC-4047) MONOTHERAPY FOR CHILDREN AND YOUNG ADULTS WITH RECURRENT OR PROGRESSIVE PRIMARY BRAIN TUMORS

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# A PHASE 2 CLINICAL STUDY OF POMALIDOMIDE (CC-4047) MONOTHERAPY FOR CHILDREN AND YOUNG ADULTS WITH RECURRENT OR PROGRESSIVE PRIMARY BRAIN TUMORS

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# PROTOCOL SUMMARY

**Study Title**

A Phase 2 clinical study of pomalidomide (CC-4047) monotherapy for children and young adults with recurrent or progressive primary brain tumors.

**Indication**

Treatment of children and young adults aged 1 to < 21 years with recurrent or progressive primary brain tumors in one of four primary brain tumor types: high-grade glioma, medulloblastoma, ependymoma and diffuse intrinsic pontine glioma (DIPG).

**Objectives**

*Primary:*

- To identify potential tumor type(s) for further development by establishing the preliminary efficacy of pomalidomide in children and young adults with recurrent or progressive primary brain tumors within four distinct tumor types.

*Secondary:*

- To evaluate the safety of pomalidomide within the study populations.
- To estimate the long-term efficacy of pomalidomide treatment.

*Exploratory:*

- To assess the pharmacokinetics (PK) of pomalidomide in children and young adults with recurrent or progressive primary brain tumors.

**Study Design**

This is a Phase 2, multicenter, open-label, parallel-group study that will assess the efficacy, safety and tolerability of pomalidomide in children and young adults aged 1 to < 21 years with recurrent or progressive brain tumors after at least one prior standard therapy.

The study will consist of 4 parallel strata, one for each of the following primary brain tumor types: high-grade glioma, medulloblastoma, ependymoma and DIPG. A Simon's Optimal two-stage study design will be applied to each stratum and enrollment will occur as follows:

- Stage 1: Nine subjects will be enrolled.
- Stage 2: If during Stage 1, ≥ 2 subjects achieve either an objective response (OR; either complete response [CR] or partial response [PR]) within the first 6 cycles of treatment (within 3 cycles for DIPG) or a long-term SD (SD maintained for ≥ 6 cycles [≥ 3 cycles for DIPG]), an additional 11 subjects shall be enrolled; otherwise no additional subjects will be enrolled into that stratum.
- If a total of 5 or more subjects across all 20 subjects in a given stratum (Stage 1 and 2) evaluable for the primary endpoint are observed as having either an OR (either CR or PR) within the first 6 cycles of treatment (within 3 cycles for DIPG) or a long-term SD, pomalidomide will be considered effective in that disease indication.

Subjects who withdraw from either stage for reasons other than PD prior to completing Cycle 1 of study treatment will be replaced. Subjects completing at least one cycle of study therapy but not having a post-baseline disease assessment will be considered a non-responder.

An independent Data Monitoring Committee (DMC) will monitor the study conduct. Details of the DMC structure, composition, and roles/responsibilities will be outlined within a DMC charter described in Section 9.9.2.

The study will be conducted in compliance with International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practices (GCPs) and applicable regulatory requirements.

**Study Population**

Male or female children and young adults aged 1 to < 21 years with recurrent or progressive primary brain tumors after at least one prior standard therapy, in 1 of 4 primary brain tumor types: high-grade glioma, medulloblastoma, ependymoma and DIPG will be enrolled. Up to 80 subjects (36 subjects in Stage 1 and 44 subjects in Stage 2) will be included should all strata enroll the maximum number of subjects and assuming no subjects are replaced. Approximately 80% of subjects across all strata will be < 17 years of age.

**Length of Study**

The study will have the following sequential periods for all subjects: Screening Period, Treatment Period and Follow-up Period. The Screening Period will start from the time of obtaining informed consent/assent and will last no more than 28 days, at which time the Treatment Period will begin (Cycle 1 Day 1, first day of actual study drug administration). Each subject will receive treatment for up to 24 cycles. Once treatment has been discontinued, subjects will enter the Follow-up Period which will continue for up to 5 years from the enrollment of the last subject, unless consent/assent is withdrawn, the subject is lost to follow-up, or death.

The Stage 1 portion of the study is expected to last up to approximately 18 months prior to reaching the decision point. The Stage 2 portion of the study is expected to last up to approximately 27 months should all strata enroll the maximum number of subjects and assuming no subjects are replaced.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

**Study Treatments**

Pomalidomide will be provided by Celgene in 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg gelatin capsules and as an oral suspension. Subjects will be administered pomalidomide on Days 1 to 21, followed by a 7-day rest period, of each 28-day treatment cycle and will continue treatment for up to 24 cycles or until documented PD, withdrawal of consent/assent, treatment becomes intolerable or death. The starting dose will be 2.6 mg/m$^2$/day which has been determined as the maximum tolerated dose (MTD) in the Phase 1 trial conducted by the Pediatric Brain Tumor Consortium (PBTC-043).

**Overview of Key Efficacy Assessments**

Response evaluations will be based on MRI results obtained at each site and will be assessed locally and by an independent central reviewer. Corticosteroid use and clinical assessments (ie, neurologic status) will also be considered when determining overall response. The local Investigator's assessment will be used for subject eligibility and treatment decisions. Efficacy based endpoints incorporating tumor assessments (primary and secondary) will be based on the independent central assessment.

Tumor assessments will be conducted by standard MRI with and without contrast (ie, gadolinium) using three MRI sequences (T1-weighted pre- and post-contrast, T2-weighted, fluid-attenuated inversion recovery [FLAIR]). Overall radiographic objective response will be assessed utilizing the sequence(s) best representative of tumor in the opinion of the neuroradiologist. Subjects who do not meet the criteria for an objective response or disease progression by the end of Cycle 6 (end of Cycle 3 for DIPG subjects) will be considered as having long-term SD.

**Overview of Key Safety Assessments**

Subject safety, including hematology (complete blood count with differential), serum blood chemistry analyses, physical examinations, vital signs, body weight measurement, Lansky/Karnofsky performance status, symptom review for adverse events (AEs), and pregnancy testing for females of childbearing potential/female children of childbearing potential (FCBP/FCCBP) will be assessed.

Second primary malignancies (SPMs) will be monitored as events of interest and should be included as part of the assessment of AEs throughout the course of the study from the time of signing the informed consent form (ICF)/ informed assent form (IAF) until the end of the Long-term Follow-up Period. Investigators are to report any SPM as a serious adverse event (SAE) regardless of causal relationship to study treatment.

**Overview of Pharmacokinetics Assessments**

Pharmacokinetics evaluations will include the following parameters:

- PK endpoints as assessed by population pharmacokinetic analysis.
- Clinically relevant intrinsic/extrinsic covariates of pomalidomide exposure from population PK analysis.

**Statistical Methods**

This study consists of 4 independent strata for each distinct disease indications (high-grade glioma, medulloblastoma, ependymoma and DIPG). The primary endpoint, objective response and long-term stable disease rate (ORSDR), is defined as the total number of subjects achieving either an OR (CR or PR) within the first 6 cycles of treatment (within 3 cycles for DIPG) or a long-term SD (SD maintained for ≥ 6 cycles [≥ 3 cycles for DIPG]) over the total number of subjects evaluable for analysis. An evaluable subject is defined as completing at least one cycle of study therapy or stopping earlier due to a PD. Subjects completing at least one cycle of study therapy but not having a disease assessment (post baseline) will be considered a non-responder.

Under Simon's Optimal two-stage design with a 5% significance level and 90% power, assuming a lower boundary of interest in the response rate of 10% and an upper boundary of interest in the

response rate of 40%, a total of 20 subjects evaluable for the primary endpoint are required per stratum; 9 per stratum (36 total) in Stage 1 and an additional 11 per stratum (44 total) in Stage 2. All efficacy based endpoints will be presented by stratum.

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# 1. INTRODUCTION

## 1.1. Disease Background

### 1.1.1. Pediatric Brain Tumors

Central nervous system (CNS) tumors (including brain and spinal cord) are the most common solid tumors among children and account for up to 25% of all childhood cancer cases (Fleming, 2012). Although overall survival (OS) is estimated to be over 70% at 5 years for the less aggressive tumor types such as pilocytic astrocytoma (PA), medulloblastoma and low-grade gliomas, these rates drop to below 50% for children with aggressive variants such as high-grade gliomas and diffuse intrinsic pontine glioma (DIPG) (Kohler, 2011). Outcomes for children with recurrent/progressive disease are much lower and once a child with a malignant brain tumor has suffered a recurrence, survival outcomes diminish considerably (Dolecek, 2012; Fangusaro, 2009). In the United States, approximately 2500 children are diagnosed annually with brain tumors (Gajjar, 2013). Brain tumors occur most commonly in the first decade of life.

Pediatric brain tumors vary greatly in histology, and there is a great deal of heterogeneity even among specific diagnoses (Fangusaro, 2009). The most common brain tumors fall under the broad category of glioma and account for 53% of tumors in children ages 0 to 14 years and 37% in adolescents ages 15 to 19 years (Dolecek, 2012). Other common pediatric CNS tumors include medulloblastomas and ependymomas.

Gliomas are primary brain tumors of glial origin with different cell lineages. Some of the more common tumors of this class found in children include fibrillary astrocytomas, PA, ependymomas, glioblastoma multiforme, and pleomorphic xanthochromic astrocytomas. Gliomas are classified by the World Health Organization (WHO) into I to IV grades (Kleihues, 2002). Most (80%) of these tumors in children are low grade (grade I and II) including the most frequently occurring pilocytic astrocytoma (WHO grade I) and diffuse astrocytoma (WHO grade II) and approximately 20% are WHO grade III or IV (high-grade gliomas) (Grondin, 2009; Sie, 2014). Survival rates for patients with low grade glioma are reported to be in excess of 90% for OS and 60% to 85% for progression-free survival (PFS) (Heath, 2012).

High-grade gliomas are a heterogeneous group of tumors that can originate from any location in the CNS, but are primarily in the supratentorial brain or in the brainstem. High-grade gliomas account for 3% to 7% of primary brain tumors in children and include anaplastic astrocytomas (WHO grade III), anaplastic pleomorphic xanthochromic astrocytomas (WHO grade III) and glioblastomas (WHO grade IV) with glioblastoma multiforme (GBM) being the most aggressive type (Cage, 2012; Kleihues, 2002; Sie, 2014). High-grade gliomas are particularly difficult to treat due to their infiltrative nature and resistance to radiotherapy and current chemotherapy regimens. Diffuse intrinsic brain stem gliomas which are mainly grade III or IV astrocytomas have the worst prognosis with a median OS of approximately 9 to 12 months, and most patients die from the disease within 2 years (Sie, 2014). They account for 60% to 75% of brainstem tumors and are the major cause of mortality in children with brain tumors occurring between the ages of 5 to 10 years with short time to the onset of symptoms (Walker, 1999). A review of Pediatric Brain Tumor Consortium (PBTC) trials that have included patients with DIPG show a median PFS of 4.5 months from diagnosis. DIPG are generally diagnosed by magnetic resonance imaging (MRI) in the context of a typical clinical presentation (Rao, 2008). Patients with these

types of tumors (high-grade gliomas and DIPG) generally succumb to their disease and the 5-year survival rate remains < 10 to 30% (Johnson, 2012; Gajjar, 2013).

Medulloblastomas, one of the embryonal brain tumor types, are primary brain tumors that occur in the cerebellum of children and young adults. Medulloblastomas are the most common malignant brain tumor in pediatrics and the second most common pediatric brain tumor overall, representing approximately 20% of all pediatric CNS tumors (Fangusaro, 2009). This tumor has the propensity to disseminate along the cerebrospinal fluid (CSF) pathway, and approximately 30% of patients have metastatic disease at diagnosis (Gerber, 2014). Medulloblastomas can be stratified into four distinct histological subtypes that together with age at diagnosis and the metastatic status of the disease, categorize patients into risk groups, which could be used to predict the survival outcome (Ajeawung, 2013). These groups include classical medulloblastoma, large cell/anaplastic medulloblastoma, nodular desmoplastic medulloblastoma, and medulloblastoma with extensive nodularity. Large-cell/anaplastic medulloblastomas are associated with poor prognosis especially in patients less than 3 years of age, while the nodular desmoplastic and medulloblastoma with extensive nodularity, are associated with a better prognosis (Ajeawung, 2013; Heath, 2012). The 5-year survival ranges from 60% (high-risk) to > 80% (standard-risk) (Gajjar, 2013). More recently, medulloblastomas have been molecularly subclassified and further updated risk stratifications defined.

Ependymomas, though relatively rare, are the third most common pediatric brain tumor and represent approximately 8% to 10% of all CNS tumors seen in children. Ependymomas are histologically classified into myxopapillary ependymoma (WHO grade I), grade II ependymoma (cellular, papillary, clear cell, tanycytic) and anaplastic ependymoma (WHO grade III), although there does not appear to be a correlation between grade and clinical outcome (Sie, 2014). As with medulloblastomas, molecular subclassifications of ependymoma have recently been defined. Sixty-five percent of patients with ependymoma are cured after surgery and radiation therapy depending on the degree of resection and histopathology of the tumor (Gajjar, 2013). Surgical resection remains to be a crucial factor in determining long-term disease control and survival. The 5-year survival ranges from 67 to 80% (completely resected tumor) to 22 to 47% (incompletely resected tumor) (Merchant, 2002).

### 1.1.2. Current Treatment for Pediatric Brain Tumors

The treatment approach for pediatric brain tumors in general includes surgical resection, radiotherapy, and chemotherapy. Over the last decades, significant advances in surgery, radiation therapy and chemotherapy have led to better treatment outcomes with around two thirds of patients being long-term survivors (Grondin, 2009; Hummel, 2013; Cage 2012; Gerber, 2014); however, some tumor types remain a challenge.

Surgical resection, with the aim of achieving a gross total resection (GTR), defined as > 90% resection, is usually the initial treatment approach. Surgical resection has shown to be one of the most important prognostic factors, irrespective of age, location, or histology. Surgery alone is curative for some completely resected tumors; however, GTR is not always achievable due to tumor location or involvement of critical structures (Grondin, 2009; Hummel, 2013). Therefore, depending on tumor location, GTR must be balanced against the development of disabling neurologic deficits (Grondin, 2009; Hummel, 2013).

Radiation therapy is a standard adjuvant to surgical resection in children older than 3 years, and has been shown to reduce the risk of recurrence. However, treatment-related toxicity often has a major impact on long-term quality of survival particularly in younger children and those with neurofibromatosis type-1. Radiation is often associated with an increase in long-term morbidities including intellectual impairment, impaired growth, endocrine abnormalities, vascular injury and second malignancies. Because the impact of these factors (especially intellectual impairment) is particularly severe in very young children, irradiation is usually delayed or avoided in younger children (Grondin, 2009; Hummel, 2013; Heath, 2012; Cage 2012).

Many children have disease recurrence or progression, require multiple sequential therapies, and suffer significant treatment-related toxicities. Novel approaches, including noncytotoxic therapies and targeted therapies, offer the potential for improved outcomes in these patients. Most recently, a number of immune modulating therapies have been explored in both pediatric and adult malignancies, including CNS tumors (Grothey, 2012; Gururangan, 2012; Gururangan 2010). The immunomodulatory compounds (IMiDs®) are a group of drugs with structural characteristics similar to thalidomide. These agents, which also include lenalidomide and pomalidomide, have multiple pharmacologic properties and potential antitumor effects including antiangiogenesis, immune-modulation, anti-inflammatory properties and cytotoxic activity. The complete and exact antitumor mechanisms of action are unclear and may be multipronged and disease-dependent (Li, 2010). The immunomodulatory compounds have shown significant efficacy in patients with multiple myeloma (MM) and myelodysplastic syndrome (MDS), and their activity against hematologic and non-hematologic malignancies, autoimmune diseases, and fibrotic disorders are being evaluated due to their tolerability, multiple mechanisms of action and efficacy data in a variety of tumor models and patients.

## 1.2. Pomalyst® (Pomalidomide) Background

Pomalidomide (CC-4047) (Pomalyst) is the third member of a series of drugs known as immunomodulatory compounds, which also include thalidomide and lenalidomide. Pomalidomide was granted accelerated approval by the Food and Drug Administration (FDA) on 08 Feb 2013, for the treatment of adult patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. A new marketing authorization application (MAA) for pomalidomide, later changed to Imnovid, was also approved in the European Union (EU) on 05 Aug 2013 in combination with low-dose dexamethasone for the treatment of adult patients with relapsed and refractory MM who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. Imnovid was first launched in the EU in September 2013. Imnovid has also been approved with the same indication in Iceland and Norway. As of 07 Aug 2017, pomalidomide is approved in 65 countries worldwide: 28 countries in the EU, 3 countries in the European Economic Area (EEA) outside of the EU, and 34 countries outside of the EEA.

A pomalidomide formulation for constitution to oral suspension has been developed for use in clinical trials. The oral suspension is available for use in subjects who are unable to swallow the capsules or at the discretion of the Investigator. The oral suspension of pomalidomide is not approved by any regulatory agency worldwide for any indication.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of pomalidomide.

### 1.2.1. Pomalidomide Mechanism of Action

Pomalidomide has several potential antitumor mechanisms. Its exact antitumor mechanism may be disease-specific, although this is not entirely clear. Pomalidomide has in vitro and in vivo antiproliferative and antineoplastic activity against hematologic B cell malignancies such as MM and non-Hodgkin's lymphoma (NHL). Pomalidomide is directly tumoricidal for MM cells and it also has immunomodulatory activity with direct effects on T and natural killer (NK)-mediated immunity. Pomalidomide's pleiotropic activities in a range of cell types including MM cells and immune effector cells suggests the existence of multiple molecular targets and downstream modulation of multiple molecular pathways. The possibility exists that a common molecular mediator present in various cell types that is proximal to the downstream modulation of multiple signaling pathways is involved in the inhibition of proliferation and induction of apoptosis in tumor cells and in the activation of immune effector cells. One such molecular target is cereblon (encoded by the *CRBN* gene), a protein that forms a ubiquitin E3 ligase complex with DNA damage-binding protein 1 (DDB1), cullin 4 (CUL4) and protein Roc1. Pomalidomide binding to cereblon induces the polyubiquitination of two substrate proteins – Ikaros (encoded by the gene *IKZF1*) and Aiolos (encoded by the gene *IKZF3*) (Gandhi, 2014; Kronke, 2014; Lu, 2014), which are key transcription factors regulating immune cell development and homeostasis (John, 2011). This pomalidomide-induced ubiquitination targets these substrates for destruction by the proteasome resulting in enhanced production of interleukin (IL-2) and other cytokines known to regulate T cell function (Gandhi, 2014; Kronke, 2014; Lu, 2014). In activated human T cells in which cereblon was transiently decreased, IL-2 and tumor necrosis factor-alpha (TNF-α) induction by pomalidomide was markedly reduced. Since IL-2 and TNF-α are important for tumor surveillance by activated T cells, these results indicate that some of the immunomodulatory effects of pomalidomide are mediated via initial binding to cereblon. Therefore, the pomalidomide-induced reduction in Ikaros and Aiolos levels represents one possible mechanism for the pharmacological effects of pomalidomide, although other mechanisms may also play a role.

The activity of pomalidomide is cell type- and context-dependent (Bartlett, 2004; Davies, 2001; Dredge, 2002; Escoubet-Lozach, 2009; Teo, 2005; Xu, 2009). Activities include effects on the cell cycle such as G0/G1 arrest associated with the upregulation of the cyclin-dependent kinase (CDK) inhibitor $p21^{WAF-1}$(Escoubet-Lozach, 2009), downregulation of the expression of interferon regulatory factor 4 (IRF4) in MM cell lines (Li, 2011), and modulation of Rho guanosine-5'-triphosphate binding and hydrolyzing enzymes, which are critical for actin hyperpolymerization and immune synapse formation (Xu, 2009).

It has become clear that inflammation plays an important role in the pathogenesis of many diseases, including cancer. Pomalidomide has numerous anti-inflammatory effects, including enhancing T cell and NK cell-mediated immunity and inhibition of pro-inflammatory cytokine production (eg, TNF- $\alpha$ and IL-6) by peripheral blood mononuclear cells. Pomalidomide augments T helper cell type 1 (Th1) (cell-mediated), and inhibits Th2 (humoral-mediated) T cell responses. Pomalidomide enhances T cell proliferation and production of the Th1 cytokines IL-2

and interferon-gamma (IFN-γ) by freshly isolated human peripheral T cells in vitro (Reddy, 2008; Corral, 1999).

Pomalidomide also inhibits angiogenesis by blocking the migration and adhesion of endothelial cells. Angiogenesis plays an important role in the growth and progression of hematopoietic and solid tumors and depends on proper activation, proliferation, adhesion, migration, and maturation of endothelial cells in order to form functional vessels. In vitro, pomalidomide inhibited umbilical cord microvessel formation as well as the vascular endothelial growth factor (VEGF)-induced endothelial cord formation (Payvandi, 2005; Lu, 2009). Furthermore, pomalidomide inhibited endothelial cell invasion (through fibronectin-coated membranes) toward VEGF, basic fibroblast growth factor (β-FGF), transforming growth factor alpha (TGF-α), and TNF-α, suggesting that the pomalidomide antiangiogenic activity is in part due to inhibition of endothelial cell migration (Dredge, 2002).

### 1.2.2. Pharmacokinetics and Pharmacodynamics of Pomalidomide

#### 1.2.2.1. Pharmacokinetics in Adults

Pomalidomide has been evaluated with respect to its absorption, distribution, metabolism and elimination characteristics. Pomalidomide was absorbed in healthy subjects under fasting conditions at single, orally administered doses of 0.5 mg to 50 mg with a maximum plasma concentration ($C_{max}$) at a median time to maximum plasma concentration ($T_{max}$) of approximately 3 hours postdose at clinically relevant doses. The systemic exposure of single dose pomalidomide as determined from the area under the plasma concentration-time curve ($AUC_{0-tz}$ and $AUC_{0-\infty}$) increased in an approximately dose-proportional manner, whereas $C_{max}$ increased in a proportional manner over 0.5 mg to 2 mg and in a less than dose proportional manner over the 1 mg to 50 mg dose range. Exploratory analysis suggests absorption rate decreases at doses greater than 10 mg. Multiple dose exposure over the 0.5 mg to 2 mg dose range was approximately dose proportional, with pomalidomide reaching steady-state by Day 3.

