CLINICAL STUDY PROTOCOL

Full Study Title: **Phase II Trial of Niraparib in Patients with Recurrent Glioma**

Brief Title: **PARP Inhibition for Gliomas (PI-4G or π4g)**

Sponsor ID Number: **OU-SCC-PI-4G**

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Test Product: Niraparib

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1.0 BACKGROUND INFORMATION

1.1. Study Hypothesis

Poly (ADP-ribose) polymerase (PARP) is a family of proteins involved in many cellular processes such as DNA repair and programmed cell death [1]. Cancer cells may use PARP to repair DNA damage and become resistant to treatment. Therefore PARP inhibitors have been developed as novel drugs that may be used to enhance the antitumor activity of some agents, like temozolomide which can induce DNA damage and is the drug of choice for glioblastoma multiforme (GBM) [2]. Moreover, PARP inhibitors demonstrated cytotoxic effects in monotherapy and can selectively kill a subset of cancer cells with deficiencies in DNA repair pathways [3, 4]. Niraparib is an oral potent PARP inhibitor and has shown to significantly improve progression-free survival for patients with ovarian cancer with manageable toxicities [5]. Studies in pre-clinical setting suggested niraparib could cross the blood brain barrier and inhibited intracranial tumor growth in animal models [6, 7]. It will be worthwhile to investigate the clinical safety and anti-cancer benefit of niraparib on patients with GBM in a prospective study.

1.2. Disease Background

GBM is the most common, highest grade, and most malignant primary brain tumor [8]. With introduction of the Stupp protocol in 2005, patients diagnosed with a GBM have a median survival of 14.5 months [9, 10]. The annual incidence of primary brain malignant neoplasms in the U.S. is 4.3 per 100,000 with a total of 23,770 people diagnosed per a year [11]. This number is expected to grow as the nation's population ages. The standard treatment with radiotherapy and chemotherapy (temozolomide) provide patients with, approximately 2.5 months benefit. The unfortunate reality in the current treatment of GBM is that it inevitably recurs after initial treatment with radiation and temozolomide, and it has a high mortality despite second line treatments such as bevacizumab and carmustine [12]. By default that necessitates that at least some of the tumor cells are resistant to these therapies. Novel treatments are needed to focus on the mechanisms of resistance in glioblastoma.

1.3. PARP Inhibitor on Brain Tumor

PARPs play critical roles in DNA repair which can promote cancer cells resistant to DNA damaging therapy. Microarray analysis of PARP-1 gene expression in more than 8000 samples revealed that PARP-1 is more highly expressed in several types of tumors compared with the equivalent normal tissue [13]. By using immunohistochemical staining, positive nuclear PARP-1 staining was found in all GBM samples collected from patients (n=27), but not in normal neurons from controls (n=4) and GBM patients (n=27) [14]. In non-clinical studies, combining PARP inhibitor (veliparib) with radiation and/or temozolomide yielded enhanced cell killing in GBM cell lines [15]. In addition, PARP inhibition by olaparib could overcome apoptotic resistance and sensitizes GBM cell lines for death receptor-mediated apoptosis [16].

Niraparib is a novel drug that selectively inhibits PARP-1 and PARP-2 and produced anti-cancer effect in preclinical studies. Comparing to olaparib and veliparib, niraparib was the most potent drug in trapping PARP and revealed the highest cytotoxicity to *BRCA*-deficient cancer cells [4]. Furthermore, niraparib showed cytotoxic activity in *BRCA*1 and *BRCA*2 negative or mutant

cancer cells while sparing the normal cells [17, 18]. More importantly, niraparib could cross the blood brain barrier in rodents or mice and inhibited tumor growth in the *BRCA*2-mutant or non-mutant intracranial tumor models [6, 7].

Chornenkyy and colleagues reported the therapeutic potential of PARP1 inhibitors in preclinical models of pediatric high-grade astrocytomas (pHGA) and diffuse intrinsic pontine gliomas (DIPG) [7]. The positive PARP1 protein expression was found in 28 of 33 pHGA and 13 of 17 DIPG patient tumor samples. When compared to veliparib and olaparib, niraparib was the most effective at reducing *In-Vitro* cell viability and proliferation [7]. Furthermore, treatment with a three-day course of niraparib was sufficient to completely inhibit PARP1 activity in intracranial tumor in mice model [7]. Pre-treatment with niraparib could enhance anti-cancer effect of ionizing radiation and extended survival of mice bearing orthotopic pHGA xenografts, indicating that niraparib may be an effective radiosensitizer for pHGA and DIPG [7]. Similar results were reported by Mueller et al showing that niraparib could reduce clonogenicity of neuroblastoma cell lines; and combination of niraparib with radiation prolonged survival of murine model bearing metastatic neuroblastoma [19]. Interestingly, niraparib mediated radiosensitization was selective to cancer cell lines but not for normal cell lines [20].

A recent study by Sulkowski, et al., identified that the isocitrate dehydrogenase 1 (IDH1) and IDH2 mutations induce a homologous recombination (HR) defect that would render tumor cells sensitive to PARP inhibitors [21]. The IDH mutations are primarily present in Grade II and III gliomas, but can also be seen in Grade IV glioblastoma. Inevitably, the vast majority of Grade II and III gliomas will recur and progress to a higher grade at which time there are few therapeutic options. Given this intrinsic deficit in HR, it is likely that gliomas will respond well to PARP inhibition in clinical practice. Previous trials may not have been successful because (1) the PARP inhibitor did not cross the blood brain barrier and (2) they did not target the subpopulations of gliomas that are more responsive because they have deficits in HR.

Several clinical studies have reported the safety and efficacy of niraparib for the treatment of a variety of advanced solid tumors, including primary or secondary brain tumors [2, 22, 23]. A phase I dose escalation trial of niraparib demonstrated significant antitumor activity in *BRCA* mutant and sporadic cancers within a large therapeutically effective dosing window (60–300 mg/day); and established 300 mg/day as the maximum tolerated dose (MTD) [22]. Among 100 patients enrolled, dose-limiting toxicities reported in the first cycle were one grade 3 fatigue (30mg/day), one grade 3 pneumonitis (60 mg/day) and two grade 4 thrombocytopenia (400mg/day). Ten of 24 patients with *BRCA*1 or *BRCA*2 mutation achieved partial tumor response. In addition, anti-cancer activity was also reported in 17 of 48 patients with sporadic cancer including high-grade serous ovarian cancer, non-small-cell lung cancer, and prostate cancer [22]. A phase I trial of niraparib plus temozolomide reported that niraparib at 40 mg/day continuously in combination with 150 mg/m2/day Temozolomide was considered as the MTD and demonstrated antitumor activity, with one glioblastoma patient achieved a partial response after six treatment cycles of niraparib (40 mg) [24]. The U.S. Food and Drug Administration (FDA) has approved niraparib (ZEJULA, GSK, Inc.) for the maintenance treatment of adult patients with recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer.

1.4. Summary of Investigational Drug

1.4.1 Pharmacology of Niraparib

Niraparib is a potent, orally active PARP1 and PARP2 inhibitor being developed as a treatment for patients with tumors that harbor defects in the HR DNA repair pathway or that are driven by PARP-mediated transcription factors.

1.4.2 Non-clinical Study of Niraparib

Nonclinical data on niraparib are discussed in detail in the Investigator's Brochure. Briefly, in nonclinical models, niraparib has been observed to inhibit normal DNA repair mechanisms and induce synthetic lethality when administered to cells with HR defects. In a *BRCA*1-mutant xenograft study, niraparib dosed orally caused tumor regression, which was mirrored by > 90% reduction in tumor weight compared with control. In a *BRCA*2-mutant xenograft study, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.
Niraparib displayed strong antitumor activity in in vivo studies with *BRCA*1-mutant breast cancer (MDA-MB-436), *BRCA*2-mutant pancreatic cancer (CAPAN-1), ATM-mutant mantle cell lymphoma (GRANTA-519), serous OC (OVCAR3), and colorectal cancer (HT29 and DLD-1) xenograft models and with patient-derived Ewing sarcoma mice models. Utilizing patient-derived ovarian and breast cancer xenograft models, niraparib demonstrated response in both *BRCA* mutation and *BRCA* wild-type tumors.

1.4.3 Clinical Safety of Niraparib

Niraparib clinical data are discussed in detail in the niraparib IB. In the Phase 1 clinical program, niraparib, as a monotherapy or in combination with chemotherapy, has been administered to 144 patients.

Phase 1 Study of Niraparib Monotherapy in Advanced Solid Tumors

Niraparib clinical data are discussed in detail in the niraparib IB. In the Phase 1 clinical program, niraparib, as a monotherapy or in combination with chemotherapy, has been administered to 144 patients.

Phase 1 Study of Niraparib Monotherapy in Advanced Solid Tumors

Clinical activity data for niraparib administered as monotherapy in patients with ovarian cancer are available from 1 early-phase clinical study. In Parts A and B of the Phase 1 study PN001 (ClinicalTrials.gov identifiers: MK-4827-001 and 2008_501), 100 patients with advanced solid tumors who had received a median of 3 prior therapies were enrolled; 49 patients had ovarian cancer (13 platinum-sensitive, 35 platinum-resistant, and 1 platinum-refractory).[22] An additional 4 patients were enrolled in Part D of the study, which assessed pharmacokinetics only.
The most common nonhematological TEAEs were nausea, fatigue, anorexia, constipation, vomiting, and insomnia. These TEAEs were mainly mild to moderate in severity, self-limiting, and manageable with standard treatments. Hematological toxicity appeared to be dose proportional and most frequently arose in the setting of cumulative doses. Anemia was reported in 48 (48%) of 100 patients and was Grade ⩾3 in 10 (10%) of 100 patients. Thrombocytopenia was less common (35 [35%] of 100 patients) and was Grade ⩾3 in 15 (15%) of 100 patients.