Pomalidomide was evaluated for potential food effect interaction as a capsule formulation that was used during development but not commercialized. The effect of food, such as a high-fat meal, was evaluated with that formulation in a single dose study in healthy subjects according to the appropriate FDA Guidance "Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies" December 2002. The median $T_{max}$ observed in the fed state was approximately 3 hours later than that observed in the fasted state. Exposure to pomalidomide was slightly decreased with food. The mean ratio estimates for $C_{max}$ and $AUC_{0-t}$ were 75.6% and 91.5% in the fed state relative to the fasted state, respectively. The mean plasma terminal elimination half-life ($t_{1/2}$) of pomalidomide was not affected by food administration. In summary, a high-fat meal decreased the rate of absorption but had minimal effect on overall extent of absorption; therefore, pomalidomide can be administered without regard to food intake.

The distribution of pomalidomide to brain has been characterized in mice and rats. An oral administration of pomalidomide to mice and rats resulted in pomalidomide brain to plasma/blood ratios ranging from 0.39 to 0.49, indicating adequate pomalidomide distribution into the brain (Report AP1505/AP1506). The distribution of pomalidomide has been characterized in humans with a mean volume of distribution (Vd/F) (coefficient of variation %) of pomalidomide in healthy subjects after a single dose ranging from 74 L (20%) to 138 L (30%) across a dose range

of 1 mg to 10 mg daily. Pomalidomide distributes into semen, with a geometric mean concentration of 16.4 ng/mL at 4 hours postdose after 4 daily doses of 2 mg. This value was approximately 67% of pomalidomide plasma concentration observed at the same time point on Day 5 (ie, 24.5 ng/mL). In vitro data indicate that pomalidomide protein binding in human plasma was low to moderate (15.8% for R-enantiomer, 42.2% for S-enantiomer) and the binding was concentration independent.

The metabolism of pomalidomide has been evaluated both preclinically and in healthy human subjects. In vitro, pomalidomide (up to 30 μM) did not inhibit cytochrome P450 (CYP) 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4/5 activities in human liver microsomes. Treatment of cultured human hepatocytes with up to 3 μM pomalidomide twice daily for 3 consecutive days had little inductive effect on the enzymatic activities of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. In transporter-expressing cells, pomalidomide had little to no inhibitory effects on P-glycoprotein, breast cancer resistant protein, organic anion transporter (OAT)1, OAT3, OATP1B1, OATP1B3 or organic cation transporter (OCT)2. When evaluated in the human absorption, distribution, metabolism, and excretion study, eight metabolites were detected in plasma, each at exposures < 10% of the plasma pomalidomide. The metabolites observed were formed primarily via hydroxylation with subsequent glucuronidation or hydrolysis of the parent compound. CYP-dependent metabolites accounted for approximately 43% of the excreted radioactivity, while non-CYP-dependent hydrolytic metabolites accounted for 25%, and excretion of unchanged pomalidomide accounted for 10%.

The elimination of pomalidomide occurs predominantly through renal excretion (~73% of the administered dose), with < 3% of the administered dose excreted in urine as unchanged pomalidomide across all dose levels.

Pomalidomide has been evaluated for potential drug interaction effects in healthy subjects. Pomalidomide is partly metabolized by CYP1A2 and CYP3A4/5 and is also a substrate for P- glycoprotein. In CC-4047-CP-008 study, co-administration of pomalidomide with the strong CYP3A4/5 and P-glycoprotein inhibitor "ketoconazole", or the strong CYP3A4/5 inducer "carbamazepine", had no clinically relevant effect on exposure to pomalidomide. Co-administration of a strong CYP1A2 inhibitor (fluvoxamine) with pomalidomide in the presence of a strong CYP3A4 inhibitor (ketoconazole) approximately doubled the mean exposure to pomalidomide compared to pomalidomide with ketoconazole alone. In this study, co-administration with moderate to strong CYP1A2 inhibitors (eg, ciprofloxacin, enoxacin, fluvoxamine, etc) are not permitted due to the potential drug interactions with pomalidomide. Subjects taking a known moderate to strong CYP1A2 inhibitor are excluded.

#### 1.2.2.2. Pharmacokinetics in Pediatric Populations

A Phase 1, dose escalation trial of pomalidomide in pediatric subjects with recurrent, refractory or progressive CNS tumors performed within the PBTC (PBTC-043) is currently ongoing. To date, pharmacokinetic (PK) data have been collected from 17 pediatric subjects. In general, pomalidomide exposures for both AUC and $C_{max}$ appeared to increase in a dose dependent manner from 1.9 mg/m$^2$ to 3.4 mg/m$^2$. Mild to moderate between-subject variability was observed for both AUC and $C_{max}$ in pediatric subjects. Preliminary PK data analyses suggest that the clearances (CL/F) in pediatric subjects correlate with body surface area, body weight, and age.

### 1.2.3. Adult Clinical Trials of Pomalidomide

Pomalidomide has been studied in adult hematologic malignancies and solid tumors as part of Celgene-sponsored and Investigator initiated trials (IITs). The majority of the current safety and efficacy profile has been generated on studies in the approved indication, relapsed and/or refractory MM. As of 07 Feb 2016, approximately 41,000 patients are estimated to have received 1 or more doses of pomalidomide ranging from 0.5 mg to 50 mg in clinical studies and the commercial setting.

Pomalidomide was well tolerated in Phase 1 studies in healthy volunteers at doses of up to 50 mg. All AEs were considered by the Investigators to be mild or moderate in severity and there was no discernible trend in type of AE. Overall, the healthy subject studies did not result in any new safety signals.

Pomalidomide was generally well tolerated in solid tumor studies, including studies in small cell lung cancer, castration-resistant prostate cancer, soft tissue sarcomas, pancreatic cancer and advanced solid tumors, with no significant safety findings (Amato, 2011; Ellis, 2013).

The most frequently occurring treatment emergent adverse events (TEAEs) across clinical studies (in hematologic and solid tumors) were fatigue, anemia, and neutropenia, except for study in patients with myelofibrosis (MF), where the most frequently reported TEAE in pomalidomide-treated subjects was peripheral edema. Other less frequently occurring TEAEs observed in the majority of studies were constipation, nausea and dyspnea. The most frequently occurring Grade 3 or 4 TEAEs across studies were neutropenia, thrombocytopenia, and anemia. As shown in a Phase 1 study (Richardson, 2013), the incidence of Grade 3 or 4 neutropenia in subjects with relapsed and refractory MM appeared to have a relationship to the dose of pomalidomide. In this study, Grade 4 neutropenia was managed by dose reductions and/or interruptions and growth factor support (granulocyte colony-stimulating factor [G-CSF] treatment).

Across most of the completed studies of efficacy and safety, serious adverse events (SAEs) were reported by approximately 40% to 70% of subjects. Infections, particularly pneumonia, were the most frequently reported SAE in subjects across studies

Overall pomalidomide was tolerated at doses of up to 50 mg in a Phase 1 single-dose study, well tolerated when orally administered at doses of 1 mg and 2 mg daily in subjects with prostate cancer, up to 2 mg daily, 5 mg every other day, or 4 mg/day for 21 of 28 days in a multiple-dose study in subjects with relapsed or refractory MM, and at 0.5 mg daily in subjects with MF. Data from the ongoing studies are consistent with the completed studies and demonstrate that pomalidomide has an acceptable safety profile in the intended subject populations studied to date.

### 1.2.4. Pediatric Clinical Trials of Pomalidomide

In the Phase 1 dose escalation trial of pomalidomide monotherapy in children with recurrent, progressive or refractory CNS tumors (PBTC-043), subjects were treated at doses levels of 1.9, 2.6 and 3.4 mg/m$^2$/day on Days 1 through 21 of a 28-day cycle. The maximum tolerated dose (MTD) of 2.6 mg/m$^2$/day was reached with 3 subjects experiencing a total of 4 dose limiting toxicities (DLTs) at the 3.4 mg/m$^2$/day dose level. These DLTs included Grade 4

absolute neutrophil count (ANC) decrease ≥ 5 days during treatment rest period, Grade 3 diarrhea, Grade 3 platelet count decrease and Grade 3 lung infection.

The main toxicity (most commonly reported Grade 3/4 AE) associated with pomalidomide treatment was myelosuppression (decreased neutrophils, platelets, lymphocytes and anemia). Myelosuppression is a known adverse effect of pomalidomide treatment and can be managed effectively with supportive care. Myelosuppression was also the main toxicity observed in the Phase 1 studies of lenalidomide in children with CNS tumors (Warren, 2011; Berg, 2011). The majority of cases observed during the PTBC-043 study resolved without sequelae.

Per protocol, expansion cohorts were initiated with further enrollment at the MTD stratified based on age (< 12 years vs. ≥ 12 years) and steroid use (not on steroids [or on physiologic doses alone] vs. those taking therapeutic doses of steroids). No excessive toxicities or unexpected safety concerns have further been identified. One subject in the expansion cohort experienced a DLT of Grade 4 platelet count decrease; however, per protocol, the criteria for modifying the already identified MTD was not reached. This study is currently ongoing.

## 1.3. Rationale

### 1.3.1. Study Rationale and Purpose

Although the prognosis for pediatric patients with brain tumors has improved over the last few decades with diverse intensive therapeutic modalities such as neurosurgery, chemotherapy and radiation, many brain tumors remain difficult to treat and are associated with a poor prognosis. Overall, brain tumors are still the leading cause of cancer morbidity and mortality among children. Therefore, alternative therapeutic strategies are desperately needed and pomalidomide is considered to be well suited to treat pediatric brain tumors given its multi-modal mechanism of action and seeming ability to cross the blood-brain barrier.

**Pomalidomide can cross the blood-brain barrier**

Central nervous system tumors may have a specialized immunobiology that allows evasion of immune clearance and promotion of tumor growth, and the tissue milieu within which a CNS tumor grows may be especially important in supporting this immunobiology. This immunology of the CNS excludes or attenuates effective immune responses in malignancies, which may contribute to resistance to standard radiation and chemotherapy. The presence of the blood-brain barrier limits the CNS penetration of many chemotherapeutic agents and although it does not block lymphocytes or myeloid cells from migrating to sites of inflammation or tumor growth, these components of the immune system are ineffective in producing an immune response thus maintaining the "immune privilege" status of the CNS (Johnson, 2012). Pomalidomide has been shown to have moderate CNS penetration in murine models of CNS lymphoma with significant therapeutic activity and a major impact on the CNS tumor microenvironment (Li, 2013). Approximately 39% of systemically administered pomalidomide penetrated the CNS. These data indicate that pomalidomide may be suitable for treatment of primary CNS tumors and brain metastases. Consistent with this, there are clinical reports in adults demonstrating pomalidomide's effectiveness against myeloma meningitis and CNS myelomatosis, again suggesting adequate CNS penetration and efficacy within the CNS (Gertz, 2013; Mussetti, 2013).

**Pomalidomide has anti-angiogenic properties**

Angiogenesis plays a role in tumor growth and metastases in CNS tumors (Sie, 2014). Pediatric brain tumors have previously been shown to possess significant neovascularization and can produce potent angiogenic factors (Ozer, 2004; Sie, 2014). Many of the common histologies among pediatric brain tumors, such as embryonal tumors (medulloblastoma, atypical teratoid rhabdoid tumor [ATRT], low grade-gliomas, and high-grade gliomas exhibit significant angiogenic activity. Similar to other tumors, pediatric brain tumors secrete cytokines with varying angiogenic properties, such as acidic and basic fibroblastic growth factor (α, β-FGF), angiogenin, TNF-α, and VEGF, which assist in cell proliferation, metastases and survival. Alternatively, tumor cells can release angiogenic peptides through the production of proteases and the subsequent breakdown of the extracellular matrix where some cytokines are stored (ie, β-FGF). Angiogenesis can also be induced indirectly through the recruitment of inflammatory cells (particularly macrophages) and their subsequent release of angiogenic cytokines (ie, TNF-α, β-FGF) (Jain, 2007). Pomalidomide has demonstrated antiangiogenic activity (Section 1.2.1), which makes it an ideal candidate for treating pediatric brain tumors.

**Lenalidomide (related agent) is well tolerated in children with brain and solid tumors**

A pediatric Phase 1 study of lenalidomide was performed within the Children's Oncology Group (COG) in subjects with relapsed or refractory solid tumors or MDS (ADVL0319) (Berg, 2011). The primary objectives were to determine the MTD or the recommended Phase 2 dose (RP2D) for children with refractory solid tumors and describe the toxicities in this population. Forty-nine subjects treated at doses up to 70 mg/m$^2$/day x 21 days followed by a 7-day rest were evaluated. Although 6 episodes of DLTs were observed, the DLTs were sporadic and not clearly associated with dose. These DLTs included Grade 3 hypercalcemia, Grade 3 hypophosphatemia, Grade 3 hypokalemia, Grade 4 neutropenia, Grade 3 somnolence, and Grade 3 urticaria occurring at doses ranging from 15 mg/m$^2$ to 55 mg/m$^2$. The MTD was not reached. No objective responses were observed; however, there was evidence of immunomodulatory activity of lenalidomide with a significant increase in serum IL-2, IL-15, granulocyte-macrophage colony-stimulating factor, NK cells, NK cytotoxicity, and lymphokine activated killer cytotoxicity, and a significant decrease in CD4+/CD25+ regulatory T cells.

A Phase 1 trial of lenalidomide in pediatric subjects with recurrent, refractory or progressive CNS tumors was performed within the PBTC (PBTC-018) (Warren, 2011). Fifty-one subjects were enrolled; 44 subjects were evaluable for toxicity and response. Subjects were treated at doses levels of 15, 20, 25, 32, 40, 52, 68, 88, 101 and 116 mg/m$^2$/day for Days 1 through 21 of a 28-day cycle. A MTD was not reached and lenalidomide was relatively well tolerated. Two DLTs were reported with an unclear association with lenalidomide. One subject treated at the 20 mg/m$^2$/day dose level experienced a cardiac DLT with a presumed myocardial infarct and elevated troponin; however, this subject was subsequently found to have had multiple risk factors for thromboembolism. One subject at a dose level 68 mg/m$^2$/day had dose-limiting fatigue associated with concurrent disease progression. Twenty-three subjects representing all dose levels received 6 or more cycles of treatment and 9 subjects have received 12 or more cycles.

In the PBTC-018 study (Warren, 2011), myelosuppression was the primary toxicity and occurred sporadically. No subject had Grade 4 myelosuppression during Cycle 1. Myelosuppression for subjects treated for ≥ 6 cycles was also sporadic and not clearly associated with dose although data at the higher dose levels (≥ 68 mg/m$^2$/day) showed a possible trend toward more frequent

episodes of Grades 3 and 4 myelosuppression. Other common toxicities included fatigue (30%), gastrointestinal symptoms including nausea (10%), emesis (4%), diarrhea (16%), and constipation (8%), as well as rash (14%) and muscle cramping (10%). In this study, it was unclear if responses were dose-related. Objective responses (two partial responses) were reported; one in a subject diagnosed with PA treated with 88 mg/m$^2$/day for 18 cycles and another subject diagnosed with optic pathway glioma treated with 116 mg/m$^2$/day for 11 cycles. Long-term stable disease (SD; SD sustained for ≥ 6 cycles), particularly in patients with low grade glioma, was observed in 52% of patients. Of note, the 12-month PFS rate for patients with low grade glioma was 67%. Results from PK analysis show that the lenalidomide AUC and $C_{max}$ increased with dosage over the range studied. The median lenalidomide plasma $t_{1/2}$ and apparent oral clearance were 2.5 hours (range, 0.9 to 4.2 hours) and 11.4 L/h/m$^2$ (range, 5.1 to 33.9 L/h/m$^2$), respectively.

Based on the apparent activity profile of lenalidomide in children with low-grade gliomas enrolled in the pediatric Phase 1 study (PBTC-018), a Phase 2 trial (ACNS1022) of lenalidomide monotherapy in PA and optic pathway gliomas was initiated. This study compares low dose (20 mg/m$^2$/day) with high dose (115 mg/m$^2$/day) lenalidomide. A planned interim analysis for futility and efficacy, evaluating both objective responses and PFS, was performed after the first 20 subjects were enrolled in each arm. Both arms met the criteria for continued accrual and this study is currently ongoing.

**Pomalidomide is a more potent antiproliferative and immunomodulating agent than lenalidomide**

Although there is overlap between pomalidomide and lenalidomide in terms of pharmacologic effects, there are data suggesting that they may also have different targets. Notably, pomalidomide has demonstrated activity in lenalidomide-resistant cell lines and in adult patients with MM refractory to lenalidomide treatment, suggesting unique targets and properties between these two agents (Li, 2010; Lopez-Girona, 2012; Cooney, 2012; Schey, 2011; Richardson, 2014). In addition, pomalidomide exhibits greater potency than lenalidomide in anti-proliferative effects, augmentation of CD4$^+$ and CD8$^+$ T cell proliferation, Th1 cytokine production and NK T cell activation (Corral, 1999; Muller, 1999). These differences allow the administration of pomalidomide at relatively lower doses compared with lenalidomide in adult patients with MM and may allow for lower therapeutic doses in pediatric patients as well.

### 1.3.2. Rationale for the Study Design

This is a Phase 2, multicenter, open-label, parallel-group study that will assess the efficacy, safety and tolerability of pomalidomide in children and young adults with recurrent or progressive brain tumors.

The proposed age groups to be studied are subjects 1 to < 21 years of age. Subjects < 1 years of age are more likely to be undergoing first line therapy for their brain tumors, are less likely to have already experienced recurrence or progression of disease, have a rapidly developing immune system and tolerability of pomalidomide is unknown. The upper age limit was selected because the treatment options and number of clinical trials for young adult subjects between 18-21 years of age are limited due to the significant differences in histologic subtypes and biology of brain tumors between these subjects and younger children or adults (Bleyer, 2004). In the absence of treatment options tailored for adolescents and young adults with brain cancer,

treatments used in younger children tend to have improved efficacy when treated with pediatric based regimens rather than those designed for adults.

A Simon's Optimal two-stage study design will be applied across the strata (Section 3.1), conducted in parallel. The design was chosen to limit subject's exposure to pomalidomide in each group prior to confirmation of preliminary efficacy and enrollment of additional subjects into that tumor type cohort. Objective response (OR; either complete response [CR] or partial response [PR]) rate (ORR) and long-term SD (SD maintained for ≥ 6 cycles [≥ 3 cycles for DIPG]) rate will be evaluated as a combined endpoint for defining antitumor activity in each stage. Long-term SD was chosen to be included since it has been reported to correlate with OS (Warren, 2013).

This study design will provide further information on the antitumor activity and safety of pomalidomide in children and young adults and establish if any of these brain tumors are sensitive to pomalidomide and should be further explored.

### 1.3.3. Rationale for Dose, Schedule and Regimen Selection

In the Phase 1 study conducted by the PBTC (PTBC-043), pomalidomide dose was escalated to establish the MTD in children with histologically confirmed diagnosis of recurrent, progressive or refractory CNS tumors. Subjects were treated at dose levels of 1.9, 2.6 and 3.4 mg/m$^2$/day on Days 1 through 21 of a 28-day cycle. A MTD of 2.6 mg/m$^2$/day was reached with three subjects each experiencing one DLT at the 3.4 mg/m$^2$/day dose level. The MTD of 2.6 mg/m$^2$/day is comparable to the FDA-approved adult dose (4 mg/day) of pomalidomide taken orally on Days 1-21 of a 28-day cycle, assuming an average adult body surface area (BSA) of 1.7 m$^2$ (4 mg/1.7 m$^2$ = 2.35 mg/m$^2$).

The starting dose in this Phase 2 study will be 2.6 mg/m$^2$/day on Days 1 to 21 of a 28-day cycle. Four consecutive weeks will constitute one cycle and subsequent cycles will immediately follow as long as criteria to continue pomalidomide therapy are met. A cycle may be repeated every 28 days, for up to 24 cycles or until documented progressive disease (PD), withdrawal of consent/assent, treatment becomes intolerable or death, whichever comes first.

Dosing will be based on the subject's actual BSA calculated at the beginning of each cycle of therapy.

# 2. STUDY OBJECTIVES AND ENDPOINTS

**Table 1: Study Objectives**

| **Primary Objective(s)** |
|---|
| The primary objective of the study is:<br>• To identify potential tumor type(s) for further development by establishing the preliminary efficacy of pomalidomide in children and young adults with recurrent or progressive primary brain tumors within four distinct tumor types. |
| **Secondary Objective(s)** |
| The secondary objectives are:<br>• To evaluate the safety (type and rate of treatment-related toxicity) of pomalidomide within the study populations.<br>• To estimate the long-term efficacy of pomalidomide treatment. |
| **Exploratory Objective(s)** |
| The exploratory objectives are:<br>• To assess the PK of pomalidomide in children and young adults with recurrent or progressive primary brain tumors. |

PK= Pharmacokinetics.

**Table 2: Study Endpoints**

| Endpoint | Name | Description | Timeframe |
|---|---|---|---|
| Primary | Objective response and long-term stable disease rate | Total number of subjects achieving an OR (either CR or PR) or a long-term SD under study treatment, among total subjects evaluable for analysis per stratum | Cycle 1, Day 1 to completion of Cycle 6 (completion of Cycle 3 for DIPG) |
| Secondary | Objective response rate | Total number of subjects achieving an OR (either CR or PR) under study treatment, among total subjects evaluable for analysis per stratum | Cycle 1, Day 1 of Treatment Period to end of Follow-up Period |
| | Long-term stable disease rate | Total number of subjects achieving a long-term SD under study treatment, among total subjects evaluable for analysis per stratum | Cycle 1, Day 1 to completion of Cycle 6 (completion of Cycle 3 for DIPG) |
| | Duration of response | The time from first achievement of CR or PR under study treatment, whichever occurs first, until first documentation of progressive disease (PD) or death of any cause | Cycle 1, Day 1 of Treatment Period to end of Follow-up Period |
| | Progression-free survival | The time from enrollment until first documentation of PD and/or death of any cause | Cycle 1, Day 1 of Treatment Period to end of Follow-up Period |
| | Overall Survival | The time from enrollment until death of any cause | Cycle 1, Day 1 of Treatment Period to end of Follow-up Period |
| | Safety | Type, frequency, and severity of AEs and relationship to study drug | Signing of informed consent form (ICF)/informed assent form (IAF) until the end of Follow-up Period |
| Exploratory | Pomalidomide PK | Plasma PK parameters (eg, pomalidomide apparent clearance and volume of distribution) | Cycle 1: Days 8 and 15 |

AEs = adverse events; CR= complete response; DIPG = diffuse intrinsic pontine glioma; IAF = informed assent form; ICF = informed consent form; OR = objective response; PD = progressive disease; PK = pharmacokinetic; PR= partial response; SD = stable disease.