Neutropenia was the least commonly reported (24 [24%] of 100 patients), and was Grade 3 in 4 (4%) of 100 patients at niraparib doses of 300 and 400 mg. In all cases, hematological TEAEs were uncomplicated and reversible. Twenty patients required dose reductions (usually by 1 dose level) for recurrent anemia or thrombocytopenia. Treatment was discontinued due to AEs in 7 patients, including the 4 patients who had DLTs during the first cycle and 3 patients who had Grade 3 vomiting, Grade 2 prolongation of QT interval, and Grade 3 prolongation of QT interval. No treatment-related deaths occurred.
Of the 49 patients, 22 had confirmed BRCA1 or BRCA2 mutation, of whom 20 were radiologically assessable. Eight (40%) of these 20 patients achieved a confirmed partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST) and cancer antigen 125 (CA 125) Gynecologic Cancer Intergroup criteria at doses ranging from 80 to 400 mg per day. Median response duration was 387 days (range: 159 to 518 days). Three (33%) of 9 patients with platinum-resistant BRCAmut ovarian cancer had PR by RECIST and CA-125 criteria. In patients with platinum-sensitive disease, 5 (50%) of 10 patients (95% CI: 19 to 81) with BRCA1 or BRCA2 mutations had RECIST and CA-125 responses.

Please refer to Niraparib IB for more details.

1.4.4 Clinical Efficacy of Niraparib

Clinical activity data for niraparib administered as monotherapy or combination therapy in patients with various cancer are discussed in detail in the niraparib Investigator's Brochure v11.0.

1.4.5 Baseline Platelet Count and Weight as Predictors of Thrombocytopenia

An analysis was conducted using the data collected in ENGOT-OV16/NOVA and the initial phase I study, PN001. This analysis determined that baseline platelets had an impact on platelet nadir; lower baseline platelets (<180 109/L) were associated with an increased frequency of thrombocytopenia Grade ⩾1 (76%) or Grade ⩾ 3 (45%) compared to patients with higher baseline platelet counts. Further, an exploratory analysis of clinical data versus baseline body weight from ENGOT-OV16/NOVA was conducted. For this analysis, the weight categories were based on quartiles with the lowest quartile (patients with a body weight less than 58 kg at baseline) compared to the highest quartile (patients with a body weight greater than or equal to 77 kg at baseline). While TEAEs occurred in most patients regardless of body weight, Grade ⩾ 3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the weight <58 kg cohort than in the ⩾77 kg cohort. In the cohort of patients with a body weight <58 kg, approximately 80% of patients had a dose reduction compared to 59% of patients with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the subjects with lower body weight (24%) compared to patients in the highest quartile (10%).

The potential relationship between body weight and TEAEs was further explored in an analysis to evaluate the correlation of grade 3 or 4 thrombocytopenia and baseline body weight. The

lowest platelet count in the first 30 days was plotted versus baseline body weight to determine if low body weight identified a subgroup of patients with higher levels of thrombocytopenia during Cycle 1. In the first 30 days of treatment, a baseline body weight ≥77 kg is associated with a lower incidence of grade 3 or 4 thrombocytopenia (14%) relative to the group with body weight <58 kg (43%).

Finally, a classification tree approach was used to refine the best cut-off points for predicting the likelihood of a patient developing ⩾Grade 3 thrombocytopenia within 30 days after the first dose of niraparib. The results of the model show that the subgroup of patients with a baseline body weight <77 kg or baseline platelet count <150,000 μL had a grade 3/4 thrombocytopenia rate in the first 30 days of 35.4% compared to 11.5% in the group of patients with a body weight >77 kg and a platelet count >150,000 μL. Further, the average daily dose was 258 mg through the first two cycles for patients with a body weight >77 kg and platelet count >150,000 μL, and was only 206 mg for patients with body weight < 77 kg or platelet count <150,000 μL. Thus, the actual delivered dose approximated a starting dose of 200 mg despite the intended delivery of a starting dose of 300 mg. These observations are to be confirmed in the present study with the inclusion of study treatment dosed at 200 mg (2 capsules of niraparib or placebo) in patients whose baseline weight is <77 kg or baseline platelet count is <150,000 μL.

1.5. **Rationale for this study**

Patients with primary brain cancer have a poor prognosis and few effective treatment options. Niraparib crossed the blood brain barrier and inhibited intracranial tumor growth in animal models [6, 7]. In addition, niraparib could mediate radio-sensitization selective to cancer cell lines but not for normal cell lines [20]. Furthermore, loss of PTEN (phosphatase and tensin homologue) was found in 70% of GBM patients, with somatic mutations occurring in 25–40% of cases [28]; cancers with PTEN loss or homologous recombination deficiency are sensitive to PARP inhibitors [29, 30]. We anticipate that Niraparib can cross the blood-brain barrier and produce anti-cancer effect on patients with GBM. Our study plan is to conduct a safety lead-in with individualized starting dose (ISD) , followed by dose expansion study to determine the safety and efficacy of niraparib for patients with recurrent brain tumor. The patient's tumor will be evaluated for the presence of IDH1 and IDH2 as they could contain intrinsic HR defects.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Co-primary Objectives:

- For safety lead-in phase: To evaluate the safety and tolerability of niraparib using individualized starting dose (ISD) in patients with recurrent brain tumor.
- For Phase II Dose Expansion Cohorts: To evaluate the efficacy (monitored by disease control rate; DCR) of niraparib in patients with recurrent brain tumor using Response Assessment in Neuro-Oncology Criteria (RANO); and to evaluate the safety of niraparib in patients with recurrent brain tumor at safety lead-in dose.