# 3. OVERALL STUDY DESIGN

## 3.1. Study Design

This is a Phase 2 multi-center, open-label, parallel-group study that will assess the efficacy, safety and tolerability of pomalidomide in children and young adults aged 1 to < 21 years with recurrent or progressive primary brain tumors after at least one prior standard therapy.

The study will consist of 4 parallel strata, one for each of the following primary brain tumor types: high-grade glioma, medulloblastoma, ependymoma and DIPG. A Simon's Optimal two-stage study design will be applied to each stratum and enrollment will occur as follows:

- Stage 1: Nine subjects will be enrolled.
- Stage 2: If during Stage 1, ≥ 2 subjects achieves either an OR (either CR or PR) within the first 6 cycles of treatment (within first 3 cycles for DIPG), or a long-term SD, an additional 11 subjects shall be enrolled; otherwise no additional subjects will be enrolled into that stratum.
- If a total of 5 or more subjects across all 20 subjects in a given stratum (Stage 1 and 2) evaluable for the primary endpoint are observed as having either an OR (either CR or PR) within the first 6 cycles of treatment (within first 3 cycles for DIPG) or a long-term SD, pomalidomide will be considered effective in that disease indication.

Subjects who withdraw from either stage for reasons other than PD prior to completing Cycle 1 of study treatment will be replaced. Subjects completing at least one cycle of study therapy but not having at least one post-baseline disease assessment will be considered a non-responder.

The study will have the following sequential periods for all subjects (Figure 2): Screening Period (Section 6.1), Treatment Period (Section 6.2) and Follow-up Period (Section 6.3). Upon enrollment, subjects will receive oral pomalidomide for the first 21 days, followed by a 7-day rest period, of each 28-day treatment cycle for up to 24 cycles or until documented PD, withdrawal of consent/assent, treatment becomes intolerable or death, whichever occurs first.

Radiographic response (brain and spine) will be assessed by MRI with and without contrast (ie, gadolinium). Brain MRI assessments will be conducted during screening (within 21 days prior to first dose of study treatment) and then on Day 1 of Cycles 3, 5, 7, 10, 13, 16, 19, 22 (or within 7 days prior to dosing), after completion of Cycle 24 (or within 7 days prior) and as clinically indicated. **Note:** For DIPG subjects only, post-baseline brain MRI assessments will be performed on Day 1 of Cycles 4, 7, 10, 13, 16, 19, 22 (or within 7 days prior to dosing), after completion of Cycle 24 (or within 7 days prior) and as clinically indicated.

Spine MRI will be also performed during screening (within 21 days prior to first dose of study treatment) for all subjects. If no spinal or leptomeningeal disease is present at screening, subsequent spine MRIs will be obtained on Day 1 of Cycles 7, 13, 19 (or within 7 days prior to dosing) after completion of Cycle 24 (or within 7 days prior) and as clinically indicated. If there is spinal or leptomeningeal disease present at screening/baseline, spine MRIs will be obtained at the same time points as the brain MRI as specified above.

A response assessment should also be performed at EOT visit if the subject has discontinued for reasons other than progression of disease and it has been more than 8 weeks since their most recent scan/response assessment.

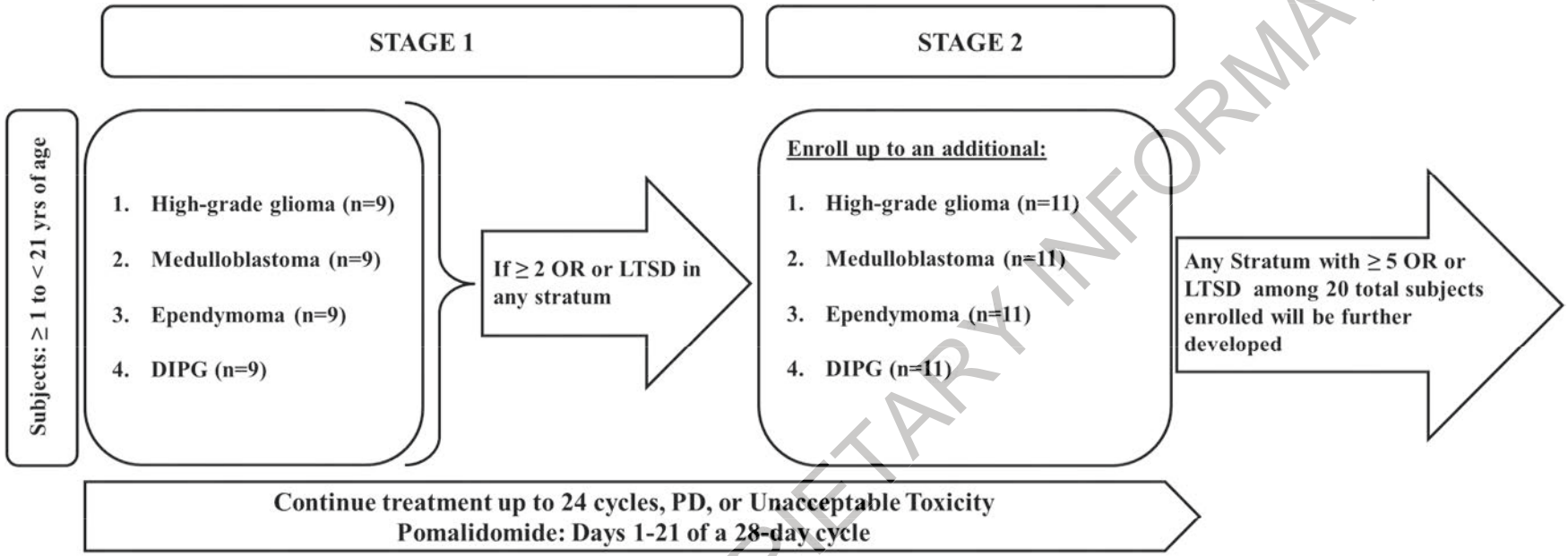
Response evaluations will be performed locally and by independent central reviewer according to criteria detailed in Section 6.4.1.

Subjects who discontinue treatment will enter a Follow-up Period which will continue every 3 months (± 14 days) for up to 5 years from enrollment of the last subject, unless consent/assent is withdrawn, the subject is lost to follow-up or dies. Subjects will be followed by phone or clinic visits for emergence of second primary malignancies (SPMs) (regardless of causal relationship), drug-related SAEs, survival status, and start of any new anticancer therapies. Additionally, subjects who discontinue treatment prior to progression will be followed with MRI tumor response disease assessments every 6 months from treatment discontinuation for the first year off treatment, then annually thereafter, until disease progression or until another anticancer therapy is started, whichever comes first.

An external data monitoring committee (DMC) (Section 9.9.2) with multidisciplinary representation will evaluate activity of the study treatment and safety data periodically to monitor benefit-to-risk of this protocol. The function of the DMC is to monitor the safety and activity of the study treatment and to provide recommendations about the study continuation, as appropriate. Details of the DMC structure, composition, and roles/responsibilities will be outlined within a DMC charter.

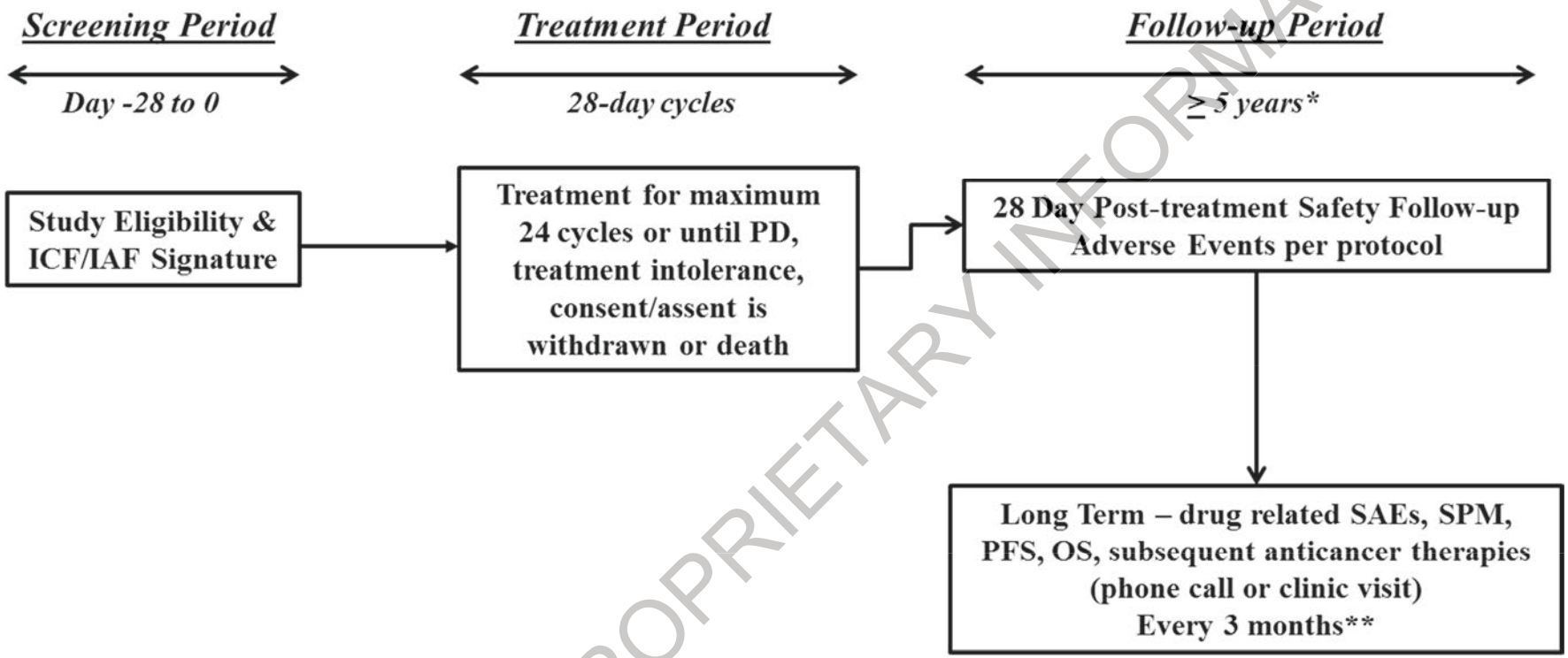
The study will be conducted in compliance with the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

**Figure 1: Simon's Optimal Two-Stage Parallel Design**




**DIPG:** Diffused Intrinsic Pontine Glioma
**PD:** Progressive Disease
**OR:** Objective Response (CR or PR within 6 cycles)
**LTSD:** Long Term Stable Disease (SD sustained for ≥ 6 cycles [> 3 cycles for DIPG])

**Figure 2: Overall Study Design**




*ICF = Informed Consent Form; IAF = Informed Assent Form; MRI = Magnetic Resonance Imaging; OS = Overall Survival; PD = Progressive Disease; PFS = Progression Free Survival; SAE = Serious Adverse Event; SPM = Second Primary Malignancy*

**From last subject enrolled*

***Subjects without PD at time of treatment discontinuation will continue to be followed for MRI tumor assessments (every 6 months for first year from treatment discontinuation, then annually thereafter)*

## 3.2. Study Duration for Subjects

The Screening Period will start from the time of obtaining informed consent/assent and last no more than 28 days, at which time the Treatment Period will begin (Cycle 1 Day 1, first day of actual study drug administration). Each subject shall receive treatment for up to 24 cycles or until documented PD, consent/assent is withdrawn, treatment becomes intolerable, or death, whichever occurs first. Once treatment has been discontinued, subjects will enter into a Follow-up Period with phone call/clinic visit every 3 months (± 14 days), for up to 5 years from enrollment of the last subject, unless consent/assent is withdrawn, the subject is lost to follow-up, or death.

Stage 1 portion of the study is expected to last up to approximately 18 months prior to reaching the decision point. The Stage 2 portion of the study is expected to last up to approximately 27 months should all strata enroll the maximum number of subjects and assuming no subjects are replaced.

## 3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

# 4. STUDY POPULATION

## 4.1. Number of Subjects

The study population will consist of children and young adults aged 1 to < 21 years with recurrent or progressive primary brain tumors after at least one prior standard therapy, in 1 of 4 primary brain tumor types: high-grade glioma, medulloblastoma, ependymoma and DIPG. Eighty subjects (36 subjects in Stage 1 and 44 subjects in Stage 2) will be included should all strata enroll the maximum number of subjects and assuming no subjects are replaced. Approximately 80% of subjects across all strata will be < 17 years of age.

## 4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is 1 to < 21 years of age at the time of signing the ICF/IAF.
2. Subject (when applicable, parental/legal representative) must understand and voluntarily sign an ICF/IAF prior to any study-related assessments/procedures being conducted. Note: Adult individuals who lack capacity to consent for themselves will be excluded from the study.
3. Subject has received at least one prior standard therapy (or generally accepted upfront therapy if no standard exists) and have no known curative therapy.
4. Subject has a diagnosis of high-grade glioma, medulloblastoma, ependymoma or DIPG that is recurrent or progressive with the primary location in the CNS. Subjects with neurofibromatosis type 1 (NF-1) associated tumors are eligible if the meet all other eligibility criteria.
5. Subject has histological verification of tumor either at the time of diagnosis or recurrence. Subjects with DIPG are exempt from histologic verification if they have typical MRI findings of DIPG (ie, hypo- or isointense on T1-weighted imaging, hyperintense on fluid-attenuated inversion recovery (FLAIR) or T2-weighted imaging, epicenter in the pons, > 50% of pons involved).
6. Subject has measurable disease (including subjects that have undergone a surgical resection prior to enrollment), defined as a primary brain tumor that is measurable in 2 perpendicular diameters on MRI. For a lesion to be considered measurable, it must be at least twice the slice thickness on MRI (ie, visible on 2 or more axial slices).

   Note: MRI should be performed with cuts of 3 mm or less in slice thickness contiguously. Further details regarding MRI acquisition requirements are outlined in the Imaging Manual.
7. To document the degree of tumor at study baseline, the following scan(s) must be obtained:
   - A brain MRI for all subjects with and without contrast (ie, gadolinium) and a spine MRI with contrast (ie, gadolinium) within 21 days prior to first dose of study treatment. For subjects on steroids, baseline MRI scans must be performed while on stable or decreasing dose of steroids for at least 5 days.

8. Subject has Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status score ≥ 50 at screening (Appendix D).
9. Subject has adequate bone marrow function defined as:
   - Peripheral ANC ≥ 1000/mm$^3$
   - Platelet count ≥ 100,000/mm$^3$ (transfusion independent defined as no platelet transfusion within 7 days and recovery from nadir)
   - Hemoglobin ≥ 8 g/dL (red blood cell [RBC] transfusion is allowed)
10. Subject has adequate renal function defined as:

    Serum creatinine based on age/gender as described in Table 3. Subjects that do not meet the criteria but who have a 24-hour creatinine clearance or radioisotope glomerular filtration rate (GFR) (radioisotope or iothalamate) ≥ 70 mL/min/1.73 m$^2$ are eligible.

**Table 3: Serum Creatinine by Age and Gender**

| Age | Maximum Serum Creatinine (mg/dL) | |
|---|---|---|
| | Male | Female |
| 1 to <2 years | 0.6 | 0.6 |
| 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 glomerular filtration rate (Schwartz, 1985) utilizing child length and stature data published by the Centers for Disease Control.

11. Subject has adequate liver function defined as:
    - Total bilirubin ≤ 1.5 X upper limit of normal (ULN) for current age (≤ 3 X ULN if increase in bilirubin is attributable to Gilbert's Syndrome)
    - Alanine aminotransferase (ALT) (SPGT) is ≤ 3 X ULN for age
    - Serum albumin ≥ 3 g/dL
12. Subject has adequate pulmonary function defined as:
    - No evidence of dyspnea at rest
    - A pulse oximetry ≥ 93%
13. Subject has recovered from clinically significant acute treatment related toxicities from all prior therapies. Recovery is defined as a toxicity Grade ≤ 2 (common terminology criteria for adverse events [CTCAE] v. 4.03).
14. Subject has no significant worsening in clinical status for a minimum of 7 days prior to first dose of study drug.

15. Subject (and when applicable, with parental/legal representative) is willing and able to adhere to the study visit schedule and other protocol requirements.
16. Females of childbearing potential (FCBP), female children of childbearing potential (FCCBP), and male subjects who have reached puberty (and when applicable, with parental/legal representative) must agree to undergo physician-approved reproductive education and discuss the side effects of the study therapy on reproduction.
17. All subjects and/or parents/legal representative must have an understanding that pomalidomide could have a potential teratogenic risk. Female children of childbearing potential, defined as females who have achieved menarche and/or breast development in Tanner Stage 2 or greater and have not undergone a hysterectomy or bilateral oophorectomy and FCBP, defined as a female who has achieved menarche at some point, not undergone a hysterectomy or bilateral oophorectomy and has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months) must agree and meet the following conditions below (Note: amenorrhea following previous anticancer therapy does not rule out childbearing potential):

    - Medically supervised (ie, performed in a clinic) pregnancy tests with a sensitivity of at least 25 mIU/mL must be conducted in FCCBP/FCBP, including those who commit to true abstinence*. Two pregnancy tests must be conducted prior to starting pomalidomide. The first pregnancy test must be performed 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to starting pomalidomide.

      **NOTE**: The pregnancy test 10 to 14 days prior to initiation of pomalidomide may be omitted, at the discretion of the investigator, for any FCCBP/FCBP who has high acuity disease requiring immediate treatment with pomalidomide. The pregnancy test within 24 hours prior to the first dose of pomalidomide is required to be performed.

      The subject may not receive pomalidomide until the Investigator has verified that the results of these pregnancy tests performed on Cycle 1, Day 1 are negative. Female children of childbearing potential/females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days study participation, every 28 days while on study, at study treatment discontinuation visit, and at Day 28 following pomalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of study participation and then every 14 days while on study, at study treatment discontinuation visit, and at Days 14 and 28 following pomalidomide discontinuation.
    - Female subjects must, as appropriate to age and at the discretion of the study Investigator, either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis) and/or agree to the use of two reliable forms of approved and effective contraceptive methods simultaneously. The two methods of reliable contraception must include one highly effective method (ie, oral, injectable, or implantable hormonal contraceptive; tubal ligation; intrauterine device; vasectomized partner) and one additional effective barrier method (ie, male condom, diaphragm, cervical cap) 28 days prior to starting pomalidomide, throughout the

entire duration of study treatment including dose interruptions and 28 days after discontinuation of pomalidomide.

Note: Only a progestin-suppressing ovulation pill is acceptable as an oral contraceptive. Copper intrauterine devices are not recommended.

- All male and female subjects must follow all requirements defined in the pomalidomide Pregnancy Prevention Program.

18. Male subjects must, as appropriate to age and the discretion of the study physician:
    - Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a FCBP while participating in the study, during dose interruptions and for at least 28 days following pomalidomide discontinuation, even if he has undergone a successful vasectomy or practices complete abstinence.

*True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

19. **For subjects screened/enrolled in France only**: Subject must be affiliated with a Health Insurance Scheme or be a beneficiary of one.

## 4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has a history of non-central line related thrombosis (arterial or venous), more than one prior central-line related thrombosis (excluding small clots in central lines that are resolved with tissue plasminogen activator [tPA] flush) or known coagulopathy.
2. Subject has first degree family member with a known hereditary coagulopathy.
3. Subject is actively on anticoagulation therapy.
   **Note:** The use of tPA to flush subject's central-line is allowed.
4. Subject has had major (per Investigator discretion) surgery, with the exception of tumor resection, within 21 days from first dose of study drug.
5. Subject has previously received (presence of any of the following will exclude a subject from enrollment):
    - Any prior treatment with pomalidomide. Subjects who have prior treatment with other immunomodulatory compounds (thalidomide, lenalidomide) ARE eligible if they meet all other eligibility criteria and did not have allergic reactions or other "significant toxicity" per Investigator discretion associated with lenalidomide or thalidomide use.
    - Myelosuppressive chemotherapy, immunotherapy, or any investigational agent: ≤ 21 days (≤ 42 days if a nitrosourea) prior to screening.
    - Biological (anti-neoplastic) therapy: ≤ 7 days prior to screening.

- Immunomodulatory therapy (ie, thalidomide, lenalidomide): ≤ 28 days prior to screening.
- Monoclonal antibody treatment and agents with known prolonged half-lives: < 3 half-lives have elapsed or ≤ 28 days prior to screening, whichever is longer.
- Prior radiation:
  - Cranial irradiation, total body irradiation (TBI), or ≥ 50% radiation of pelvis: ≤ 3 months prior to screening.
  - Focal irradiation: ≤ 3 weeks prior to screening if radiation field involved a non-target lesion; ≤ 6 weeks prior to screening if radiation field involved a target lesion.

  **Note**: True disease progression following prior irradiation therapy must be confirmed by Investigator prior to screening.
- Bone marrow transplant:
  - Presence of graft versus host disease (GVHD)
  - < 6 months since allogeneic bone marrow transplant prior to screening.
  - < 3 months since autologous bone marrow/stem cell transplant prior to screening.
  - < 3 months since stem cell transplant (SCT) or Rescue without TBI with no evidence of GVHD prior to screening.
- Radioisotopes: fluorothymidine ($^{18}$FLT) ≤ 72 hours prior to first dose of study drug

6. Subject has received therapy with a known moderate to potent CYP1A2 inhibitor within 14 days or 5 half-lives of first dose of study treatment (whichever is longer). The treating Investigator should consult a current drug information reference for a complete list (http://medicine.iupui.edu/clinpharm/ddis/main-table/).
7. Subject has received colony-stimulating growth factor(s) within 7 days prior to screening (or within 14 days if subject received polyethylene glycol formulations).
8. Subject is pregnant, breast-feeding or lactating.
9. Subject has an untreated or uncontrolled infection defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy and/or other treatment.
10. Subject has active infectious hepatitis, type A, B, or C, or chronic carriers of hepatitis C. Note: Hepatitis B serological status must be known prior to enrollment. If unknown at screening, a Hepatitis B serology test **must** be performed.
11. Subject has any prior history of malignancies, other than high-grade glioma, medulloblastoma, ependymoma or DIPG (Note: radiation-associated gliomas are excluded from enrollment)
12. Subject who, in the opinion of the Investigator, has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
13. Subject has any condition including the presence of laboratory abnormalities which, in the opinion of the Investigator, places the subject at unacceptable risk if he/she were to participate in the study.

14. Subject has any condition that confounds the ability to interpret data from the study.
15. Subject has symptomatic cardiac disorders (CTCAE v. 4.03 Grade 3 and 4)

# 5. TABLE OF EVENTS

## Table 4: Table of Events

| Period | Protocol Reference Section | Screening Period | Treatment Period[b] | | | | | | | | Follow-up Period[b] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Each 28-day Cycle | | | | | | | End of Treatment (± 3 days) | 28-Day Post Treatment Safety Follow-Up | Long-Term Follow-Up (± 14 days) |
| | | Screening[a] | Cycles 1 - 2 (± 3 days) | | | | Cycles 3 - 12 (± 3 days)[i] | | Cycles 13 - 24 (± 3 days)[i] | | | |
| **Day** | | **-28 to 0** | **1** | **8** | **15** | **22** | **1** | **15** | **1** | | | |
| **Study Entry and General Assessments** | | | | | | | | | | | | |
| Obtain Informed Consent/Assent | 13.3 | X | - | - | - | - | - | - | - | - | - | - |
| Interactive Response Technology | 7.3 | X | X | - | - | - | X | - | X | X | - | |
| Enrollment | 6.1.5 | - | X[o] | - | - | - | | - | - | - | - | - |
| Demographics | 6.1.2 | X | - | - | - | - | - | - | - | - | - | - |
| Inclusion/Exclusion Criteria | 4.2, 4.3 | X | X[o] | - | - | - | - | - | - | - | - | - |
| Complete Medical History | 6.1.3 | X | - | - | - | - | - | - | - | - | - | - |
| Prior Disease Therapies and History | 6.1.4 | X | - | - | - | - | - | - | - | - | - | - |
| Prior/Concomitant Medication and Procedures | 8.0 | After signing ICF/IAF and until 28-day post-treatment Safety Follow-up Visit | | | | | | | | | | - |
| **Safety Assessments** | | | | | | | | | | | | |
| Adverse Events | 10 | After signing ICF/IAF and until 28-day post-treatment Safety Follow-up Visit | | | | | | | | | | - |
| Assessment of Second Primary Malignancy | 6.4.2.10 | After signing ICF/IAF and until end of Long-term Follow-up Visit | | | | | | | | | | |
| Physical Exam (including vital signs) | 6.4.2.1 | X | X[c] | - | - | - | X | - | X | X | X | - |
| Pomalidomide Education and Counseling[d] | 6.4.2.9 | X | X | - | - | - | X | - | X | X | X | - |
| Height | 6.4.2.2 | X | X | - | - | - | X | - | X | X | X | - |
| Body Weight | 6.4.2.3 | X | X | - | - | - | X | - | X | X | X | - |
| BSA calculation | 6.4.2.4 | X | X | - | - | - | X | - | X | - | - | - |
| Lansky/Karnofsky Performance Status | 6.4.2.5 | X | X | - | - | - | X | - | X | X | X | - |

**Table 4: Table of Events (Continued)**

| Period | Protocol Reference Section | Screening Period | Treatment Period[b] | | | | | | | | Follow-up Period[b] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Each 28-day Cycle | | | | | | | | | |
| | | | Cycles 1 – 2 (± 3 days) | | | | Cycles 3 - 12 (± 3 days)[i] | | Cycles 13 - 24 (± 3 days)[i] | End of Treatment (± 3 days) | 28-Day Post Treatment Safety Follow-Up | Long-Term Follow-Up (± 14 days) |
| Day | | Screening[a] -28 to 0 | 1 | 8 | 15 | 22 | 1 | 15 | 1 | | | |
| Hematology[e] | 6.4.2.6 | X | X[c] | X | X | X | X | X | X | X | X | - |
| Serum blood chemistry[e] | 6.4.2.6 | X | X[c] | X | X | X | X | X | X | X | X | - |
| Hepatitis B serology (if applicable) | 6.4.2.6 | X | - | - | - | - | - | - | - | - | - | - |
| Pulse oximetry ($O_2$ saturation) | 6.4.2.7 | X | As clinically indicated | | | | | | | | | - |
| Serum or Urine β-hCG Testing (FCBP/FCCBP)[f] | 6.4.2.9 | X[g] | X[g] | X[o] | X[o] | X[o] | X | - | X | X | X | - |
| Neurological assessment | 6.4.2.8 | X | X | - | - | - | X | - | X | X | X | - |
| **Treatment Administration, Accountability and Compliance** | | | | | | | | | | | | |
| Pomalidomide Dispensing | 7.1 | - | X | - | - | - | X | - | X | - | - | - |
| Pomalidomide Administration | 7.2 | - | Days 1-21 | | | - | Days 1-21 | | Days 1-21 | - | - | - |
| **Response Assessments (High-grade glioma, Medulloblastoma and Ependymoma)** | | | | | | | | | | | | |
| Brain MRI with and without gadolinium | 6.4.1 | X[h] | - | - | - | - | Day 1 of Cycles 3, 5, 7, 10, 13, 16, 19, 22 and after Cycle 24[i] | | | X[j] | - | X[k] |
| Spine MRI with gadolinium | 6.4.1 | X[h] | - | - | - | - | Day 1 of Cycles 3, 5, 7, 10, 13, 16, 19, 22 and after Cycle 24[i, i] | | | X[j] | - | X[k] |
| Cerebrospinal fluid cytology | 6.4.1 | As clinically indicated[m] | | | | | | | | | | |
| **Response Assessments (DIPG)** | | | | | | | | | | | | |
| Brain MRI with and without gadolinium | 6.4.1 | X[h] | - | - | - | - | Day 1 of Cycles 4, 7, 10, 13, 16, 19, 22 and after Cycle 24[i] | | | X[j] | - | X[k] |
| Spine MRI with gadolinium | 6.4.1 | X[h] | - | - | - | - | Day 1 of Cycles 4, 7, 10, 13, 16, 19, 22 and after Cycle 24[i, l] | | | X[j] | - | X[k] |
| Cerebrospinal fluid cytology | 6.4.1 | As clinically indicated[m] | | | | | | | | | | |

**Table 4: Table of Events (Continued)**

| Period | Protocol Reference Section | Screening Period | Treatment Period[b] | | | | | | | | Follow-up Period[b] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Each 28-day Cycle | | | | | | | | | |
| | | | Cycles 1 – 2 (± 3 days) | | | | Cycles 3 - 12 (± 3 days)[i] | | Cycles 13 - 24 (± 3 days)[i] | End of Treatment (± 3 days) | 28-Day Post Treatment Safety Follow-Up | Long-Term Follow-Up (± 14 days) |
| Day | | -28 to 0 | 1 | 8 | 15 | 22 | 1 | 15 | 1 | | | |
| **Pharmacokinetics – Optional** | | | | | | | | | | | | |
| Optional Pharmacokinetic blood sampling | 6.5 | - | - | X[o] | X[o] | - | - | - | - | - | - | - |
| **Follow-Up** | | | | | | | | | | | | |
| PFS, DoR, OS, drug related SAEs, SPMs, new anticancer therapies | 6.3 | - | - | - | - | - | - | - | - | - | - | X[n] |

β-hcg = beta human chorionic gonadotropin; BSA = body surface area; DoR = duration of response; FCBP = females of childbearing potential; FCCBP = female children of childbearing potential; IAF = informed assent form; ICF = informed consent form; MRI = magnetic resonance imaging; $O_2$ = oxygen; OS = overall survival; PFS = progression free survival; SAE = serious adverse event; SPM = second primary malignancy.

[a] Clinical evaluations to establish eligibility can be obtained up to 28 days prior to Cycle 1, Day 1 (first dose of study drug) unless noted otherwise. Brain/Spine MRI assessments can be obtained up to 21 days prior to Cycle 1, Day 1. Assessments should be re-evaluated as needed if there is a change in clinical status.

[b] Deviations within the provided study visit windows are allowed unless noted otherwise for a particular assessment.

[c] Safety laboratory (hematology and serum blood chemistry) and physical examinations do not need to be repeated on Cycle 1, Day 1 if performed within 7 days of starting treatment, unless clinically indicated. FCBP/FCCBP must have pregnancy test performed within 24 hours prior to the initial dosing of pomalidomide.

[d] Can also be conducted verbally via phone from the site. Subjects must also be counseled against sharing pomalidomide and donating blood, semen or sperm during therapy until the 28-day post-treatment Safety Follow-up Visit. Pregnancy counseling and potential risks must be conducted on Day 1 of each cycle prior to pomalidomide dispensing or at a minimum of every 28 days during the Treatment Period.

[e] Subjects who experience toxicity should have appropriate laboratory testing at least twice weekly (3 to 4 days apart or more frequently) until the toxicity has resolved. It is the responsibility of the Investigator to obtain and review laboratory results for subject safety, and follow up with subjects in a timely manner.

[f] Testing with a sensitivity of at least 25 mIU/mL will be performed in FCBP/FCCBP subjects; refer to Section 6.4.2.9 for details. It is the responsibility of the Investigator to obtain and review pregnancy test results for subject safety, and follow up with subjects in a timely manner. The subject may not receive pomalidomide until the Investigator has verified that the result of the pregnancy test performed on Day 1 (within 24 hours prior to treatment) of every cycle is negative.

[g] Obtain 10 to 14 days prior to first dose of study drug and again within 24 hours prior to first dose of study drug. **NOTE:** The pregnancy test 10 to 14 days prior to initiation of pomalidomide may be omitted, at the discretion of the investigator, for any FCCBP/FCBP who has high acuity disease requiring immediate treatment with pomalidomide. The pregnancy test within 24 hours prior to the first dose of pomalidomide is required to be performed.

[h] Screening/baseline MRI can be obtained up to 21 days prior to Cycle 1 Day 1.

[i] Brain/Spine MRIs can be performed within 7 days prior to scheduled timepoint.

[j] Response/MRI assessment will be performed at the End of Treatment Visit only if the subject has discontinued for reasons other than PD and has been more than 8 weeks since their most recent scan/response assessment.

[k] Subjects that discontinue treatment prior to disease progression will be followed with MRI tumor assessments every 6 months from treatment discontinuation for the first year off treatment, then annually thereafter until PD, start of a new anticancer therapy, consent/assent is withdrawn, is lost to follow-up, or death.

[l] If no spinal or leptomeningeal disease is present at screening/baseline, subsequent spine MRIs will be obtained on Day 1 of Cycle 7, 13, 19 (or within 7 days prior to dosing), after completion of Cycle 24 (or within 7 days prior) ) and as clinically indicated at the discretion of the primary treating physician. If there is spinal or leptomeningeal disease present at screening/baseline, spine MRIs will be obtained at the same time points as the brain MRI.

[m] As clinically indicated to follow disease at the discretion of the primary treating physician. It is recommended to follow at the same interval as required MRIs if positive at screening/baseline.

[n] SPMs should be reported regardless of causality. After treatment discontinuation, all subjects will be followed every 3 months from the 28-Day post-treatment Safety Follow-Up Visit for up to 5 years after the last subject enrolled.

[o] Cycle 1 only

# 6. PROCEDURES

All procedures will be performed as outlined in the Table of Events (Table 4) and further detailed in the respective protocol referenced sections below. In the table, required assessments are indicated with an "X" at the visits for which the assessments are to be performed. All data obtained from these assessments must be supported in the subject's source documentation. No electronic case report form (eCRF) will be used as a source document. Scheduled assessments should be completed **prior** to study treatment administration unless noted otherwise.

## 6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. All clinical evaluations to establish eligibility must be performed within 28 days prior to Cycle 1, Day 1 (first dose of study drug), unless noted otherwise. MRI assessments must be performed within 21 days prior to Cycle 1, Day 1. Eligibility waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Safety laboratory analyses and all assessments will be performed locally. Screening laboratory values may be repeated within the screening window, if necessary. **If any** laboratory value does not meet eligibility criteria prior to the first dose (Cycle 1, Day 1) of study treatment, the subject will be considered a screen failure. Subjects who fail screening may be rescreened at the Investigator's discretion. For subjects who are rescreened, a new ICF/IAF will need to be signed and screening procedures will need to be repeated (if rescreening occurs > 28 days prior to the original screening date). A new subject identification (ID) will be issued once the rescreening transaction is registered in Interactive Response Technology (IRT).

The following will be performed at screening as specified in the Table of Events (Table 4), and further detailed in the protocol referenced Section 6.4, after informed consent/assent has been obtained:

- Registration of screening via IRT
- Demographics
- Inclusion/exclusion criteria
- Complete medical history
- Prior disease therapies and history
- Prior/concomitant medications and procedures
- Assessment of adverse events
- Assessment of SPM
- Physical examination including vital signs
- Height
- Body weight
- BSA calculation

- Lansky/Karnofsky performance status. Karnofsky will be utilized for subjects age ≥ 16 years and Lansky will be utilized for subjects age < 16 years.
- Hematology
- Serum blood chemistry
- Hepatitis B serology (if required)
- Oxygen saturation
- Serum (or urine) beta human chorionic gonadotropin (β-hCG) pregnancy testing: Performed in FCCBP/FCBP at screening within 10 to 14 days prior to first dose of study drug and again to assess subject eligibility within 24 hours prior to the first dose of study drug (this pregnancy test can be done on Cycle 1 Day 1). **NOTE:** The pregnancy test 10 to 14 days prior to initiation of pomalidomide may be omitted, at the discretion of the investigator, for any FCCBP/FCBP who has high acuity disease requiring immediate treatment with pomalidomide. The pregnancy test within 24 hours prior to the first dose of pomalidomide is required to be performed. Negative result(s) are **required** to start treatment administration (see Section 6.4.2.9).
- Neurological assessment
- Brain MRI with and without gadolinium (for tumor evaluation of response assessment).
- Spine MRI with gadolinium (for tumor evaluation of response assessment)
- Cerebrospinal fluid cytology (if clinically indicated)
- Pomalidomide education and counseling is required for all subjects at screening. Education and counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted by trained personnel at the site prior to each dispensing of pomalidomide. The individual conducting the training must sign the appropriate counseling form prior to administration of study treatment to document that the education and counseling was performed.

### 6.1.1. Information to be Collected on Screen Failures

- Informed consent/assent date
- Demographics
- Inclusion and exclusion criteria eligibility information
- Reason for screen failure
- Adverse events. Concomitant medications to treat the AE(s) will be recorded on the eCRF and captured in the source document.

### 6.1.2. Demographics

Demographics including gender, race, ethnicity, and date of birth, where allowed by local regulations, will be documented at screening only.

### 6.1.3. Complete Medical History

A complete medical history including evaluation for preceding medical disorders and past (up to 5 years) or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematological, immunological, dermatological, psychiatric, genitourinary, obstetrical, surgical history (including those related to disease under study) or any other disorders will also be documented at screening.

### 6.1.4. Prior Disease History and Therapies

The subject's current disease (ie, diagnosis, date of diagnosis, grading/staging, and histology), as well as all prior disease therapies including surgery, radiation, SCT, chemotherapy, systemic or any other therapy for the subject's disease will be recorded on the respective eCRF at screening.

### 6.1.5. Enrollment

Prior to enrolling a subject, written informed consent/assent must be obtained, all screening evaluations must be completed, and eligibility criteria must be verified by the Investigator. Once these actions have been completed, the Investigator or designated staff will log into IRT and confirm that the subject still fulfills all the inclusion and exclusion criteria. After enrollment, the subject will retain his/her Subject ID number (Section 7.3.1) during participation in the study.

## 6.2. Treatment Period

The subject will begin treatment upon re-confirmation of eligibility (ie, safety assessments) and subsequent enrollment. The subject must start treatment within 28 days of signing the ICF/IAF. For all subsequent visits, an administrative window of ± 3 days is permitted unless noted otherwise for a particular assessment. Brain and spine MRI assessments can be conducted within 7 days prior to the scheduled timepoint (ie, during study drug rest period). Study visit windows should take into account the subject's investigational product (IP) supply and administration.

**Note:** Safety laboratory (hematology, serum blood chemistry) and physical examinations do not need to be repeated on Cycle 1, Day 1 if performed within 7 days of starting treatment unless clinically indicated; however, for FCCBP/FCBP subjects, a urine or serum pregnancy test must be performed to assess subject eligibility 10 to 14 days prior to and again within 24 hours prior to the first administration of pomalidomide. The pregnancy test 10 to 14 days prior to initiation of pomalidomide however may be omitted, at the discretion of the investigator, for any FCCBP/FCBP who has high acuity disease requiring immediate treatment with pomalidomide. The pregnancy test within 24 hours prior to the first dose of pomalidomide is required to be performed (refer to Section 6.4.2.9).

The Treatment Period is defined as the time starting from first study drug administration (Cycle 1, Day 1) until permanent study treatment discontinuation. Subjects will be administered pomalidomide on Days 1 to 21 of each 28-day treatment cycle for a maximum of 24 cycles. Pomalidomide will not be administered on Days 22 through 28 of the 28-day treatment cycle.

The following evaluations will be performed at the frequency specified in the Table of Events (Table 4) and further detailed in the protocol referenced Section 6.4. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

- Reconfirm eligibility (Cycle 1, Day 1 only)

- IRT registration (Day 1 of each treatment cycle)
- Enrollment via IRT: Day 1, Cycle 1 only
- Concomitant medications and procedures
- Adverse event evaluation
- Assessment of SPM
- Physical examination (including vital signs)
- Height
- Body weight
- BSA calculation
- Lansky/Karnofsky performance status. Karnofsky will be utilized for subjects age ≥ 16 years and Lansky will be utilized for subjects age < 16 years.
- Hematology
- Serum blood chemistry
- Oxygen saturation (as clinically indicated)
- Serum (or urine) β-hCG pregnancy testing in FCCBP/FCBP (see Section 6.4.2.9)
- Neurological assessment
- Pomalidomide administration
- Brain MRI with and without gadolinium (for tumor evaluation of response assessment)
- Spine MRI with gadolinium (for tumor evaluation of response assessment)
- Cerebrospinal fluid cytology (as clinically indicated)
- Pomalidomide education and counseling. For applicable subjects, confirmation of use of two effective methods of birth control, agree to use condom (male) or confirmation of complete abstinence
- Optional PK blood sampling (Cycle 1, Day 8 and 15 only)

### 6.2.1. End of Treatment

All subjects discontinuing treatment, regardless of reason, should undergo treatment discontinuation procedures and evaluation as soon as possible after the decision to permanently discontinue treatment has been made.

The following evaluations will be performed as specified in the Table of Events (Table 4) and further detailed in protocol referenced Section 6.4:

- Registration of treatment discontinuation via IRT
- Concomitant medications and procedures

- Adverse event evaluation
- Assessment of SPM
- Physical examination (including vital signs)
- Pomalidomide education and counseling
- Height
- Body weight
- Lansky/Karnofsky performance status. Karnofsky will be utilized for subjects age ≥ 16 years and Lansky will be utilized for subjects age < 16 years.
- Hematology
- Serum blood chemistry
- Oxygen saturation (as clinically indicated)
- Serum (or urine) β-hCG pregnancy testing for FCCBP/FCBP (see Section 6.4.2.9)
- Neurological assessment
- Brain MRI with and without gadolinium (for tumor evaluation of response assessment) will be performed only if subject has discontinued for reasons other than progression of disease and it has been more than 8 weeks since their most recent scan/response assessment
- Spine MRI with gadolinium (if applicable, for tumor evaluation of response assessment) will be performed only if subject has discontinued for reasons other than progression of disease and has been more than 8 weeks since their most recent scan/response assessment
- Cerebrospinal fluid cytology (as clinically indicated)

## 6.3. Follow-up Period

### 6.3.1. Safety Follow-up

All subjects will be followed for 28 days after the last dose of treatment for AE reporting, as well as concomitant medications/procedures used to treat the AEs. SAEs made known to the Investigator at any time thereafter that are suspected of being related to study drug will be reported, as described in Section 10.1. At this visit, the following evaluations will be performed as specified in the Table of Events (Table 4) and further detailed in the protocol referenced Section 6.4:

- Concomitant medications and procedures
- Adverse event evaluation
- Assessment of SPM
- Physical examination (including vital signs)

- Pomalidomide education and counseling
- Height
- Body weight
- Lansky/Karnofsky performance status. Karnofsky will be utilized for subjects age ≥ 16 years and Lansky will be utilized for subjects age < 16 years.
- Hematology
- Serum blood chemistry
- $O_2$ saturation (as clinically indicated)
- Serum (or urine) β-hCG pregnancy testing for FCCBP/FCBP (see Section 6.4.2.9)
- Neurologic examination

### 6.3.2. Second Primary Malignancy Follow-up Period

Second primary malignancies will be monitored as events of interest and must be reported as SAEs. This includes any SPM, regardless of causal relationship to study drug, occurring throughout the subject's entire participation in the study. Subjects that do not receive treatment (eg, screen failures) will not be followed for SPM. Further details are described in Section 6.4.2.10.

### 6.3.3. Long-term Follow-up

After permanent study drug discontinuation, all subjects will be followed every 3 months (± 14 days) from the 28-day post-treatment Safety Follow-up Visit for SPMs (regardless of causal relationship), any drug-related SAEs, OS, and start of any new anticancer therapies. Follow-up will continue every 3 months for up to 5 years after the last subject enrollment, unless consent/assent is withdrawn, the subject is lost to follow-up, or death.

Note: The Long-term Follow-up Period may not be terminated because of starting a new anticancer treatment.

In addition, subjects that discontinue treatment prior to disease progression will be followed for MRI tumor response assessments every 6 months from treatment discontinuation for the first year off treatment, then annually thereafter until PD, withdrawal of consent/assent, start of new anticancer therapy, lost to follow up or death, whichever occurs first. These MRI scans will continue to be sent for independent central review.

Survival/long-term follow-up may be conducted by clinic visits, by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

## 6.4. Assessment Types

### 6.4.1. Efficacy Assessments

Brain tumor assessments will be conducted by MRI with and without contrast (ie, gadolinium) using 3 standard MRI sequences (T1-weighted pre- and postcontrast, T2-weighted, FLAIR). A

spine MRI with contrast (ie, gadolinium) will also be performed as specified in Table 4. The neuroradiologist may select the appropriate sequence that best highlights the tumor (T1-weighted postcontrast or T2-weighted or FLAIR) and the same sequence should be used for serial measurements (Section 6.4.1.2). Further details regarding MRI acquisition requirements are outlined in the Imaging Manual.

Brain MRI assessments will be conducted during screening (within 21 days prior to first dose of study treatment) and then on Day 1 of Cycles 3, 5, 7, 10, 13, 16, 19, 22 (or within 7 days prior to dosing), after completion of Cycle 24 (or within 7 days prior) and as clinically indicated. **Note:** For DIPG subjects only, post-baseline brain MRI assessments will be performed on Day 1 of Cycles 4, 7, 10, 13, 16, 19, 22 (or within 7 days prior to dosing), after completion of Cycle 24 (or within 7 days prior) and as clinically indicated.