2.1.2 Secondary Objectives:

- To evaluate Progression free survival (PFS) and overall survival (OS) time for patients enrolled in dose expansion cohorts.

- To evaluate the duration of disease control (DDC) in patients enrolled on study.

2.1.3 Exploratory Objectives:

- To identify potential biomarkers associated with tumor response to niraparib based on the molecular profile of tumor tissue biomarkers.
- To correlate homologous recombination deficiency (HRD) score obtained via myChoice test (Myriad Genetics) with other biomarkers such as IDH1/IDH2 mutation and with treatment outcomes.

2.2 Study Endpoints

2.2.1 Co-Primary Endpoints:

- For safety lead-in dose and expansion cohorts, monitor safety and tolerability of niraparib with individualized starting dose (ISD) in patients with recurrent brain tumor. Determination of safety will utilize adverse event occurrence monitoring and grade using CTCAE v5.0.
- For Phase II dose expansion cohorts, define the anti-cancer efficacy of niraparib in patients with recurrent brain tumor by disease control rate (DCR; complete and partial response, and stable disease) as assessed by the RANO. DCR is the percentage of patients with a SD or better from start of treatment (cycle 1, day 1) to 3 months, 6 months, 9 months, and 12 months per RANO.

2.2.2 Secondary Endpoints:

- Anticipate to have prolonged PFS and OS for patients enrolled in dose expansion cohorts
- DDC is elapsed time from the first documented CR, PR, pathological CR, or SD until first documentation of disease progression or death, whichever comes first.

2.2.3 Exploratory Endpoints:

- Obtain preliminary data about the molecular profile of tumor tissue biomarkers and their association with tumor response to niraparib.
- Obtain preliminary data about the association of HRD status with other biomarkers and with the anti-cancer effect of niraparib.

3.0 INCLUSION / EXCLUSION CRITERIA

3.1 Inclusion Criteria

1. Patients must be able to understand and willing to sign the informed consent form.
2. Patients must be ≥ 18 years of age.
3. Patients must have histologically proven high grade gliomas - GBM, Astrocytoma, or Oligodendroglioma (glioma WHO Grade III or IV) that is now recurrent by MRI or surgical pathology. If there is clinical evidence (such as MRI contrast enhancement) that supports a Grade 3 diagnosis of the glioma, the patient will be eligible for the study (even if the initial diagnosis was a Grade 2).
4. Patients must have measurable or evaluable lesions by RANO.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2

6. Patient has archival tumor tissue available; or a fresh biopsy of recurrent or persistent tumor must be obtained for molecular assay by myChoice test (Myriad Genetics) prior to study treatment initiation. Patient will be requested to share reports from *any* prior genetic testing with the study investigators.
7. Participants have systolic BP< 140 mmHg or diastolic BP <90 mmHg that has been adequately treated or controlled.
8. Have adequate organ function defined by ANC > 1500 cells/mcl, platelets > 100,000/mcl, Hemoglobin ≥ 9 g/dL, calculated creatinine clearance ≥ 50 mL/min (by Cockcroft-Gault formula); total bilirubin < 1.5 times ULN, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels < 2.5 x ULN.
9. Be able to take oral medications
10. Life expectancy ≥ 3 months, allowing adequate follow up of toxicity evaluation and antitumor activity;
11. Female patient, if of childbearing potential, has a negative serum pregnancy test within 72 hours of taking study medication and agrees to abstain from activities that could result in pregnancy from enrollment through 180 days after the last dose of study treatment or is of nonchildbearing potential. Nonchildbearing potential is defined as follows (by other than medical reasons):
    - ≥45 years of age and has not had menses for >1 year
    - Patients who have been amenorrhoeic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation
    - Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Verbal confirmation of hysterectomy, oophorectomy, or tubal ligation from the patient of non-childbearing potential to study staff is sufficient in lieu of records from actual procedure and/or confirmation by ultrasound. In this case, the patient must be willing to use two adequate barrier methods throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. This information must be captured appropriately within the site's source documents. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
12. Male participant agrees to use an adequate method of contraception starting with the first dose of study treatment through 180 days after the last dose of study treatment. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
    In addition, men must not donate sperm during niraparib therapy and for 90 days after receiving the last dose of niraparib.
13. Patient must agree to not breastfeed during the study or for 30 days after the last dose of study treatment.
14. Participant must agree to not donate blood during the study or for 90 days after the last dose of study treatment.
15. Participant receiving systemic corticosteroids may continue as long as their dose is stable for at least 4 weeks prior to initiating protocol therapy. Topical and nasal steroids are not considered contraindicative and may be used.

3.2 Exclusion Criteria

1. Patient has a known additional malignancy that progressed or required active treatment within the last 3 years (exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer).
2. Prior treatment with a known poly(ADP-ribose) polymerase (PARP) inhibitor
3. Participants with human immunodeficiency virus (HIV) with detectable viral load. Participants with HIV on effective anti-retroviral therapy with documented undetectable viral load and CD4 count ≥ 350 within 6 months of the first dose of study treatment are eligible for this trial.
4. Known active hepatitis B or hepatitis C.
5. Known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).
6. Participant is pregnant or expecting to conceive while receiving study treatment and/or for up to 180 days after the last dose of study treatment.
7. Patient currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first dose of study drug.
8. Received prior anticancer therapy (chemotherapy, targeted therapies, radiotherapy, or immunotherapy) within 4 weeks.
9. Patients must not have a known hypersensitivity to the components of niraparib or the excipients (lactose monohydrate and magnesium stearate).
10. Patients must not have had major surgery within 4 weeks (including craniotomy) of starting the study and patient must have recovered from any effects of any major surgery. Stereotactic biopsy by burr hole is considered a minor surgery, and those patients undergoing this surgery will be eligible for the study 2 weeks post-procedure.
11. Patients must not have had radiotherapy encompassing > 20% of the bone marrow within 2 weeks; or any radiation therapy within 1 week prior to Day 1 of protocol therapy.
12. Patients must not have received a transfusion (platelets or red blood cells), colony stimulating factors (eg, granulocyte colony-stimulating factor, granulocyte macrophage colony stimulating factor, or recombinant erythropoietin) ≤ 4 weeks of the first dose of study treatment.
13. Patient has had any known Grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to the most recent treatment.
14. Participants have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.
15. Participants have received live vaccine within 30 days of planned start of study randomization.

16. Patients have medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent
17. Any medical condition not yet specified above that is considered to possibly, probably or definitely interfere with study procedures, including adequate follow-up and compliance and/or would jeopardize safe treatment.

4.0 SUBJECT REGISTRATION AND ENROLLMENT

4.1 Required protocol specific regulatory documents

This protocol, the Informed Consent document, any information to be given to the patient, and relevant supporting information must be submitted to the IRB by the Principal Investigator and reviewed and approved by the IRB before the study is activated by the Sponsor.

The Sponsor must pre-approve the informed consent document prior to submission to the IRB. All regulatory documents must be available to the Sponsor prior to site activation. Before the study can be initiated at any site, the following documentation must be provided to Stephenson Cancer Center Clinical Trials Office (SCC CTO):

- A copy of the IRB approval letter
- CV and medical licensure for the principal investigator
- Form FDA 1572 appropriately completed and signed
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certifications and institution lab normal values
- Executed clinical research contract

4.2 Patients Registration and Enrollment

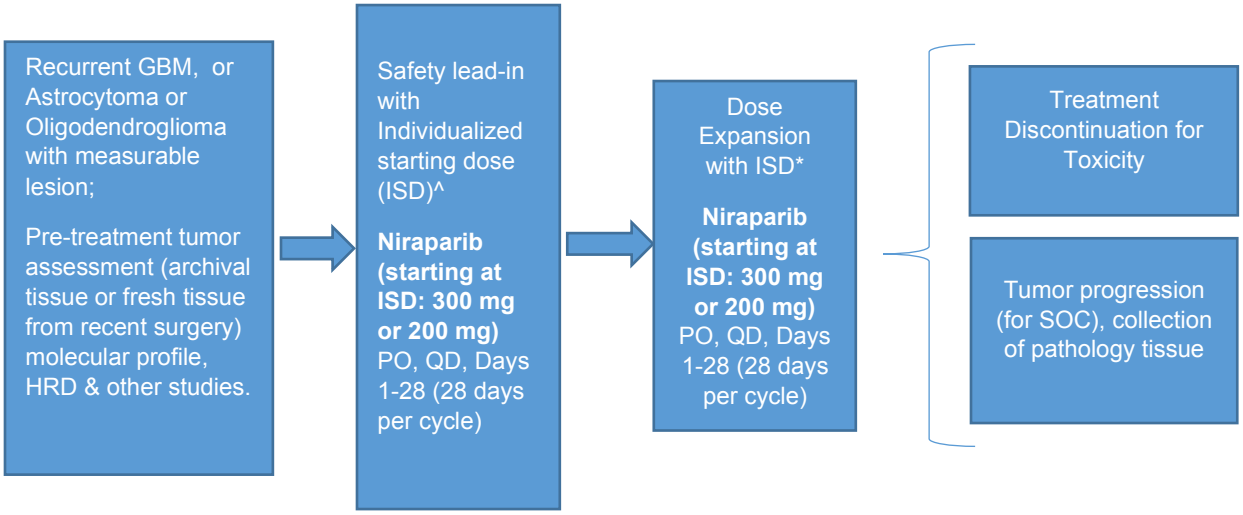
Sites must confirm with The University of Oklahoma Stephenson Cancer Center (OU-SCC) that a slot is available before proceeding with consenting any patient. A Screening identification (Screening ID) number will be provided by OU-SCC research staff after the patient has been consented. After all screening procedures and assessments have been completed, the study site should complete the Subject Enrollment Form and send along with the required documentation to DataIntegrity@ouhsc.edu, for confirmation of eligibility. The Study ID number will be generated by OU-SCC once eligibility has been confirmed. Once the patient has been provided a Study ID number, only the Study ID number should be used.