Spine MRI will be also performed during screening (within 21 days prior to first dose of study treatment) for all subjects. If no spinal or leptomeningeal disease is present at screening, subsequent spine MRIs will be obtained on Day 1 of Cycles 7, 13, 19 (or within 7 days prior to dosing), after completion of Cycle 24 (or within 7 days prior) and as clinically indicated. If there is spinal or leptomeningeal disease present at screening/baseline, spine MRIs will be obtained at the same brain MRI time points specified above.

In addition, if clinically indicated and at the discretion of the Investigator, CSF cytology will also be assessed to follow disease. It is recommended to follow at the same interval as required brain MRIs if positive at initiation of treatment. Corticosteroid use and clinical assessments (ie, neurologic status) will also be considered when determining overall response (Section 6.4.1.7).

A response assessment should be performed at EOT visit if the subject has discontinued for reasons other than progression of disease and it has been more than 8 weeks since their most recent scan/response assessment. Subjects that discontinue treatment prior to disease progression will be followed for MRI tumor response every 6 months from treatment discontinuation for the first year off treatment, then annually thereafter until PD, start new anticancer therapy, withdrawal of consent/assent, lost to follow-up or death, whichever occurs sooner.

The same method of assessment and sequence/technique must be used to characterize each reported target and non-target lesions at baseline and subsequent scans after start of study treatment.

Tumor response will be assessed both locally and by an independent central reviewer (Section 6.4.1.7) according to the criteria described below. The local Investigator's radiological assessment will be used for subject eligibility and treatment decisions. Efficacy based endpoints incorporating tumor assessments (primary and secondary) will be based on the independent central assessment.

#### 6.4.1.1. Selection of Target and Non-Target Lesions

**Screening/baseline requirement:**

Screening MRI evaluations will be performed within 21 days of first dose of study treatment. For subjects on steroids, screening MRI scans **must** be performed while on a stable or decreasing

dose of steroids for at least 5 days. Subjects must have measurable disease (including subjects that have undergone a surgical resection prior to enrollment).

- **Measurable disease** is defined as lesions that are (all criteria below are met):
  - Brain lesions which are the primary tumors
  - Measurable in 2 perpendicular diameters
  - At least twice the slice thickness on MRI (ie, visible on 2 or more axial slices) **Note:** MRI should be performed with cuts of 3 mm or less in slice thickness contiguously.
  - Do not include cavity or cyst in measurement (see Section 6.4.1.2)
- **Nonmeasurable disease** is defined as (any criteria below are met):
  - Spinal lesions
  - Lesions with poorly defined margin on MRI
  - Cerebrospinal fluid
  - Cystic or necrotic components (see Section 6.4.1.2)

All target and non-target lesions should be identified and recorded at screening.

- For most CNS tumors, only one lesion/mass is present and therefore this single lesion is considered a "target" for measurement to assess tumor response and progression.
- Spinal lesions should be considered as nonmeasurable disease (ie, non-target lesions); however, size should be noted and change in size should be evaluated.
- All subjects should have at least one measurable, target lesion confirmed by MRI. Target lesions should be selected on the basis of size (eg, largest) and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions.
- Leptomeningeal tumor spread is usually not a target lesion, and cannot be measured accurately; however, presence and location of leptomeningeal tumor spread should be noted and change in extent/thickness should be evaluated on assessments.

#### 6.4.1.2. Methodology to Determine Tumor Measurement

Tumor dimensions will be determined by two-dimensional measurement of the longest diameter (width [W]) and the longest perpendicular diameter (transverse [T]) for each target lesion (Figure 3). Radiologist at each institution may select the appropriate sequence that best highlights the tumor (T1-weighted postcontrast or T2-weighted or FLAIR) and the same sequence should be used for serial measurements.

Radiographic response determination will be based on a comparison of an area (W x T) between the baseline assessment (or smallest disease measurements recorded since the start of protocol therapy [nadir]) and the assessments post-treatment. Assessments post treatment should reiterate the measurements obtained at baseline for each target lesion.

Tumor response criteria are determined by changes in size using the longest tumor diameter and its perpendicular diameter (W x T). The following describes the measurement method:

- The **longest diameter** measurement (W) can be measured from the axial plane or the plane in which the tumor is best seen or measured. The same plane chosen at baseline should be used in subsequent assessments.
- The **perpendicular diameter** measurement (T) is maximal perpendicular to the W in the selected plane.
- The cystic or necrotic components of a tumor are not considered in tumor measurements. Therefore, only the solid component of cystic tumors should be measured. If cyst/necrosis composes the majority of the lesion, the lesion may not be "measurable." In general, such lesions should be considered non-target.

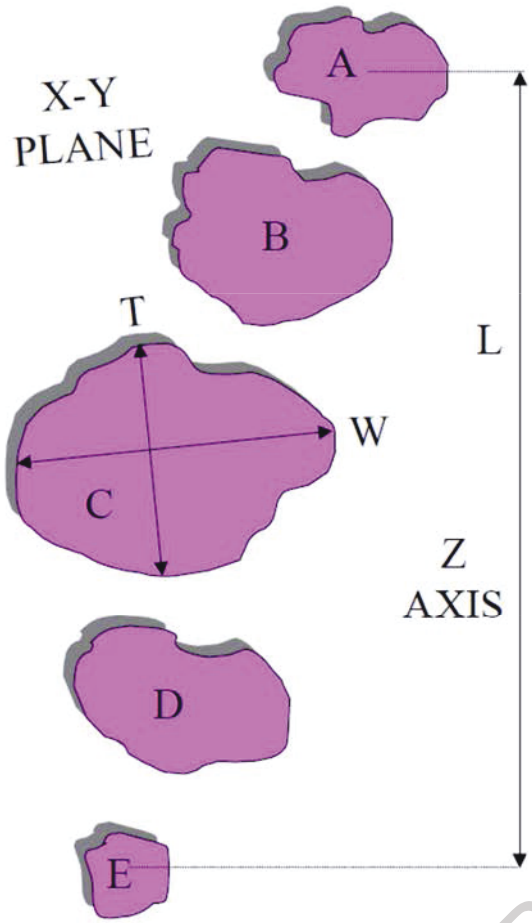
  Options:

  – If the cyst/necrosis is eccentric, the W and T of the solid portion should be measured, and the cyst/necrosis portion should be excluded from measurement.

  – If the cyst/necrosis is central but represents a small portion of the tumor (< 25%), the cyst/necrosis should be disregarded, and the entire tumor should be measured.

  – If the cyst/necrosis is central and represents a large portion of the tumor, identify a solid aspect of the tumor mass that can be reproducibly measured.

**Figure 3: Guidelines for Measurement of Tumor Size**




**MEASUREMENT BASED ON CROSS-SECTIONAL IMAGING**

- A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor
- W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area
- Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference in table position of the first and last slices showing the tumor + one slice thickness), or [b] the product of (slice thickness + gap) and the number of slices showing the tumor

Source: Children's Oncology Group (COG) guideline

### 6.4.1.3. Tumor Response Criteria for Target Lesions

1. Response criteria are assessed in 2 dimensions - the product of W x T
2. The overall measurement of target lesions for a particular assessment is quantified by the sum of the products of the perpendicular diameters of all target lesions (eg, $W_1 \times T_1 + W_2 \times T_2 + \ldots$).
3. To assess response/progression, the ratio is calculated:

$$\frac{sum\ of\ products\ (W1xT1+W2xT2+\cdots)\ (current\ scan)}{sum\ of\ products\ (W1xT1+W2xT2+\cdots)\ (reference\ scan)}$$

4. Radiographic response should be made in comparison to the tumor measurement obtained at baseline for the determination of response, and the smallest tumor measurement (nadir) either at baseline or after initiation treatment for determination of progression.

5. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions, eg, when multiple lesions show opposite responses, the progressive disease takes precedence.

The tumor response categories for target lesions are CR, PR, SD and PD and are further defined in Appendix B.

#### 6.4.1.4. Tumor Response Criteria for Non-Target Lesions

The tumor response categories for non-target lesions are CR, incomplete response (IR)/SD and PD and are further defined in Appendix B. Non-target lesions are assessed subjectively and the decision when progression is evident is at the discretion of the radiologist/Investigator.

#### 6.4.1.5. Clinical Status (Neurologic Symptoms/Examination)

The definition of clinical status and deterioration is left to the discretion of the Investigator. Clinical deterioration should be attributable to neurologic abnormalities or worsening neurologic status not explained by causes unrelated to tumor progression (eg, anticonvulsant or corticosteroid toxicity wean, electrolyte disturbances, sepsis, hyperglycemia, etc.) or changes in corticosteroid dose.

#### 6.4.1.6. Corticosteroid Administration

An increase in corticosteroid dose alone will not cause determination of progression in the absence of clinical deterioration or radiographically documented lesion growth. For corticosteroid dose to be considered "stable or decreasing," it should not be a greater dose than compared with baseline. For overall assessment of response (Section 6.4.1.7), physiologic replacement doses of corticosteroids, defined as no more than 0.75 mg/m$^2$/day of dexamethasone or equivalent, will be considered.

#### 6.4.1.7. Overall Response Assessment

The overall response assessment takes into account response in both target and non-target lesions, the appearance of new lesions, current corticosteroid use (compared to screening/baseline) and neurologic symptoms/examination (clinical status) according to the criteria described in Appendix C.

Subjects who do not meet the criteria for an objective response or disease progression by the end of Cycle 6 (end of Cycle 3 for DIPG subjects) will be considered as having long-term SD.

#### 6.4.1.8. Independent Central Response Review

Response evaluations will be based on MRI results obtained at each site and will assessed locally and by an independent central reviewer. Corticosteroid use and clinical assessments (ie, neurologic status) will also be considered when determining overall response. The local Investigator's assessment will be used for subject eligibility and treatment decisions. Efficacy based endpoints incorporating tumor assessments (primary and secondary) will be based on the independent central assessment.

Imaging/response data will be centrally collected and checked for quality by an imaging contract research organization (CRO) designated by Celgene. Independent central review (screening/

baseline and post-baseline assessments) will be performed for all MRIs collected for response assessment. Further details regarding MRI acquisition requirements and image submission procedures are outlined in the Imaging Manual.

Details of the central review process and requirements for central imaging review will be described in the independent review charter. Results of the central review will not be provided to the sites.

### 6.4.2. Safety and Tolerability Assessments

Safety assessments will consist of monitoring and recording all AEs, including SAEs, concomitant medications, SPMs, dose discontinuations, reductions and interruptions, the regular monitoring of hematology and blood chemistry, regular monitoring of vital signs and physical condition. These assessments should be performed within the prescribed window of the scheduled day of assessment (Table 4) and at any unscheduled visit if clinically indicated; however, AEs, concomitant medications and review for SPMs will be evaluated and recorded continuously throughout the study.

**Note:** Pomalidomide experience in subjects < 3 years of age is limited. As such, subjects < 3 years of age should be carefully monitored for safety and side effects (adverse effects). In addition, as pomalidomide is metabolized hepatically, subjects with hepatic impairment should also be carefully monitored. In response to any safety concerns in subjects with hepatic impairment, Investigators should have a low threshold for performing additional safety evaluations (ie, hematology, blood chemistry, physical exams, vital signs, etc) as needed.

#### 6.4.2.1. Physical Examinations (Including Vital Signs)

A complete physical examination will include (as applicable) the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological (Section 6.4.2.8). For other indicated areas, based on medical history and/or symptoms, examinations will be performed.

Physical examination will be source documented only; however significant findings that were present prior to the signing of the ICF/IAF must be included in the Medical History page on the subject's eCRF. Clinically significant new findings that begin or worsen after informed consent/assent must be recorded on the AE page of the subject's eCRF.

At screening, the Investigator or designee performing the physical examination will characterize the findings as either normal or abnormal in the source. If abnormal, a description of the abnormality and clinical importance should be source documented. Clinically significant changes from screening/baseline will be recorded in the AE section of the eCRF.

Vital signs assessment will include temperature, blood pressure, heart rate and respiratory rate. On-treatment vital sign measurements will be source documented only; however, if an abnormal (out of range) value is reported at any given visit and clinically significant, that parameter should be collected in the eCRF at every subsequent scheduled visit until it returns to normal or not clinically significant (NCS), and recorded as an AE if appropriate.

#### 6.4.2.2. Height

Height in centimeters (cm) without shoes will be measured. For each height assessment, measurements should be performed three times and the average taken for calculation of BSA.

#### 6.4.2.3. Weight

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. For each weight assessment, measurements should be performed three times and the average taken for calculation of BSA.

#### 6.4.2.4. Body Surface Area Calculation

Body surface area, in $m^2$, will be calculated using the following formula, where weight (W) is in kg and height (H) is in cm (Dubois, 1916):

$$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$$

The subject's pomalidomide dose should be calculated on the first day of Cycle 1 based upon the subject's current BSA. Measurements of the subject's height and body weight will be repeated on Day 1 of each subsequent cycle and BSA recalculated at these visits.

#### 6.4.2.5. Lansky/Karnofsky Performance Status

For subjects < 16 years of age, the Lansky performance status will be determined. For subjects ≥ 16 years of age, the Karnofsky performance status will be determined (Appendix D). Each subject must continue to be assessed with the same performance status scale used at screening throughout his/her duration in the study (regardless of changing age over time).

#### 6.4.2.6. Laboratory Evaluations

Screening and other laboratory assessments will be performed locally at each scheduled visit according to Table of Events (Table 4) and collection plan in Table 5 below.

Note: Additional assessments should be performed between visits as clinically required to follow AEs or determine dose modifications. All laboratory assessments should be performed prior to treatment administration on that particular visit unless indicated otherwise.

It is the responsibility of the Investigator to obtain and review laboratory results for subject safety, and follow up with subjects in a timely manner. The Investigator will evaluate the clinical significance of each applicable laboratory value outside of the reference range. This decision shall be based upon the nature and degree of the observed abnormality. Values which are considered clinically significant and/or related to study treatment will be noted in source document(s). The Investigator may choose to repeat any abnormal result, in order to rule out laboratory error. "Not clinically significant" or "NCS" will be recorded on the original laboratory sheet for all laboratory values which are outside the reference range, but are judged "not clinically significant." The Investigator making these assessments shall date and initial each form.

Hematology, serum chemistry and viral serology laboratory values will not be collected on the laboratory eCRF; instead, laboratory abnormalities that are considered AEs should be reported on the AE eCRF (see Section 10).

**Table 5: Local Clinical Laboratory Parameters Collection Plan**

| Test Category | Test Name |
|---|---|
| Hematology | Hematocrit, Hemoglobin, Mean corpuscular volume, Platelets, RBC, White Blood Cells (WBC) absolute and differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils) |
| Chemistry | Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Blood Urea Nitrogen, Calcium, Chloride, Creatinine, Direct Bilirubin, Total Bilirubin, Glucose, Potassium, Phosphorous, Magnesium, Sodium, Total Protein |
| Viral Serology | Hepatitis B serology is required at screening if status is not known |

ALT = alanine aminotransferase; AST = aspartate transaminase; RBC = red blood cell; SGPT = serum glutamic-pyruvic transaminase; SGOT = serum glutamic-oxaloacetic transaminase.

#### 6.4.2.7. Pulse Oximetry (Oxygen Saturation)

Oxygen ($O_2$) saturation will be measured by pulse oximetry at screening and repeated as clinically indicated throughout the study.

#### 6.4.2.8. Neurological Assessment

A basic neurological exam (including, but not limited to, cranial nerve examination, motor function, sensory function, reflexes and cerebellar function) will be conducted as part of the physical examination.

#### 6.4.2.9. Pregnancy Testing and Pregnancy Risk Counseling

Medically supervised (ie, performed in a clinic) serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL must be conducted in FCCBP/FCBP, including those who commit to complete abstinence. Female children of childbearing potential is defined as a female who has achieved menarche and/or breast development in Tanner Stage 2 or greater and has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries).

A female of childbearing potential is defined as a female who has achieved menarche at some point, not undergone a hysterectomy or bilateral oophorectomy and has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

For all applicable subjects during the Screening Period, 2 pregnancy tests (with sensitivity of at least 25 mIU/mL) must be conducted prior to starting treatment. The first pregnancy test in both FCCBP and FCBP must be performed within 10 to 14 days prior to the start of treatment (Screening Period) and the second pregnancy test must be performed within 24 hours prior to the start of treatment (Cycle 1, Day 1). Amenorrhea following cancer therapy does not rule out childbearing potential.

**Note:** The pregnancy test 10 to 14 days prior to initiation of pomalidomide may be omitted, at the discretion of the investigator, for any FCCBP/FCBP who has high acuity disease requiring immediate treatment with pomalidomide. The pregnancy test within 24 hours prior to the first dose of pomalidomide is required to be performed.

Female children of childbearing potential and FCBP with regular or no menstrual cycles must agree to have subsequent pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at End of Treatment Visit and at day 28 following treatment discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study End of Treatment Visit, and at Days 14 and 28 following treatment discontinuation. It is the responsibility of the Investigator to obtain and review pregnancy test results for subject safety, and follow up with subjects in a timely manner.

The subject must not receive pomalidomide until the Investigator has verified that the results of the pregnancy test performed are negative. See inclusion criteria (Section 4.2) for pregnancy testing requirements.

The Investigator must confirm the FCCBP/FCBP subject is continuing to use 2 reliable methods of birth control if not committing to complete abstinence or plans not to commit to complete abstinence. Counseling about pregnancy precautions and the potential risks of fetal exposure to pomalidomide must be conducted at screening, on Day 1 (within 24 hours prior to treatment) of each cycle prior to pomalidomide dispensing or at a minimum of every 28 days (can also be conducted verbally from the site), at the End of Treatment Visit, and at the 28-day post-treatment Safety Follow-up Visit. If pregnancy or a positive pregnancy test does occur in a study subject, treatment must be immediately discontinued. Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Treatment must be discontinued during this evaluation as well. Female children and adult females must agree to abstain from breastfeeding during study participation and for at least 28 days after treatment discontinuation. If pregnancy or a positive pregnancy test does occur in the partner of a male study subject during study participation, the Investigator must be notified immediately.

Furthermore, FCCBP/FCBP and male subjects that have reached puberty must agree to undergo physician-approved reproductive education and discuss the side effects of pomalidomide on reproduction with parent(s) and/or guardian(s) when appropriate. Pregnancy testing is not required for non-FCCBP subjects, unless deemed necessary by the Investigator.

Any pregnancy occurring in either a female subject or partner of a male subject while in the Treatment Period, or within 28 days thereafter, are considered immediately reportable events (see Section 10.4).

#### 6.4.2.10. Assessment of Second Primary Malignancy

Second primary malignancies will be monitored as events of interest and must be reported as SAEs. This includes any SPM, regardless of causal relationship to treatment, occurring at any time for the duration of the study, for at least 5 years from enrollment of the last subject, unless consent/assent is withdrawn, the subject is lost to follow-up, or death. Subjects that do not receive treatment (eg, screen failures) will not be followed for SPM.

Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the eCRF (ie, AE and SPM eCRF) and subject's source

documents. Documentation on the diagnosis of the SPM must be provided at the time of reporting as a SAE (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc).

## 6.5. Pharmacokinetics – Optional

Sparse whole blood samples for PK analysis will be collected from consenting subjects at the time points specified in Table 6. Blood samples MUST be drawn from the arm contra lateral to the arm with the intravenous infusion of concomitant medications (if applicable). For each PK sample, draw approximately 1 mL blood and prepare plasma by centrifugation at 4°C. The dose of pomalidomide (Cycle 1: Day 8 and 15) should be administered to subjects in the morning after the collection of the pre-dose PK blood samples. To reduce PK variability on PK sampling days, subjects will be asked not to eat for 2 hours prior and 2 hours after pomalidomide administration. Specific details regarding the collection, processing, storage, and shipment of PK samples are provided in Appendix E.

Note: Blood samples for PK analysis can be obtained through a central line, if applicable. The use of the central line to collect PK samples and any concomitant medications given via the central line prior to sampling must be captured in the appropriate section of the subject's eCRF and source documents.

**Table 6: Pharmacokinetic Sampling Time Points**

| Collection Time Relative to Pomalidomide Administration | Collection Window | Cycle 1, Day 8 | Cycle 1, Day 15 |
|---|---|---|---|
| 0 hour (pre-dose) | -90 min | x | x |
| 2 hours | ± 30 min | x | x |

The following information must be captured on the PK visit days:

- Actual date and time for PK blood collections
- Administered dose of pomalidomide
- Actual date and time of pomalidomide oral administration

# 7. DESCRIPTION OF STUDY TREATMENTS

## 7.1. Description of Investigational Product

Investigational product will be provided as capsule formulation and oral suspension.

Pomalidomide oral capsules for this clinical study will be supplied by Celgene Corporation in 0.5 mg gelatin capsules (size 4 reddish brown), 1 mg hard gelatin capsules (size 4 reddish brown) and 2 mg, 3 mg and 4 mg hard gelatin capsules (size 2 reddish brown) labeled appropriately as IP for this study. Each bottle contains 21 capsules with each capsule containing pomalidomide as the active ingredient and the following inactive ingredients: mannitol, pre-gelatinized starch and sodium stearyl fumarate. The capsules are supplied in tamper-evident, child-resistant, opaque, high density polyethylene (HDPE bottles) with polypropylene caps.

Celgene Corporation will also supply pomalidomide active pharmaceutical ingredient in individually sealed vials for constitution to an oral suspension. Each vial contains 20 mg of pomalidomide, mannitol, pre-gelatinized starch and sodium stearyl fumarate. The pomalidomide powder in each vial is constituted with 4 ml of water and 5 ml of suspending agent to create a pomalidomide oral suspension with a final volume of 10 mL and a concentration of 2 mg/ml. This suspension is intended for oral administration only.

Please refer to the pomalidomide study drug label for more details on preparation, storage conditions, approved indications, known precautions, warnings and adverse reactions. Additional information may be included on the label as needed or applicable. Label(s) for study drug will contain information as required per local health authority. The pomalidomide dispensing, administration, dosing schedule and dose adjustments to be followed for this study are described in Section 7.2.

## 7.2. Treatment Administration and Schedule

The starting dose of pomalidomide will be 2.6 mg/m$^2$/day, based on the subject's actual BSA calculated at the beginning of each cycle. Pomalidomide (oral capsules or suspension) will be administered daily for the first 21 days of every 28-day cycle and only enough pomalidomide for 1 cycle (21-day supply) of treatment will be dispensed on Day 1 of each new cycle of therapy. The oral suspension is available for use in subjects who are unable to swallow the capsules or at the discretion of the Investigator. On Day 1 of each cycle, pomalidomide will be dispensed and administered after completion of all clinical procedures required for that day. Subsequent pomalidomide administration (ie, Days 2-21 of each cycle) may occur at the subject's home.