Patients must not start protocol treatment prior to enrollment. Patients will start protocol treatment only after pre-treatment evaluation is complete and eligibility criteria have been met.

NOTE: Per the Institutional Review Board (IRB) reporting, a patient is considered accrued once he or she signs a consent form for the study. A patient is considered enrolled once the patient begins treatment. Evaluable patients are defined in protocol Section 10.1.

5.0 SCHEMA AND TREATMENT PLAN

5.1 Schema



^ Up to six patients may be enrolled in the safety lead-in phase. See Section 6.1 for details.

* Up to 42 patients may be enrolled in the dose expansion phase. Total patients will be 45. See Section 6.1 for details.

5.2 Study Treatment

This is a single arm phase II trial of niraparib in patients with recurrent gliomas. Three to six patients will be enrolled in the safety lead-in phase with ISD. If no AEs are observed in the first 3 patients, they will be included in the dose expansion phase of the study. If 1/3 patients experiences an AE that is determined to be significant by the PI and medical monitor, the same dose will be expanded to 3 more patients. A safety review will be conducted following the treatment of the first three or all six patients to determine the niraparib dose for the dose expansion phase. Patients enrolled in the safety lead-in phase will be included in the dose-expansion phase. The starting dose of niraparib for the safety lead-in phase will depend on baseline platelet count and weight as summarized in Table 1.

Table 1 Niraparib Invidualized Starting Dose (ISD)

Baseline Criteria	**Starting Dose**
≥77 kg **and** ≥150,000 µL	300 mg (3 X 100 mg capsules) daily
<77 kg **or** <150,000 µL	200 mg (2 X 100 mg capsules) daily*

*For patients whose starting dose in the dose expansion phase starts at 2 capsules once daily, their dose will remain at the same level if there are no indications to reduce the dose. There will be no planned increase in the dose even if the patient tolerates it well.

5.3 Treatment Plan

5.3.1 Niraparib Dose for Safety Lead-in Phase:

Three to six patients will be enrolled in the safety lead-in phase utilizing ISD. The starting dose will be 300 mg niraparib (or modified according to Table 1), taken orally once a day for the first cycle of 28 days. The safety review will be conducted following the safety lead-in phase to review AEs, and the dosage for the dose expansion phase will be accordingly modified if required.

5.3.2 Niraparib Dose for Phase II Dose expansion cohort:

Niraparib will be continued to be administered at ISD (Table 1) on days 1-28 per 28 day cycle, or dosage will be modified based on safety review recommendations after the safety lead-in phase. See Section 7.1.3 for dose administration.

5.4 Dose Modification

Study treatment dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 28 days of the scheduled interruption, unless otherwise discussed with the Investigators.

A safety review will be conducted following the safety lead-in phase to review AEs, and niraparib dosage for the dose expansion phase will be accordingly modified if required. Dose reduction of niraparib may be implemented per the Investigator's judgement in patients enrolled in safety lead-in phase cohort and at any time in patients enrolled in phase II dose expansion cohort.

All treatment interruptions and dose reductions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded in the electronic case report form (eCRF).

5.4.1 Dose Modifications for Non-Hematologic Toxicity

Treatment with niraparib must be interrupted for any treatment-related non-hematologic CTCAE Grade 3 or 4 event. Once resolved to Grade ≤ 1, the patient may restart treatment with niraparib with a dose level reduction (see Table 2) unless prophylaxis is considered feasible. If the event recurs at a similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made to a lower dose level, if available, or niraparib dosing should be discontinued. If the toxicity requiring dose interruption has not resolved to CTCAE Grade ≤ 1 during a maximum 4-week (28-day) dose interruption period, and/or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with niraparib.

Table 2 Niraparib Dose Reductions for Non-Hematologic Toxicity

Event	Dose		
	100 mg QD, Day 1-28	200 mg QD, Day 1-28	300 mg QD, Day 1-28
1st dose reduction for treatment-related adverse reactions CTCAE ≥ Grade 3 where prophylaxis is not considered feasible or adverse reaction event persists despite treatment	N/A [a]	100 mg, QD, Day 1-28	200 mg QD, Day 1-28
2nd dose reduction [b] for treatment-related CTCAE Grade 3 or 4 AE or SAE where prophylaxis is not considered feasible or adverse reaction event persists despite treatment	N/A	N/A	100 mg QD, Day 1-28
Continued treatment-related CTCAE Grade 3 or 4 AE or SAE ≥ 28 days	Discontinue niraparib	Discontinue niraparib	Discontinue niraparib

Abbreviations: AE = adverse event; CTCAE = Common Terminology for Adverse Events; QD = once daily; SAE = serious adverse event.

a. Dose not to be decreased below 100 mg daily, day 1-28.

b. If initial dose is below 300 mg, the same dose reduction principles will apply with fewer dose modification steps available.

5.4.2 Dose Modifications for Hematologic Toxicity

Table 3 Management of Hematologic Toxicities

Laboratory Abnormality	Intervention
Monitor complete blood counts (CBC) weekly for the first two months (two cycles), monthly for the next 11 months of treatment, and periodically after this time.	
Platelet count <100,000/μL	Niraparib must be interrupted for a maximum of 28 days until platelet count is ≥ 100,000/μL with weekly CBC monitored until recovery. Niraparib may then be resumed at same dose. After recovery, blood counts once weekly for 4 weeks. If platelet count is <75,000/μL, resume at a reduced dose.

Further occurrence of platelet count <100,000/μL	Niraparib must be interrupted for a maximum of 28 days until platelet count is ≥ 100,000/μL with weekly CBCs monitored until recovery. Niraparib may then be resumed at a reduced dose (see Table 2); after recovery, blood counts once weekly for 4 weeks. A further dose reduction should be made if an additional treatment interruption is needed after resuming treatment. Discontinue niraparib if the platelet count has not returned to acceptable levels (≥ 100,000/μL) within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Platelet count < 75,000/μL	Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. Resume niraparib at a reduced dose. Dose will be maintained at reduced dose as long as platelet counts are trending upward, and considered minimal risk by treating physician. Discontinue niraparib if the platelet count has not returned to acceptable levels (≥ 100,000/μL) within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD, day 1-28.
Neutrophil < 1,000/μL	Niraparib must be interrupted until neutrophil counts are ≥ 1,000/μL with weekly CBCs monitored until recovery within 28 days. Niraparib may then be resumed at a reduced dose[a] (see Table 2); after recovery, blood counts once weekly for 3 weeks to ensure the safety of the new dose level. Discontinue niraparib if neutrophil level has not returned to acceptable levels (≥ 1,000/μL) within 28 days of the dose interruption period, or if the patient has already undergone maximum dose reductions.
Hemoglobin ≤ 8 g/dL	Niraparib must be interrupted until hemoglobin is > 8 g/dL with weekly CBCs monitored until recovery within 28 days. Niraparib may then be resumed at a reduced dose (see Table 2); after recovery, blood counts once weekly for 3 weeks to ensure the safety of the new dose level. Discontinue niraparib if hemoglobin has not returned to acceptable levels (≥ 8 g/dl) within 28 days of the dose interruption period, or if the patient has already undergone maximum dose reductions.

Hematologic adverse reaction requiring transfusion or hematopoietic growth factor support	For patients with platelet count ≤10,000/μL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. Resume niraparib at a reduced dose.
Confirmed diagnosis of MDS* or AML†	Permanently discontinue niraparib.
*MDS = myelodysplastic syndrome †AML = acute myeloid leukemia	

a. Dose not to be decreased below 100 mg daily, day 1-28.

- If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC also will be required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume.
- Any patient requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support must undergo a dose reduction upon recovery if study treatment is resumed.
- The patient must be referred to a hematologist for further evaluation (1) if frequent transfusions are required or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less after 4 weeks.
- For major surgery while on treatment, up to 28 days of study treatment interruption is allowed.
- Once the dose of study treatment has been reduced, any re-escalation must be discussed with the medical monitor.
- All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded in the eCRF.

5.5 Precaution for Concomitant Medications

Any medication the patient takes during the study other than the study treatments, including herbal and other nontraditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At screening, patients will be asked what medications they have taken during the last 30 days. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking or have taken since the previous visit.

Niraparib weakly induces Cytochrome P450 (CYP)1A2 in vitro and is a relatively poor substrate for P-glycoprotein (P-gp); therefore, investigators are advised to use caution with the substrates for CYP1A2 with a narrow therapeutic range, i.e. theophylline and tizanidine. Appendix A has a more comprehensive lists of CYP1A2 substrates. The niraparib safety profile includes risk for

thrombocytopenia; therefore, investigators should be advised to use caution with anticoagulation and antiplatelet drugs.