Pomalidomide will not be administered on Days 22 through 28 of the 28-Day treatment cycle even if a subject experiences a toxicity that requires dose interruption (see Section 7.2.2). Counting of days should continue uninterrupted and the rest period (Days 22 to 28) should be continued as planned. For example, if a subject experiences a toxicity that requires interruption and does not recover until Day 22, pomalidomide should be restarted on Day 1 of the subsequent cycle if other protocol parameters are met. Subjects will continue treatment for up to 24 cycles or until documented PD, withdrawal of consent/assent, treatment becomes intolerable or death, whichever comes first.

For subjects receiving capsules, the pomalidomide dose should be calculated and rounded up or down to the nearest 0.5 mg as the prescribed dose before each new dosing cycle. The dose

prescribed should be based on the subject's BSA and yield the minimum number of capsules to achieve the prescribed dose. However, if a subject is unable to swallow larger capsules, varying appropriate strength combinations may be considered during medication assignment. Pomalidomide capsules should not be broken, chewed or opened and should be taken at approximately the same time every day for 21 consecutive days in a cycle. If a dose is vomited within 15 minutes of taking the dose and the capsule(s) are visible in the emesis, the dose should be repeated and the Investigator should be notified to have replacement capsule(s) provided. If vomiting occurs beyond 15 minutes of dosing, do not repeat the dose and that day's dose should be skipped. Any vomiting of the capsules should be described in the subject dosing diary.

For subjects receiving the oral suspension of pomalidomide, the dose administered should correspond with a volume that is a 0.1 mL increment. The oral suspension should be taken at approximately the same time every day for 21 consecutive days in a cycle. If the dose is vomited, the dose should not be repeated for that dosing day and details entered in the subject dosing diary. If a subject is receiving the pomalidomide oral suspension, a home healthcare company can be available to assist with the preparation and administration of the oral suspension at the subject's home. The home trial support agent that may visit the subject's home would be a licensed nurse. Refer to the Pomalyst Oral Suspension Preparation Administration and Handling Guide for additional guidance.

Pomalidomide (capsules or oral suspension) can be taken with or without food or beverage; however, to reduce PK variability on PK sampling days in Cycle 1 (Days 8 and 15), consenting subjects should not eat for 2 hours prior and 2 hours after pomalidomide administration. A pomalidomide dosing table is provided in Appendix F to facilitate dosing calculation for both capsules and oral suspension. If a dose is forgotten but remembered within 8 hours, the missed dose should be taken/given immediately. If more than 8 hours have passed since the time the dose was due, that day's dose should be skipped.

Treatment administration will be accurately recorded including, but not limited to, date of administration, dose and any changes in dosage administration (eg, interruption or reduction in dosing due to an AE).

Females of childbearing potential should not handle or administer pomalidomide unless they are wearing gloves. All subjects should not extensively handle the pomalidomide capsule formulation or oral suspension and should maintain storage in the packaging until ingestion. In investigational studies, pomalidomide will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of subjects. Once trained, these healthcare staff will counsel subjects prior to pomalidomide being dispensed to ensure that the subject has complied with all requirements (including use of birth control and pregnancy testing) and that the subject understands the risks associated with pomalidomide. This step will be documented with a completed Education and Counseling Guidance Document and no pomalidomide will be dispensed until this step occurs. Counseling includes verification with the subject that required pregnancy testing was performed and results were negative.

A Pomalidomide Information Sheet will be supplied each time pomalidomide is dispensed.

### 7.2.1. Criteria for Starting Subsequent Treatment Cycles

Prior to the start (within 48 hours) of each treatment Cycle (Day 1) the following parameters **MUST** be met:

- ANC ≥ 1,000/mm$^3$
- Platelet count ≥ 100,000/mm$^3$ (transfusion independent, defined as no platelet transfusion within 7 days and recovery from nadir)
- Does not meet PD or treatment interruption/discontinuation criteria

In addition, subjects **MUST** meet the following within 24 hours prior to the start of each treatment cycle:

- Confirmation of negative serum or urine pregnancy test (sensitivity of at least 25 mIU/mL) in FCCBP/FCBP.
- Confirmation of the use of 2 forms of effective birth control for FCCBP/FCBP and sexually mature males or confirmation of commitment to complete abstinence.
- Completion and documentation of required pomalidomide education and counseling.

If a subject does not meet the above parameters by Day 28 of a treatment cycle, then the subsequent cycle should not be started until these parameters are met. Refer to Section 7.2.2 for dose interruptions/reductions or next cycle delays due to count recovery or non-hematological toxicities.

### 7.2.2. Dose Reductions, Interruptions and Discontinuation Criteria for Toxicities

Hematological and non-hematological toxicity will be graded using CTCAE version 4.03. In all cases, the reason for dose modification/interruption/discontinuation must be recorded in the subject's medical record. If the subject discontinues the protocol-prescribed therapy due to an AE, this event must be reported in accordance with the procedures outlined in Section 10.

Subjects who experience significant toxicity as listed below (Table 8) will have pomalidomide interrupted or reduced as specified in Table 7. Up to two dose reductions of pomalidomide are allowed across the Treatment Period in the event of specific protocol defined toxicity with no evidence of disease progression.

In addition:

- If a subject experiences a toxicity that requires interruption and does not recover until Day 22, pomalidomide (dose-reduced) should be restarted on Day 1 of the subsequent cycle if other protocol parameters are met.
- The dose will not be re-escalated following a dose reduction, even if there is minimal or no toxicity with the subsequent reduction in dose.
- Subjects who again experience dose modifying toxicity after 2 dose reductions will be taken off pomalidomide therapy.

- Subjects who experience hematologic toxicity (eg, neutropenia or thrombocytopenia) should have appropriate laboratory testing at least twice weekly (3 to 4 days apart) until the toxicity has resolved.
- If there is a > 14-day delay in starting the subsequent cycle for a pomalidomide-related toxicity, the investigator should consider pomalidomide dose reduction or pomalidomide discontinuation, based upon clinical judgment and the required dose modification criteria outlined in Table 8.

**Table 7: Dose Reductions of Pomalidomide**

| Dose Level | Dose |
|---|---|
| Starting dose | 2.6 mg/m$^2$/day |
| Dose Level -1 | 1.9 mg/m$^2$/day |
| Dose Level -2 | 1.3 mg/m$^2$/day |
| Dose Level -3 | Discontinue treatment |

### 7.2.2.1. Dose Modifications

**Table 8: Dose Modification Criteria**

| Toxicity | Dose Modification and Discontinuation |
|---|---|
| Grade 4 neutropenia that occurs during the 21-day dosing period<br>Grade 3 or 4 febrile neutropenia<br>Grade 4 neutropenia of ≥ 5 days duration during the treatment rest period | • Interrupt pomalidomide until the neutrophil count recovers to ≥ 1000/mm$^3$ and no fever (≤ 38.3 °C) (if applicable).<br>• If the toxicity resolves and the subject meets eligibility parameters to resume as described in the protocol within 14 days (eg, ANC ≥ 1000/mm$^3$; platelets ≥ 100,000/mm$^3$), the subject should re-initiate treatment at one dose level lower.<br>• If the dose modifying toxicity does not resolve to meet the parameters as described in the protocol within 14 days of treatment being held, pomalidomide should be permanently discontinued. |
| Grade 3 or 4 platelet count decreased that occurs during the 21 day dosing period | • Transfuse platelets to a post-transfusion plate target of ≥ 100,000/µL if platelet count is < 50,000/mm$^3$.<br>• Interrupt pomalidomide until the platelet count recovers to ≥ 100,000/mm$^3$ unsupported (defined as no platelet transfusion within 7 days and recovery from nadir).<br>• If the toxicity resolves and the subject meets eligibility parameters to resume as described in the protocol within 14 days (eg, ANC ≥ 1000/mm$^3$; platelets > 100,000/mm$^3$), the subject should re-initiate treatment at one dose level lower.<br>• If the toxicity does not resolve to meet the eligibility parameters as described in the protocol within 14 days of treatment being held, pomalidomide should be permanently discontinued. |

**Table 8: Dose Modification Criteria (Continued)**

| Toxicity | Dose Modification and Discontinuation |
|---|---|
| Any Grade 4 non-hematological toxicity related to pomalidomide<br>Any Grade 3 non-hematological toxicity related to pomalidomide with the specific exclusion of following:<br>• Grade 3 nausea and vomiting controlled by anti-emetics (≤ 3 days)<br>• Grade 3 fever or infection (≤ 3 days)<br>• Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation | • Interrupt pomalidomide until toxicity returns to baseline or ≤ Grade 2.<br>• If the toxicity resolves and the subject meets eligibility parameters to resume as described in the protocol within 14 days the subject should re-initiate treatment at one dose level lower.<br>• If the toxicity does not resolve to ≤ Grade 2 or meet the eligibility parameters as described in the protocol within 14 days of treatment being held, the investigator, based on clinical judgment, should consider discontinuing pomalidomide permanently. |
| Any other medically significant or sufficiently intolerable AEs ≥ Grade 2 related to pomalidomide that requires treatment interruption | Interrupt pomalidomide until resolution of symptoms.<br>• If resolves (< Grade 2) ≤ 3 days, the subject may resume treatment at the same pomalidomide dose level.<br>• If the toxicity recurs upon drug re-challenge, treatment should be interrupted again until the toxicity resolves (< Grade 2), and subject should re-initiate treatment at a lower dose level.<br>• If the ≥ Grade 2 toxicity recurs at the lower dose level and is considered medically significant or intolerable, pomalidomide should be interrupted again until the toxicity resolves (< Grade 2), and the subject should re-initiate at the next lower dose level.<br>• If the ≥ Grade 2 toxicity recurs after two dose reductions (Dose level -2) and is considered medically significant or intolerable, pomalidomide should be permanently discontinued.<br>• If the toxicity resolves (< Grade 2) after > 3 days but ≤ 14 days, subject may resume treatment at a lower dose level.<br>• If the toxicity does not resolve (< Grade 2) within 14 days of treatment being held, the investigator, based on clinical judgment, should consider discontinuing pomalidomide permanently. |
| Grade 4 rash or blistering, Steven's Johnson or TEN (toxic epidermal necrolysis) or anaphylaxis | Pomalidomide should be discontinued permanently. |
| Non-central line related thromboembolic event | Pomalidomide should be discontinued permanently. |

AEs = adverse events; ANC = absolute neutrophil count.

### 7.2.3. Overdose

Overdose, as defined in this protocol, refers to pomalidomide dosing.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of pomalidomide assigned to a given subject, regardless of any associated AE(s) or sequelae.

- > 10% over the protocol-specified dose.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol-required schedule or frequency.

Complete data about treatment administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the eCRF. See Section 10 for the reporting of AEs associated with overdose.

## 7.3. Method of Treatment Assignment

Subjects will be enrolled (Section 6.1.5) into the study via IRT. For detailed IRT screening and enrollment procedures, please refer to the IRT User Manual. Subjects will enroll and be assigned to one of 4 parallel strata based on the following tumor types: high-grade glioma, medulloblastoma, ependymoma and DIPG.

### 7.3.1. Subject Numbering

All subjects will be screened and subsequently enrolled into the study using IRT. The Investigator or designated site staff will be assigned password protected, coded identification numbers that give them authorization to log into IRT. At screening, the Investigator or designated staff will log into the IRT and provide the requested identifying information for the subject. IRT will then confirm the assignment of a 2-part unique subject ID number consisting of 7 digits. The first part is a 3-digit site number and the second part is a 4-digit number (always starting with "1" for the initial screening) assigned sequentially to subjects at that site (eg, 101-1001, 101-1002, etc). If the subject is not eligible for enrollment into the study, the site is required to register the subject as a screen failure in IRT. Subjects who fail screening may be rescreened at the Investigator's discretion. For subjects who are rescreened, a new ICF/IAF will need to be signed and screening procedures will need to be repeated (if rescreening occurs > 28 days from original screening date). A new Subject ID will be issued once the rescreening transaction is registered in IRT. To identify subjects that rescreen, the 4-digit number identifier will start with "2" (eg, 101-2001) for 2nd rescreen, "3" (eg, 101-3001) for third rescreen, etc.

Once the subject is enrolled into the study, the subject will retain their Subject ID number which will be used to identify that specific subject during participation in the study.

## 7.4. Packaging and Labeling

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

## 7.5. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and/or in the Investigator's Brochure.

Accountability for all treatment administered during the course of the study is the responsibility of the Investigator (or designee). The Investigator (or designee) is responsible for taking an inventory of each shipment pomalidomide received, and comparing it with the accompanying accountability form. The Investigator (or designee) will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene.

The investigational site must maintain accurate records demonstrating dates and amounts of treatment received, to whom it was administered (subject-by-subject accounting), and accounts of any pomalidomide accidentally or deliberately destroyed or returned. Accurate recording of all treatment administration will be made in the appropriate section of the subject's eCRF and source documents.

All IP that is dispensed during the course of the study will be reconciled and accounted for by the Investigator (or designee). Applicable information such as lot number, dose information, date dispensed, numbers of capsules or oral suspension kit components dispensed/returned, date returned, etc. should be collected as well as information provided by the subject or the caregiver (eg, subject dosing diary). Treatment accountability should be completed on Cycle 1 Day 1, at the end of every treatment cycle (Day 1 of subsequent cycle) and at the end of treatment (EOT) Visit.

Unless otherwise notified, all pomalidomide both used and unused must be saved for study treatment accountability.

## 7.6. Investigational Product Compliance

Compliance for pomalidomide administrated during the course of the study is the responsibility of the Investigator or designee and accurate recording of all treatment will be captured in the appropriate section of the subject's eCRF and source document. Compliance will be defined as taking between 75% and 110% of the intended quantity of study treatment.

Compliance of the IP will be based on what drug is returned and/or written in the subject dosing diary.

# 8. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from study treatments or disease progression. Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator.

All concomitant treatments, including blood and blood products, used from 28 days prior to first dose of study drug, except for those taken for the subject's disease, must be reported on the eCRF. Medications and procedures associated with the disease under study prior to screening will be captured under "Prior disease therapies." Concomitant treatments must be reported until the 28-day post-treatment Safety Follow-up Visit on the eCRF.

For information regarding other drugs that may interact with treatment and affect its metabolism, pharmacokinetics, or excretion, please see the Investigator's Brochure and/or local package insert and prescribing information.

## 8.1. Permitted Concomitant Medications and Procedures

All supportive care (eg, antibiotics, blood products, anti-emetics, fluids, electrolytes, etc.), with exception of prohibited concomitant medicines and procedures listed in Section 8.2, is permitted when necessary and clinically indicated. This includes but not limited to:

### 8.1.1. Anti-emetics

Anti-emetics should not be administered prophylactically prior to the first dose of pomalidomide. Subsequent use of anti-emetics should be given as needed at the Investigator's discretion.

### 8.1.2. Corticosteroids

Corticosteroid therapy should be used at the lowest dose consistent with good management for treatment of increased intracranial pressure or physiologic replacement. Physiologic replacement doses will be defined on this protocol as no more than 0.75 mg/m$^2$/day of dexamethasone or equivalent of corticosteroids. Doses higher than this will be considered therapeutic.

Corticosteroids should **not** be used as a first-line anti-emetic. Subjects on steroids who require an increase in steroid dose for worsening neurologic symptoms should have a brain and/or spine MRI performed within 72 hours to rule out tumor progression.

Note: Subjects who are receiving corticosteroids at screening must be on a stable or decreasing dose for at least 5 days prior to the screening/baseline MRI.

### 8.1.3. Colony Stimulating Growth Factors

Routine use of growth factors (eg, filgrastim, sargramostim) in clinically well subjects awaiting count recovery is not recommended. Therapeutic use of growth factors in subjects with serious neutropenic conditions (eg, ANC < 500/mm$^3$), such as sepsis, may be considered at the Investigator's discretion.

### 8.1.4. Anticonvulsants

Subjects on anti-epileptic drugs (AEDs) may continue taking these medications as clinically indicated. Due to the unknown effects of pomalidomide on the metabolism of AEDs, it is recommended that anticonvulsant levels be followed closely while on this study.

### 8.1.5. Neurosurgical or Other Surgical Procedure

If a neurosurgical procedure or other surgical procedure is required for a reason other than tumor progression (ie, the onset of hydrocephalus), these procedures should be documented, but will not constitute criteria for declaring the subject "off therapy." Pomalidomide should be held until the subject is clinically stable and has recovered from the acute effects of surgery. Holding and restarting pomalidomide for these neurosurgical interventions should be discussed with the Sponsor and Principal Investigator when possible, and documented in the eCRF and source documents.

### 8.1.6. Alternative Supplements

Subjects on alternative supplements should strongly be encouraged to discontinue them prior to first dosing of treatment. If subjects opt to continue, they may be enrolled into the study as long as they have been receiving the supplement for at least 30 days, with no evidence of hepatic, renal or other organ dysfunction, and the administration is approved by the Investigator.

### 8.1.7. Antibiotics Associated with Febrile Neutropenia

Febrile neutropenia should be managed according to the local institutional guidelines; however, pomalidomide dosing should be modified as described in Table 8.

## 8.2. Prohibited Concomitant Medications and Procedures

Subjects must be instructed not to take any additional medications (over-the-counter, herbal or other products) during the study without prior consultation with the Investigator. Concurrent cancer therapy, including investigational, chemotherapy, immunotherapy, live vaccines (with exception to nasal influenza vaccine) or biologic therapy may NOT be administered to subjects while on this study. The use of alternative or complementary therapies is also discouraged, but if given, should be recorded in the database.

### 8.2.1. Radiotherapy

Radiotherapy is not permitted.

### 8.2.2. Deep Venous Thrombosis Prophylaxis

The use of medication for deep vein thrombosis prophylaxis is not allowed for this study. In the event of non-central line related thrombosis, pomalidomide will be discontinued permanently and not restarted.

Drugs known to be pro-thrombotic (ie, erythropoietic stimulating agents) should be avoided.

### 8.2.3. Anti-coagulation Medications

The use of anticoagulation medications is not permitted, with the exception of tPA (ie, Alteplase), which may be used to dissolve central-line related thrombosis.

### 8.2.4. Moderate to Strong CYP1A2 Inhibitors

Co-administration with moderate to strong CYP1A2 inhibitors (eg, ciprofloxacin, enoxacin, fluvoxamine, etc) are not permitted due to the potential drug interactions with pomalidomide. Subjects taking a known moderate to strong CYP1A2 inhibitor are excluded from this study. Pomalidomide is primarily metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein. Therefore, use of CYP1A2 inhibitors may increase pomalidomide exposure. The treating Investigator should consult a current drug information reference for a complete list (http://medicine.iupui.edu/clinpharm/ddis/main-table/).

**Note:** As an exception, subjects can be administered propofol (an inhibitor of CYP1A2) for sedation procedures such as a MRI.

## 8.3. Required Concomitant Medications and Procedures

Not Applicable.

# 9. STATISTICAL CONSIDERATIONS

## 9.1. Overview

This study consists of 4 independent strata for each of a distinct disease indication (high-grade glioma, medulloblastoma, ependymoma and DIPG). Each stratum will enroll up to 20 subjects in total that are eligible for analysis of the primary endpoint, ie, a maximum of 80 subjects across the 4 strata assuming no subjects are replaced. A Simon's Optimal two-stage study design will be applied to each stratum. All baseline and efficacy based endpoints (ORR, long-term SD rate, DoR, OS, and PFS) will be presented by stratum; safety data shall be presented by stratum and in aggregate. A DMC will be used to monitor the study conduct.

## 9.2. Study Population Definitions

**Informed Consent/Assent Population**

The Informed Consent/Assent Population will consist of all subjects with signed informed consent/assent provided. The Informed Consent/Assent Population will be used for describing the disposition of subjects with signed informed consent/assent.

**Response Population**

The Response Population will consist of all subjects enrolled, receiving at least 1 cycle of pomalidomide, if not discontinued therapy earlier due to PD. Subjects who withdraw from the Treatment Period for any reason other than PD prior to completing Cycle 1 of study treatment will be replaced. Subjects completing at least one cycle of study therapy but not having at least one post-baseline disease assessment will be considered a non-responder. The Response Population shall be used for analysis of the primary endpoint.

**Intent-to-Treat Population**

The Intent to Treat (ITT) Population will consist of all subjects enrolled regardless of whether the subject received the assigned study treatment or not. The ITT population will be used for analysis of efficacy endpoints. This analysis population will only be used if there is at least one subject that enrolled into the study but did not receive study medication.

**Safety Population**

The Safety Population will consist of all subjects who received at least one dose of pomalidomide. The safety population will be applied for the analysis of all safety and efficacy endpoints.

**Pharmacokinetic Population**

The PK Population will include all subjects who received at least one dose of pomalidomide and have at least one measurable pomalidomide plasma concentration. The evaluable subjects in the PK population will be included in the PK data analysis.

## 9.3. Sample Size and Power Considerations

Under Simon's Optimal two-stage design with a 5% significance level and 90% power, assuming a lower boundary of interest in the response rate of 10% and an upper boundary of interest in the

response rate of 40%, a total of 20 subjects evaluable for the primary endpoint (ie, Response Population) are required per stratum; 9 per stratum in Stage 1 and an additional 11 per stratum in Stage 2.

Enrollment will proceed as follows:

1. Stage 1: Nine subjects will be enrolled into each of the strata.
2. Stage 2: If during Stage 1, ≥ 2 subjects in a given stratum achieve either an OR (either CR or PR) within the first 6 cycles of treatment (within 3 cycles for DIPG) or a long-term SD, an additional 11 subjects shall be enrolled to that stratum; otherwise no additional subjects will be enrolled.
3. If a total of 5 or more subjects across all 20 subjects in a given stratum (Stage 1 and 2) evaluable for the primary endpoint are observed as having either an OR (either CR or PR) within the first 6 cycles of treatment (within 3 cycles for DIPG) or long-term SD, pomalidomide will be considered effective in that disease indication.

Up to 80 subjects (36 subjects in Stage 1 and 44 subjects in Stage 2) will be included should all strata enroll the maximum number of subjects (ie, 20 per stratum), assuming no subjects are replaced.

## 9.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race, and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

## 9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for the Screening Period, Treatment Period and Follow-up Period. A summary of subjects enrolled by site will be provided. Protocol deviations and violations will be summarized using frequency tabulations.

## 9.6. Efficacy Analysis

**Objective Response and Long-term Stable Disease Rate**

Objective response and long-term SD rate (ORSDR), is defined as the total number of subjects achieving either an OR (either CR or PR) within the first 6 cycles of treatment (within 3 cycles for DIPG) or a long-term SD (SD maintained for ≥ 6 cycles [≥ 3 cycles for DIPG]), over the total number of subjects evaluable for analysis. Evaluable is defined as a subject completing at least one cycle of study therapy or discontinuing treatment earlier due to a PD. Subjects completing at least one cycle of study therapy but not having at least one subsequent (post-baseline) disease assessment will be considered a non-responder. The corresponding Clopper Pearson 95% confidence interval (CI) shall be calculated for each rate per stratum. Each stratum will be analyzed separately. Analysis of this endpoint will be based on the Response Population, with secondary analyses based on the ITT Population and/or Safety Population.

**Objective Response Rate**

The ORR is defined as the total number of subjects achieving an OR (either CR or PR), over the total number of subjects evaluable for the analysis. Disease responses occurring after start of a new anticancer therapy shall not be considered. Each stratum will be analyzed separately. Analysis of this endpoint will be based on the ITT Population and/or Safety Population.

**Long-term Stable Disease Rate**

The long-term SD rate is the proportion of subjects achieving long-term SD, defined as a SD maintained for ≥ 6 cycles (≥ 3 cycles for DIPG), over the total number of subjects evaluable for the analysis. The corresponding Clopper Pearson 95% CI shall be calculated for each rate per stratum. Each stratum shall be analyzed separately. Analysis of this endpoint will be based on the ITT Population and/or Safety Population.

**Duration of Response**

Duration of response is defined as the time from first observed response (either CR or PR, whichever comes first) until either disease progression, or death. Only subjects observed with a response shall be included in the analysis of DoR. The median DoR time and the proportion of subjects remaining with a response at 3, 6, 9, 12, 18 and 24 months, and at close of study along with the corresponding 95% CI will be calculated using Kaplan-Meier methods. Subjects who are alive and remain in disease response at the time of analysis will be censored at the time of their last adequate disease assessment or at the time of starting a new anticancer therapy, whichever is first. Due to the low number of subjects to be included in the analysis, additional summary statistics will be presented. Each stratum shall be analyzed separately. Analysis of this endpoint will be based on the ITT Population and/or Safety Population.

**Progression-Free Survival**

Progression-free survival is defined as the time from enrollment until either disease progression, or death of any cause, whichever occurs first. The median PFS time and proportion of subjects remaining progression-free at 3, 6, 9, 12, 18 and 24 months, and at close of study along with the corresponding 95% CI calculated using Kaplan-Meier methods will be presented. Subjects remaining progression-free at the time of analysis will be censored at the time of their last adequate disease assessment. Additionally, subjects will be censored at the time of starting a new anticancer therapy if having not had disease progression previously. Due to the low number of subjects to be included in the analysis, additional summary statistics will be presented. Each stratum shall be analyzed separately. Analysis of this endpoint will be based on the ITT Population and/or Safety Population.

**Overall Survival**

Overall survival is defined as the time from enrollment until death of any cause. The median OS time and proportion of subjects remaining alive at 3, 6, 9, 12, 18 and 24 months, and at close of study, along with the corresponding 95% CI, calculated using Kaplan-Meier methods will be presented. Subjects remaining alive at the time of analysis will be censored at the time they were last known to be alive. Due to the low number of subjects to be included in the analysis, additional summary statistics will be presented. Each stratum shall be analyzed separately. Analysis of this endpoint will be based on the ITT Population and/or Safety Population.

## 9.7. Safety Analysis

**Toxicity Assessment**

Toxicity, including SPMs, will be monitored in real time during the course of the study. Descriptive statistics will be used to summarize the proportion of subjects experiencing any Grade 3 or higher non-hematologic toxicities and infections.

**Adverse Events**

Adverse Events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) (latest version). This study will utilize the NCI CTCAE (version 4.03) for toxicity grading and performance reporting. All AE data shall be presented by disease stratum and in aggregate, based on the Safety Population, ie, all subjects receiving at least one dose of pomalidomide.

Treatment-emergent adverse events are defined as any AE occurring or worsening on or after the first dose of the study medication until the 28-day post-treatment Safety Follow-up Visit. All TEAEs, AEs leading to study medication discontinuation, AEs leading to dose reduction/ interruption, AEs related to the study treatment, SAEs, and AEs leading to death will be summarized by cycle and 28-day follow-up period after permanent treatment discontinuation as well as by subject (worse recorded grade) per event type (organ class and preferred term) and grade. A summary of AEs with NCI CTCAE (version 4.03) Grade 3 or higher, as well as the most frequent preferred terms, will also be provided by grade and term.

Cross tabulations will be provided to summarize frequencies of abnormalities.

By-subject listings will be provided for all relevant safety data. Graphical displays and figures will be provided where useful to assist in the interpretation of results.

**Deaths**

Deaths during the Treatment Period (defined as the time between enrollment until the 28-day post-treatment Safety Follow-up Visit) and during the Follow-up Period shall be summarized by frequency of occurrence and corresponding percentage by cause of death per study period (during treatment or follow-up) as well as overall. All death data shall be presented by disease stratum and in aggregate.

## 9.8. Interim Analysis

For each stratum, there is one interim analysis planned at the end of Stage 1. The interim analysis will be informal, performed internally by Celgene personnel with input, only if needed, from the DMC and steering committee (SC). Enrollment will be suspended for each interim analysis, once the first 9 subjects evaluable for the primary endpoint have been enrolled. Enrollment for each stratum will be re-opened/closed based upon the following criteria:

- Should only one or no subjects be observed as having either an OR (either CR or PR) or a long-term SD, that stratum shall be closed to further enrollment.
- Should at least 2 subjects across Stage 1 have either an OR (either CR or PR) or a long-term SD, then that stratum will continue into Stage 2 to include up to 11 more additional subjects evaluable for the primary endpoint.

## 9.9. Other Topics

### 9.9.1. Pharmacokinetic Analysis

If warranted, population PK analysis (eg, CL/F and Vd/F) of pomalidomide plasma concentrations will be conducted, with possible pooling of data from other clinical studies with pomalidomide.

### 9.9.2. Data Monitoring Committee

An external DMC with multidisciplinary representation will be established to evaluate safety data periodically to monitor the overall benefit-to-risk of this protocol. The DMC will be comprised of medical oncologists with experience in treating pediatric subjects with brain tumors and a statistician, all of whom are not otherwise involved in the study conduct. During the course of the study, the DMC will review the safety data regularly as well as safety and efficacy data in accordance with the guidelines for the preplanned interim analyses (ie, end of Stage 1 and Stage 2).

The DMC will advise on serious safety considerations and any other issues important to the safe conduct of the study, and will make recommendations about the continuing safety of current participants and those yet to be enrolled. The DMC will also provide recommendations about stopping the study, or continuing the study as planned, or with modifications for safety reasons, and may advise on ways to improve quality.

Details regarding the operational aspects, structure, composition, roles and responsibilities of the DMC will be outlined in a DMC charter.

### 9.9.3. Steering Committee

The SC will be established comprising of Investigators participating in the study (ie, not being members of a DMC and Celgene representatives from the clinical study team).

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical study team, the SC will also develop recommendations for publications of study results including authorship rules (if applicable). The details of the role of the SC are defined in a SC charter.

# 10. ADVERSE EVENTS

## 10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to the IP should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF. (See Section 7.2.3 for the definition of overdose.) Any sequela of an accidental or intentional overdose of the IP should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for pomalidomide overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent/assent until the 28-day post-treatment Safety Follow-up Visit as well as those SAEs made known to the Investigator at any time thereafter while in Long-term Follow-up that are suspected of being related to study drug. Adverse events and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

## 10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

### 10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);

- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

### 10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the CTCAE, Version 4.03); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

### 10.2.3. Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

| | |
|---|---|
| Not suspected: | a causal relationship of the AE to the IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event. |
| Suspected: | there is a **reasonable possibility** that the administration of the IP caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the AE. |

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

### 10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

### 10.2.5. Action Taken

The Investigator will report the action taken with the IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of the IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

### 10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

## 10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of the IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

## 10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a FCBP/FCCBP or partner of childbearing potential of a male subject are immediately reportable events.

The exposure of any pregnant female (eg, caregiver, pharmacist, study coordinator or monitor) to pomalidomide is also an immediately reportable event.

### 10.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a FCBP/FCCBP regardless of disease state) occurring while the subject is on IP, or until the 28-day post-treatment Safety Follow-up Visit are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or any other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate methods, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

### 10.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

## 10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

Second primary malignancies will be monitored as events of interest and must be reported as SAEs. This includes any SPM, regardless of causal relationship to treatment, occurring at any time for the duration of the study, for at least 5 years from enrollment of the last subject, unless consent/assent is withdrawn, the subject is lost to follow-up, or death. Subjects that do not receive treatment (eg, screen failures) will not be followed for SPM. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate

page(s) of the eCRF (ie, AE and SPM eCRF) and subject's source document(s). Documentation on the diagnosis of the SPM must be provided at the time of reporting as an SAE (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc.).

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to the IP) that occur during the study (from the time the subject signs informed consent/assent until the 28-day post-treatment Safety Follow-up Visit) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF/IAF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

### 10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

## 10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to pomalidomide based on the Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and ECs concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on the IP for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of the IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (see Section 14.3 for record retention information).

**Celgene Drug Safety Contact Information:**

For Celgene Drug Safety contact information, please refer to the SAE Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

# 11. DISCONTINUATIONS

## 11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the IP(s):

- Adverse Event
- Withdrawal of consent/assent by subject/parent(s)/legal guardian(s) - under this situation, the Investigator should clarify if the family also wishes to withdraw the study ICF/IAF for continued participation in the Long-term Follow-up Period and data collection
- Death
- Lost to follow-up
- Pregnancy
- Non-compliance with IP
- Progressive disease
- Physician decision
- Protocol violation
- Completion of the Treatment Period (24 cycles)
- Study or site terminated by Sponsor
- Other (to be specified on the eCRF)

The reason for discontinuation of treatment, last dose of treatment and date subject taken off treatment should be recorded in the eCRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician and will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documentation for review and discussion.

## 11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Withdrawal of consent/assent by subject/parent(s)/legal guardian(s) for any further data collection
- Death
- Lost to follow-up
- Completion of the Follow-up Period

- Study or site terminated by Sponsor
- Other (to be specified on the eCRF)

The date and reason for study discontinuation should be recorded in the eCRF and in the source documents.

All subjects who are withdrawn from the study should complete all protocol-required evaluations scheduled for treatment discontinuation at the time of withdrawal.

Since the follow-up of subjects who discontinue prematurely is of particular importance, every attempt should be made to collect all survival information and new anticancer treatment/therapy, unless the subject has specifically withdrawn consent/assent from further follow-up.

**Note:** The Long-term Follow-up Period may not be terminated because of new anticancer treatment.

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent/assent, the Investigator should show "due diligence" by contacting the subject, family or family physician as agreed in the informed consent/assent and by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc. A subject should not be considered lost to follow-up until due diligence has been completed. Subjects lost to follow-up should be recorded as such on the appropriate eCRF.

# 12. EMERGENCY PROCEDURES

## 12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Celgene Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day, 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physicians or Medical Monitor or designee for emergency calls.

## 12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, the IP will be identified on the package labeling.

# 13. REGULATORY CONSIDERATIONS

## 13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

## 13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an ICF/IAF and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and Investigator's Brochure information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

## 13.3. Subject Information and Informed Consent/Assent

The Investigator must obtain informed consent/assent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent/assent occurred prior to the study subject's entry into the study and of the informed consent/assent process should be recorded in the study subject's source documents including the date. The original ICF/IAF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent/assent, the ICF/IAF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented/assented with the revised version of the ICF/IAF. The revised ICF/IAF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

## 13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF/IAF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

## 13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

## 13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

The IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

## 13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected AEs as soon as possible
- Periodic reports on the progress of the study
- Deviations from the protocol or anything that may involve added risk to subjects

## 13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In the case where there are subjects still being administered the investigational product, and it is the opinion of the Investigator(s) that these subjects continue to receive benefit from treatment, the Sponsor may choose to initiate an open-label, extension study under a separate protocol to allow these subjects continued access to pomalidomide following their participation in this study (CC-4047-BRN-001).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment

- GCP noncompliance
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the study protocol

# 14. DATA HANDLING AND RECORDKEEPING

## 14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the IP are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of eCRFs or CD-ROM.

## 14.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

## 14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs/IAFs for all subjects
- Subject identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the Investigator and the IRB/EC
- Composition of the IRB/EC
- Record of all communications between the Investigator, Celgene, and their authorized representative(s)
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures
- Copies of eCRFs and of documentation of corrections for all subjects
- IP accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (subject records, hospital records, laboratory records, etc.)

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. The Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

# 15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

## 15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent/assent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, facsimile, or telephone. During monitoring visits, the facilities, IP storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents/assents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

## 15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

# 16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study SC (when applicable) and contribution to abstract, presentation and/or publication development.

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# 18. APPENDICES

## Appendix A: Table of Abbreviations

**Table 9: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AE | Adverse event |
| AED | Anti-epileptic drugs |
| ALT | Alanine aminotransferase (SGPT) |
| ANC | Absolute neutrophil count |
| ATRT | Atypical teratoid rhabdoid tumor |
| AUC | Area under the curve |
| β-FGF | Basic fibroblast growth factor |
| β-Hcg | β-subunit of human chorionic gonadotropin |
| BSA | Body surface area |
| CDK | Cyclin-dependent kinase |
| CI | Confidence interval |
| CL/F | Clearance |
| $C_{max}$ | Maximum plasma concentration of drug |
| CNS | Central nervous system |
| COG | Children oncology group |
| CR | Complete response |
| CRBN | Cereblon protein |
| CRO | Contract research organization |
| CSF | Cerebrospinal fluid |
| CTCAE | Common terminology criteria for adverse events |
| CUL4 | Cullin 4 |
| CYP | Cytochrome P450 |
| DDB1 | DNA Damage-binding protein 1 |
| DIPG | Diffuse intrinsic pontine glioma |
| DLT | Dose-limiting toxicity |
| DMC | Data Monitoring Committee |
| DoR | Duration of response |
| EC | Ethics Committee |

**Table 9: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| eCRF | Electronic case report form |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| EOT | End of treatment |
| EU | European Union |
| FCBP | Females of childbearing potential |
| FCCBP | Female children of childbearing potential |
| FDA | Food and Drug Administration |
| FLAIR | Fluid-attenuated inversion recovery |
| GBM | Glioblastoma multiforme |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte colony-stimulating factor |
| GFR | Glomerular filtration rate |
| GTR | Gross total resection |
| GVHD | Graft versus host disease |
| HDPE | High density polyethylene |
| IAF | Informed assent form |
| ICF | Informed consent form |
| ICH | International Council on Harmonisation |
| ID | Identification number |
| IIT | Investigator initiated trial |
| IL | Interleukin |
| IND | Investigational new drug |
| IFN-γ | Interferon-gamma |
| IP | Investigational product |
| IR | Incomplete response |
| IRF4 | Interferon regulatory factor 4 |
| IRB | Institutional review board |
| IRT | Interactive Response Technology |
| ITT | Intent to treat |

**Table 9: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| MAA | Marketing authorization application |
| MDS | Myelodysplastic syndromes |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MF | Myelofibrosis |
| MM | Multiple myeloma |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |
| NCI | National cancer institute |
| NCS | Not clinically significant |
| NF1 | Neurofibromatosis type 1 |
| NHL | non-Hodgkin's lymphoma |
| NK | Natural killer |
| NLME | Nonlinear mixed-effect |
| $O_2$ | Oxygen |
| OAT | Organic anion transporter |
| OCT | Organic cation transporter |
| OR | Objective response |
| ORR | Objective response rate |
| ORSDR | Objective response and long-term stable disease rate |
| OS | Overall survival |
| PA | Pilocytic astrocytoma |
| PBTC | Pediatric Brain Tumor Consortium |
| PD | Progressive disease |
| PFS | Progression-free survival |
| PR | Partial response |
| PK | Pharmacokinetics |
| PNET | Primitive neuroectodermal tumor |
| RBC | Red blood cell count |
| RP2D | Recommended phase 2 dose |

**Table 9: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| SAE | Serious adverse event |
| SC | Steering committee |
| SCT | Stem cell transplant |
| SD | Stable disease |
| SOP | Standard operating procedure |
| SPM | Second primary malignancy |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{1/2}$ | Half-life |
| TBI | Total body irradiation |
| TEAE | Treatment emergent adverse event |
| TEN | Toxic epidural necrolysis |
| TGF-α | Transforming growth factor alpha |
| Th1 | T helper cell type 1 |
| $T_{max}$ | Time to maximum plasma concentration |
| TNF-α | Tumor necrosis factor-alpha |
| tPA | Tissue plasminogen activator |
| ULN | Upper limit of normal |
| Vd/F | Volume of distribution |
| VEGF | Vascular endothelial growth factor |
| WBC | White blood cell |
| WHO | World Health Organization |

# Appendix B: Tumor Response Categories for Target and Non-target Lesions

## Target Lesions

For the purpose of this study, response criteria for target lesions are defined as follows:

- **Complete Response (CR):**
  - Complete disappearance on MRI of all measurable lesions.
- **Partial Response (PR):**
  - A reduction of ≥ 50% in tumor size by bi-dimensional measurement (taking as reference the baseline measurements) quantified by the sum of the products of the perpendicular diameters of measurable lesions.
- **Stable Disease (SD):**
  - A decrease of < 50% or an increase of < 25% in the sum of the products of the perpendicular diameters of measurable lesions and no evidence of new lesions. Response does not meet the criteria for CR, PR or PD.
- **Progressive Disease (PD)**:
  - ≥ 25% increase in the bi-dimensional measurement as quantified by the sum of the products of the largest diameters of the measurable lesions taking as a reference the smallest disease measurement recorded since the start of protocol therapy (nadir).

## Non-target Lesions

For the purpose of this study, response criteria for non-target lesions are defined as follows:

- **Complete Response (CR):**
  - Disappearance of all non-target lesions.
  - If spine MRI and/or lumbar CSF cytology were previously positive, it must be negative at time of assessment.
- **Incomplete Response/Stable Disease (IR/SD):**
  - The persistence of non-target lesions, stable (no progression) or decrease in size.
  - If spine MRI and/or lumbar CSF cytology were previously positive at baseline and remains positive with no other evidence of PD.
- **Progressive Disease (PD):**
  - The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.
  - If spine MRI and/or lumbar CSF cytology were previously negative and became positive.

## Appendix C: Overall Response Assessment

The overall response assessment takes into account response in both target (Appendix B) and non-target lesions (Appendix B), the appearance of new lesions, current corticosteroid use (compared to baseline) and neurologic symptoms/examination (clinical status) according to the criteria below (Table 10). Subjects who do not meet the criteria for an objective response or disease progression by the end of Cycle 6 (end of Cycle 3 for DIPG subjects) will be considered as having long-term SD.

**Table 10: Overall Response Assessment**

| | Overall Response | | | | |
|---|---|---|---|---|---|
| **Criterion** | **Complete Response** | **Partial Response** | | **Stable Disease** | **Progression** |
| Target lesions | CR | PR | CR | SD | PD |
| Non-Target lesions | CR | CR or IR/SD | IR/SD | CR or IR/SD | PD |
| New Lesion | None | None | None | None | Present |
| Corticosteroids | None[a] | Stable or Decreasing[b] | Stable or Decreasing[b] | Stable or Decreasing[b] | Not Applicable[c] |
| Clinical Status (neurologic examination) | Stable or Improved | Stable or Improved | Stable or Improved | Stable or Improved | Decreasing[d] |
| Requirement for Response | All | All | All | All | Any[e] |

CR = complete response; IR = incomplete response; PR = partial response; SD = stable disease; PD = progressive disease.

[a] Only physiologic replacement doses allowed, defined as no more than 0.75 mg/m$^2$/day of dexamethasone or equivalent.

[b] Not greater dose than compared with baseline.

[c] An increase in corticosteroid dose alone will not cause a determination of progression in the absence of clinical deterioration or radiographically documented lesion growth.

[d] Neurologic abnormalities or worsening neurologic status not explained by causes unrelated to tumor progression (eg, anticonvulsant or corticosteroid toxicity wean, electrolyte disturbances, sepsis, hyperglycemia, etc.) or changes in corticosteroid dose.

[e] Progression occurs when any of these criteria are met present.

# Appendix D: Performance Status

## Table 11: Performance Status

| Karnofsky Scale (age ≥ 16 years) | | Lansky Scale (age < 16 years) | |
|---|---|---|---|
| Able to carry on normal activity and to work; no special care needed. | | Able to carry on normal activity; no special care is needed | |
| 100 | Normal no complaints; no evidence of disease | 100 | Fully active |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease | 90 | Minor restriction in physically strenuous play |
| 80 | Normal activity with effort; some signs or symptoms of disease | 80 | Restricted in strenuous play, tires more easily, otherwise active |
| Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed. | | Mild to moderate restriction | |
| 70 | Cares for self; unable to carry on normal activity or to do active work | 70 | Both greater restrictions of, and less time spent in active play |
| 60 | Requires occasional assistance, but is able to care for most of his personal needs | 60 | Ambulatory up to 50% of the time, limited active play with assistance/supervision |
| 50 | Requires considerable assistance and frequent medical care | 50 | Considerable assistance required for any active play, fully able to engage in quiet play |
| Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly. | | Moderate to severe restriction | |
| 40 | Disabled; requires special care and assistance | 40 | Able to initiate quiet activities |
| 30 | Severely disabled; hospital admission is indicated although death not imminent | 30 | Needs considerable assistance for quiet activity |
| 20 | Very sick; hospital admission necessary; active supportive treatment necessary | 20 | Limited to very passive activity initiated by others (eg, television) |
| 10 | Moribund; fatal processes progressing rapidly | 10 | Completely disabled, not even passive play |
| 0 | Dead | 0 | Unresponsive |

Source: Karnofsky, 1949; Lansky 1987.

# Appendix E: Plasma PK Sample Handling Instruction

Each participating institution will be provided with PK sample collection kits along with a PK laboratory manual.

**Preparation of Collection Tubes and Storage Vials**

All labels will be provided by central laboratory. The labels will contain the following information:

- Protocol No.: **CC-4047-BRN-001**
- Subject ID number: (To be added by site)
- Nominal Time (eg, 2 hours postdose)
- Sample Type (eg, Plasma Primary or Backup)

All plasma collection tubes and storage vials should be labeled and chilled on wet ice **prior to** sample collection and processing.

**Pomalidomide Plasma PK Sample Handling**

1. **Blood Sample Collection**
   - Fill an ice bucket with a sufficient amount of ice to pre-chill all collection tubes before blood draw.
   - Collect approximately 1 mL of whole blood into a pre-chilled **K2 EDTA** tube.
   - Accurately record the time of blood collection.
   - Gently invert the tube 3 to 5 times and immerse it into ice bath immediately to prevent possible compound degradation at room temperature.
2. **Blood Sample Processing to Obtain Plasma**
   - **Within 30 minutes of collection**, the blood sample must be centrifuged at 1,500 g (about 3,000 rpm) for 10 minutes at 4°C to obtain plasma.
   - Transfer approximately 0.25 mL of plasma into each of two pre-labeled, pre-chilled, polypropylene citric acid storage tubes (ie, primary and back up).
   - Keep storage tubes on ice before they are ready to be transferred into a freezer.
   - **Within 60 minutes of blood collection**, transfer plasma samples in storage vials into a –20°C freezer, where the tubes will remain stored until shipping.
   - Immediately record the time of sample entry into the freezer.

**PK Plasma Sample Shipment**

**All PK sample label information on the storage tubes have to be checked against the requisition form and then the samples must be shipped on dry ice from the sites to the central lab.**

A copy of the completed specimen manifest must accompany the shipment, and must list the following information at minimum:

- Sponsor name: Celgene Corp
- Celgene Study Number: **CC-4047-BRN-001**
- Subject ID Numbers
- Collection date (eg, dd mmm yyyy)
- Nominal collection time (ie, 2 hours postdose)
- Sample types (eg, Plasma Primary or Backup)

The central lab will then ship the samples to XBL for sample analysis of pomalidomide.

# Appendix F: Pomalidomide Dosing

**Table 12: Pomalidomide Capsule Dosing Tables**

| **2.6 mg/m$^2$/day (Starting Dose)** | | |
|---|---|---|
| **Minimum BSA (m$^2$)** | **Maximum BSA (m$^2$)** | **Daily Pomalidomide Dose (mg)** |
| 0.55 | 0.66 | 1.5 |
| 0.67 | 0.86 | 2.0 |
| 0.87 | 1.05 | 2.5 |
| 1.06 | 1.25 | 3.0 |
| 1.26 | 1.44 | 3.5 |
| 1.45 | 1.63 | 4.0 |
| 1.64 | 1.82 | 4.5 |
| 1.83 | 2.01 | 5.0 |
| 2.02 | 2.21 | 5.5 |
| 2.22 | 2.40 | 6.0 |
| 2.41 | 2.50 | 6.5 |
| **1.9 mg/m$^2$/day (Dose Level -1)** | | |
| **Minimum BSA (m$^2$)** | **Maximum BSA (m$^2$)** | **Daily Pomalidomide Dose (mg)** |
| 0.55 | 0.66 | 1.0 |
| 0.67 | 0.92 | 1.5 |
| 0.93 | 1.18 | 2.0 |
| 1.19 | 1.44 | 2.5 |
| 1.45 | 1.71 | 3.0 |
| 1.72 | 1.97 | 3.5 |
| 1.98 | 2.23 | 4.0 |
| 2.24 | 2.49 | 4.5 |
| 2.50 | 2.50 | 5.0 |

**Table 12: Pomalidomide Capsule Dosing Tables (Continued)**

| 1.3 mg/m$^2$/day (Dose Level -2) | | |
|---|---|---|
| **Minimum BSA (m$^2$)** | **Maximum BSA (m$^2$)** | **Daily Pomalidomide Dose (mg)** |
| 0.55 | 0.66 | 0.5 |
| 0.67 | 0.96 | 1.0 |
| 0.97 | 1.34 | 1.5 |
| 1.35 | 1.73 | 2.0 |
| 1.74 | 2.11 | 2.5 |
| 2.12 | 2.50 | 3.0 |

BSA = body surface area.

**Table 13: Pomalidomide Dosing Table – Oral Suspension**

For subjects receiving pomalidomide as an oral suspension, please refer to the Pomalyst Oral Suspension Preparation Administration and Handling Guide for additional guidance.

| Calculated Dose (mg/day) | Actual Dose Administered (mg/day) | Volume Administered (mL) |
|---|---|---|
| 0.50 to 0.69 | 0.6 | 0.3 |
| 0.70 to 0.89 | 0.8 | 0.4 |
| 0.90 to 1.09 | 1.0 | 0.5 |
| 1.10 to 1.29 | 1.2 | 0.6 |
| 1.30 to 1.49 | 1.4 | 0.7 |
| 1.50 to 1.69 | 1.6 | 0.8 |
| 1.70 to 1.89 | 1.8 | 0.9 |
| 1.90 to 2.09 | 2.0 | 1.0 |
| 2.10 to 2.29 | 2.2 | 1.1 |
| 2.30 to 2.49 | 2.4 | 1.2 |
| 2.50 to 2.69 | 2.6 | 1.3 |
| 2.70 to 2.89 | 2.8 | 1.4 |
| 2.90 to 3.09 | 3.0 | 1.5 |
| 3.10 to 3.29 | 3.2 | 1.6 |
| 3.30 to 3.49 | 3.4 | 1.7 |
| 3.50 to 3.69 | 3.6 | 1.8 |
| 3.70 to 3.89 | 3.8 | 1.9 |
| 3.90 to 4.09 | 4.0 | 2.0 |
| 4.10 to 4.29 | 4.2 | 2.1 |
| 4.30 to 4.49 | 4.4 | 2.2 |
| 4.50 to 4.69 | 4.6 | 2.3 |
| 4.70 to 4.89 | 4.8 | 2.4 |
| 4.90 to 5.09 | 5.0 | 2.5 |
| 5.10 to 5.29 | 5.2 | 2.6 |
| 5.30 to 5.49 | 5.4 | 2.7 |
| 5.50 to 5.69 | 5.6 | 2.8 |
| 5.70 to 5.89 | 5.8 | 2.9 |

**Table 13: Pomalidomide Dosing Table – Oral Suspension (Continued)**

| Calculated Dose (mg/day) | Actual Dose Administered (mg/day) | Volume Administered (mL) |
|---|---|---|
| 5.90 to 6.09 | 6.0 | 3.0 |
| 6.10 to 6.29 | 6.2 | 3.1[a] |
| 6.30 to 6.49 | 6.4 | 3.2[a] |
| 6.50-6.69 | 6.6 | 3.3[a] |

[a] For administered volumes > 3.0 mL, the dose should be split. For example, a volume of 3.2 mL can be administered as two doses of 1.6 mL each. A dose of 3.3 can be administered as two doses of 1.6 mL and 1.7 mL each.

# Celgene Signing Page

**This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.**

UserName: PPD
Title: PPD
Date: Wednesday, 20 December 2017, 10:31 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

# 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Clarified that only subjects with brain as the primary site of disease (primary brain tumors) will be allowed to participate**

  The inclusion criteria and the definition of measurable disease was updated to clarify that subjects must have brain tumor as a primary target lesion. This was revised to exclude subjects with metastatic brain lesions, as this trial is only targeting subjects with primary brain tumors.

  Revised sections: Section 4.2 Inclusion Criteria, No. 6; Section 6.4.1.1 Selection of Target and Non-Target Lesions

- **Updated language regarding the required screening pregnancy testing**

  Amended language to state that the pregnancy test 10 to 14 days prior to initiation of pomalidomide may be omitted, at the discretion of the investigator, for any females of childbearing potential (FCBP)/female children of childbearing potential (FCCBP) who have high acuity disease requiring immediate treatment with pomalidomide. This change was made to accommodate any potential subjects with high-risk disease, who may need immediate treatment with pomalidomide. The pregnancy test within 24 hours prior to the first dose of pomalidomide is still required to be performed.

  Revised sections: Section 4.2 Inclusion Criteria, No. 17; Section 5 Table of Events (Table 4); Section 6.1 Screening Period; 6.2 Treatment Period; Section 6.4.2.9 Pregnancy Testing and Pregnancy Risk Counseling

- **Clarified the use of anti-coagulation therapy**

  Provided clarification that small clots in central lines that are resolved with tissue plasminogen activator (tPA) flush will not be considered a central-line related thrombosis. In addition, the use of tPA (eg, Alteplase) to flush subject's central-line is allowed and would not be considered a prohibited concomitant medication.

  Revised sections: Section 4.3 Exclusion Criteria, Nos.1 and 3; Section 8.2.3 Anti-coagulation Medications

- **Updated language regarding the collection of pharmacokinetic samples**

  Clarified that blood samples for pharmacokinetic (PK) analysis can be obtained through a central line, if applicable. The use of the central line to collect PK samples and any concomitant medications given via the central line prior to sampling must be captured in the appropriate section of the subject's electronic case report form (eCRF) and source documents. In addition, removed the requirement that pomalidomide needs to be administered "at the study center" on Cycle 1, Day 8 and 15.

  Revised section: Section 6.5 Pharmacokinetics - Optional

- **Extended the collection time window for the pre-dose PK sample**

  To avoid the potential for an additional blood draw on PK days, the collection window for the 0-hour (pre-dose) PK sample on Cycle 1, Day 8 and Cycle 1, Day 15 was updated from -30 minutes to -90 minutes in order to allow the PK blood sample to be collected with the other labs that day (ie, hematology and chemistry labs).

  Revised section: Section 6.5 Pharmacokinetic Sampling Time Points (Table 6)

- **Added the Informed Consent/Assent Population**

  The Informed Consent/Assent Population was added to be consistent with the CC-4047-BRN-001 Statistical Analysis Plan. The Informed Consent/Assent Population will consist of all subjects with signed informed consent/assent provided and used for describing the disposition of subjects with signed informed consent/assent.

  Revised section: Section 9.2 Study Population Definitions

**The amendment also includes other minor clarifications and corrections including:**

- Clarified that 2.6 mg/m$^2$/day was the maximum tolerated dose (MTD), not the recommended Phase 2 dose, from the Phase 1 trial conducted by the Pediatric Brain Tumor Consortium (PBTC-043). (Protocol Summary; Section 1.2.4; Section 1.3.3).
- Updated the current approval status of pomalidomide (Section 1.2).
- Clarified that brain and spine magnetic resonance imaging (MRI) assessments can be performed within 7 days prior to the completion of Cycle 24 (Section 3.1; Section 5 Table of Events [Table 4]; Section 6.4.1).
- Clarified that prior immunomodulatory therapy refers to thalidomide and lenalidomide (Section 4.3).
- Corrected the word “Secondary” to “Second” as Second Primary Malignancy is the correct phrase to use (Section 3.1; Section 5 Table of Events [Table 4]).
- Defined FCBP = females of childbearing potential and FCCBP = female children of childbearing potential (Section 5 Table of Events [Table 4]).
- Clarified that it is the responsibility of the Investigator to obtain and review laboratory/pregnancy results for subject safety, and follow up with subjects in a timely manner (Section 5 Table of Events [Table 4], Section 6.4.2.6, Section 6.4.2.9).
- Removed “initials” from the demographic data to be collected since initials are not being captured in the study (Section 6.1.2).
- Clarified that cerebrospinal fluid, positive or negative for tumor cells, will be followed as nonmeasurable disease (Section 6.4.1.1).
- Corrected that a new informed consent/assent and screening procedures will need to be repeated if rescreening occurs > 28 days (not 21 days) from original screening date (Section 7.3.1).
- Clarified the safety population will be applied for the analysis of all safety and efficacy endpoints (Section 9.2).

- Clarified that subject disposition will be summarized for the Screening Period, Treatment Period and Follow-up Period (Section 9.5).
- Clarified that the analysis of Objective Response and Long-term Stable Disease Rate will be based on the Response Population, with secondary analyses based on the Intent-to-Treat (ITT) Population and/or Safety Population (Section 9.6).
- Clarified that the analysis of Objective Response Rate, Long-term Stable Disease Rate, Duration of Response (DoR), Progression-free Survival (PFS) and Overall Survival (OS) will be based on the ITT Population and/or Safety Population (Section 9.6).
- Added that the analysis of median PFS time and proportion of subjects remaining progressive-free will also be collected at 3, 9 and 18 months (Section 9.6).
- Added that the analysis of median DoR time and proportion of subjects remaining with a response will also be collected at 3, 9 and 18 months (Section 9.6).
- Added that the analysis of median OS time and proportion of subjects remaining alive will also be collected at 3, 9 and 18 months (Section 9.6).
- Clarified that the safety analysis of adverse events will be based on the Safety Population, ie, all subjects receiving at least one dose of pomalidomide (Section 9.7).
- Clarified that the interim analysis for each stratum will be "informal," performed internally by Celgene personnel with input, only if needed, from the data monitoring committee and steering committee (Section 9.8).
- Clarified that the plasma obtained follow pharmacokinetic blood sample processing should be transferred to polypropylene citric acid storage tubes (Appendix E).

# 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Updated Inclusion Criteria #17 regarding highly effective contraceptive methods**

  In response to health authority recommendation from the French National Agency for Medicines and Health Products Safety (ANSM), the below guidance was added regarding the use of highly effective contraceptive methods for female subjects of childbearing potential:

  - Only a progestin-suppressing ovulation pill is acceptable as an oral contraceptive
  - Copper intrauterine devices are not recommended

  Revised sections: Section 4.2, Inclusion Criteria #17

- **Clarified how subjects may continue pomalidomide following study termination**

  In response to health authority recommendation from the French ANSM, the below text was added to clarify how subjects may continue treatment with pomalidomide who would continue to benefit from it at the time of the trial closure:

  - In the case where there are subjects still being administered the investigational product, and it is the opinion of the Investigator(s) that these subjects continue to receive benefit from treatment, the Sponsor may choose to initiate an open-label, extension study under a separate protocol to allow these subjects continued access to pomalidomide following their participation in this study (CC-4047-BRN-001).

  Revised sections: Section 13.8, Termination of the Study

- **Inclusion #19 for affiliation to a health insurance scheme (France only) was added**

  In response to health authority recommendation from the French Central Ethics Committee , the country-specific inclusion criteria was added:

  - **For subjects screened/enrolled in France only:** Subject must be affiliated with a Health Insurance Scheme or be a beneficiary of one

  Revised sections: Section 4.2, Inclusion Criteria #19

- **Clarified Exclusion Criteria #10 regarding hepatitis B serological status**

  In response to health authority recommendation from the French ANSM, it was further clarified that hepatitis B serology must be known or performed at screening if unknown. The below exclusion criteria was updated:

  - Subject has active infectious hepatitis, type A, B, or C, or chronic carriers of hepatitis C. Note: Hepatitis B serological status must be known prior to enrollment. If unknown at screening, a hepatitis B serology **must** be performed.

  Revised sections: Section 4.3, Exclusion Criteria #10; Section 5, Table 4; Section 6,1, Screening Period; Section 6.4.2.6, Table 5

- **Extended the initial weekly blood count testing for an additional four weeks**

  In response to health authority recommendation from the French ANSM, safety blood testing (i.e., hematology and blood chemistry) will be now be performed weekly during the first 8 weeks of treatment (and not only during the first 4 weeks).

  Revised sections: Section 5, Table 4

- **Updated Inclusion Criteria #2 regarding adult subjects who lack capacity to consent**

  In response to a request from the PPD adult subjects who lack the capacity to consent for themselves will be excluded from enrolling into the study. The below inclusion criteria was updated:

  - Subject (when applicable, parental/legal representative) must understand and voluntarily sign an ICF/IAF prior to any study-related assessments/procedures being conducted. Note: Adult individuals who lack capacity to consent for themselves will be excluded from the study.

  Revised sections: Section 4.2, Inclusion Criteria #2

**The amendment also includes other minor clarifications and corrections including:**

- Clarified that subjects will be followed for 28 days, not 28 days (± 3 days), after the last dose of treatment for adverse events (Section 5 [Table 4]; Section 6.3.1).
- Added footnote "o" to clarify which assessments are performed in Cycle 1 only (i.e., enrollment, inclusion/exclusion criteria, weekly pregnancy testing and pharmacokinetics) (Section 5, Table 4).
- Clarified that prior to enrolling a subject, written informed consent/assent must be obtained, all screening evaluations must be completed, and eligibility criteria must be verified by the Investigator, not the Sponsor (Section 6.1.5)

# 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Pharmacokinetic assessments made optional**

  Pharmacokinetics (PK) assessments are also included in the ongoing Phase 1 pomalidomide trial conducted under the Pediatric Brain Tumor Consortium (PBTC-043). As the Phase 1 trial remains open, additional subjects are planned to be enrolled and samples obtained to satisfy the PK requirements. Therefore, PK assessments in this Phase 2 study will not be mandatory.

  Revised sections: Table 4, Table of Events; Section 6.2 Treatment Period; Section 6.5, Pharmacokinetics; Section 9.9.1, Pharmacokinetics Analysis

- **Removed requirement to obtain spine MRIs without contrast**

  It has been recommended by the study Steering Committee to remove the requirement to obtain spine MRIs without contrast as it would not provide any additional benefit to the subject in evaluating response. This further provides flexibility to sites to perform imaging assessments per institutional procedures.

  Revised sections: Section 4.2, Inclusion Criteria #7; Table 4, Table of Events; Section 6.1, Screening Period; Section 6.2, Treatment Period; Section 6.2.1, End of Treatment; Section 6.4.1, Efficacy Assessments

- **Updated study visit window for brain and spine MRIs performed during Treatment Period**

  To provide site the flexibility when scheduling MRIs during the Treatment Period, brain and spine MRI assessments can be performed within 7 days prior to dosing on Day 1 of Cycles 3, 5, 7, 10, 13, 16, 19, and 22. For DIPG subjects only, brain and spine MRI assessments can be performed within 7 days prior to dosing on Day 1 of Cycles 4, 7, 10, 13, 16, 19, and 22.

  Revised sections: Section 3.1, Study Design; Table 4, Table of Events; Section 6.4.1, Efficacy Assessments

- **Updated Exclusion Criteria #5 (prior therapy)**

  1. The time frame from the last dose of prior therapy for a subject to be excluded, was reduced from ≤ 28 days to ≤ 21 days prior to screening for subjects receiving prior myelosuppressive chemotherapy, immunotherapy, or any investigational agent. This was updated to accommodate the target population(s) that have highly aggressive disease and may require more rapid intervention with pomalidomide.
  2. Clarified that subjects cannot have received prior focal radiation ≤ 6 weeks prior to screening for target lesions and ≤ 3 weeks prior to screening for non-target lesions identified at baseline.

  Revised sections: Section 4.3, Exclusion Criteria #5

- **Exclusion Criteria #15 for pre-existing cardiac disorders was added**

  In response to health authority recommendation from the Spanish Agency for Medicinal Products and Medical Devices (AEMPS), the following exclusion criteria has been added:

  - Subject has symptomatic cardiac disorder (CTCAE v. 4.03 Grade 3 and 4)

  Revised sections: Section 4.3, Exclusion Criteria #15

- **Screening Period extended to 28 days**

  The Screening Period was increased from 21 to 28 days to accommodate the protocol requirement for female subjects of child bearing potential to use 2 reliable forms of contraception (or abstinence) for at least 28 days before starting pomalidomide.

  Revised sections: Protocol Summary; Figure 2, Overall Study Design; Section 3.2, Study Duration for Subjects; Table 4, Table of Events; Section 6.1, Screening Period

- **Provided guidance if pomalidomide dosing is vomited or forgotten**

  Additional guidance was included to clarify what to do if a dose of pomalidomide is vomited or forgotten.

  For subjects receiving capsules:

  - If a dose is vomited within 15 minutes of taking the dose and the capsule(s) are visible in the emesis, the dose should be repeated and the Investigator should be notified to have replacement capsule(s) provided. If vomiting occurs beyond 15 minutes of dosing, do not repeat the dose and that day's dose should be skipped. Any vomiting of the capsules should be described in the subject dosing diary.

  For subjects receiving the oral suspension:

  - If the dose is vomited, the dose should not be repeated for that dosing day and details entered in the subject dosing diary.

  If a dose (capsules or oral suspension) is forgotten but remembered within 8 hours, the missed dose should be taken/given immediately. If more than 8 hours have passed since the time the dose was due, that day's dose should be skipped.

  Revised sections: Section 7.2, Treatment Administration and Schedule

- **Revised dose modification criteria**

  3. Clarified febrile neutropenia must be Grade 3 or 4.
  4. Clarified in Table 8 that study drug should be permanently discontinued for subjects experiencing the following toxicities, which do not resolve per protocol within 14 days of treatment being held: Grade 3 or 4 febrile neutropenia, Grade 4 neutropenia, or Grade 3 or 4 platelet count decrease.
  5. Removed Grade 4 anemia dose modification criteria**.** Subjects being considered for enrollment into this trial are often heavily pretreated with multiple chemotherapeutic agents. As a consequence of prior therapy, it is expected that subjects will be anemic and difficult to distinguish study drug effect. In addition, Grade 4 anemia is unlikely to occur alone in the absence of neutropenia or thrombocytopenia which specifically have

parameters that must be met before each treatment cycle as well as additional dose modification criteria.

Revised sections: Table 8, Dose Modification Criteria

**The amendment also includes several other minor clarification and corrections including:**

- Change of Medical Monitor.
- Updated the word "CRF" to "eCRF" throughout the document.
- Updates to the Introduction in line with current literature and to provide further clarification (Section 1).
- Removed "having documented PD" from the study population description to align with inclusion criteria in Section 4.2 (Protocol Summary, Section 3.1, Section 4.1).
- Updated the study visit window for the Long-term Follow-up Period from ± 7 days to ± 14 days (Section 3.2, Table 4, Section 6.3.3).
- Clarified pharmacokinetic objectives are exploratory (Protocol Summary, Table 1).
- Additional reference to Imagining Manual for details regarding MRI acquisition and image submission procedures (Section 4.2, Section 6.4.1.8).
- Clarified that spinal lesions should be considered nonmeasurable disease (ie, a non-target lesion); however, size should be noted and change in size should be evaluated (Section 6.4.1.1).
- Removed reference to "Versa Plus" as the suspending agent of the pomalidomide oral suspension (Section 7.1).
- Removed the requirement that pomalidomide needs to be administered at study center by designated site staff on Day 1 of each treatment cycle (Section 7.2).
- Clarified pomalidomide (capsules or oral suspension) can be taken with or without food or beverage with exception to PK days (Section 7.2).
- Clarified that the following parameters must be met within 48 hours (updated from within 24 hours) of Day 1 to start of subsequent treatment cycles: ANC $\geq$ 1,000/mm$^3$, platelet count $\geq$ 100,000/mm$^3$, and does not meet PD or treatment interruption/ discontinuation criteria (Section 7.2.1).
- Clarified compliance of the study drug will be based on drug returned and/or written in the subject dosing diary (Section 7.6).