5.5.1 Prohibited Medications

Patients are prohibited from receiving the following therapies during the screening and treatment phase of this study:

Antineoplastic systemic chemotherapy or biological therapy

- Any anti-cancer therapy not specified in this protocol, such as Chemotherapy or Immunotherapy
- Investigational agents other than niraparib
- Radiation therapy is prohibited if encompassing > 20% of the bone marrow within 2 weeks or any radiation therapy within 1 week prior to study Day 1.
  Note: The following may be considered exceptions on a case-by-case basis after consultation with the Sponsor: Radiation therapy to pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics (excluding palliative radiotherapy encompassing > 20% of the bone marrow) as long as no evidence of disease progression is present. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy may be considered clinical progression for the purposes of determining PFS.
- The patient can receive a stable dose of corticosteroids during the study as long as their dose is stable for at least 4 weeks prior to initiating protocol therapy.
  Note: Inhaled steroids are allowed for the management of asthma.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. The combination of niraparib with live vaccines or immunosuppressant agents has not been studied. Inactive vaccines are permitted.
- Prophylactic cytokines (G-CSF) should not be administered in the first cycle of the study but may be administered in subsequent cycles.

If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy may be required. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. The decision to continue the patient on study therapy, however, requires the mutual agreement of the Investigator, the Sponsor, and the patient.

5.5.2 Study Restrictions

Participants of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation beginning with time of consent, during the study treatment and for 180 days after last dose of study treatment(s):

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral route
  - Intravaginal route
  - Transdermal route

- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence, if the preferred and usual lifestyle of the subject

In addition, men must not donate sperm during niraparib therapy and for 180 days after receiving the last dose of niraparib.

5.6 Breast Feeding

Patients must not breast-feed from the time they receive the first dose of niraparib and for 180 days following the final dose of niraparib.

5.7 Blood Donation

Patients must not donate blood during the study or for 90 days after the last dose of study treatment.

5.8 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study**.**

5.9 Duration of Therapy

Patients will be treated until disease progression or toxicity unless patient withdraws consent or in the event of severe noncompliance.

5.10 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, and for two years from the end of treatment to assess for MDS/AML and overall survival. All patients must also be followed through completion of all protocol therapy.

6.0 STUDY DESIGN AND PARAMETERS

6.1 Study Design

This phase II study will utilize a safety lead-in with an individualized starting dose (ISD) strategy, wherein up to six patients may be treated with 200 mg or 300 mg, PO, QD of niraparib on days 1-28. In order to adequately assess safety data by the conclusion of this phase, three patients will be treated with the study drug and adverse events (AEs) will be assessed in the first 28 days of treatment, i.e., one treatment cycle of niraparib. The study will continue to the dose expansion phase (with inclusion of the first three patients), unless there are Grade 4 hematological, or Grade 4 non-hematological toxicities (as per CTCAE v5.0) that are unresolved

after 4 weeks, or SUSARs (Suspected Unexpected Serious Adverse Reaction) on the study. If 1/3 patients experience any of the above, the same dose will be expanded to three more patients, and another safety review may be conducted following the treatment of all six patients to determine the niraparib dose for the dose expansion phase. The starting dose of niraparib for the safety lead-in phase will depend on baseline platelet count and weight as summarized in Table 1.

No intra-patient dose escalations are allowed. No further dose escalation will be conducted even if no SAEs are observed with either starting dose (either 200 mg or 300 mg) in the first cycle of treatment. If the starting dose for the patient is 300 mg, the dose can be decreased to either 200 mg or 100 mg depending on the severity of the AE. If the starting dose is 200 mg, the dose can be decreased to 100 mg. Refer to Table 2 for more details. No dose reduction to less than 100 mg niraparib QD, will be permitted. AEs observed at the 100 mg does level of niraparib, will be managed according to Table 3 in the protocol. Only clinically significant AEs will require change to patient treatment.

6.2 Study Parameters

6.2.1 Therapeutic Parameters

1. Pre-study scans should be performed within 4 weeks prior to registration.
2. All required pretreatment laboratory studies should be done as outlined in the study calendars in Section 6.2.2.
3. Initial H&P and laboratory tests performed during screening can be used for C1D1 if done within 7 days.

6.2.2 Study Calendar

Table 4 lists the schedule of events for screening and safety monitoring.

Table 4 Schedule of Events

Cycles	Screening	Cycle 1 and 2 [a]				Subsequent Cycles [a]	EOT	Follow -Up [l]	Post-Treatment
	Day -28 to -1	Day 1 (-3 days)	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 22 (±3 days)	Day 1 of each cycle (+/- 3 days)			Every 12 weeks
Informed Consent	X								
Inclusion/ exclusion criteria review	X	X							
History & Physical	X	X[b]							
ECOG-PS	X	X[b]				X	X	X	
Vital signs & weight [b]	X	X	X	X	X	X	X	X	
Toxicity assessment	X	X		X	X	X	X	X	X
CBC/Diff/ Plts [c]	X	X[b]	X[c]	X[c]	X[c]	X	X		
Serum chemistry[d]	X	X[b]		X	X	X	X		
PT /PTT /INR	X			X	X		X		
Urinalysis	X	X[b]				X	X		
Serum pregnancy test [e]	X					X	X		
MRI / CT [f]	X		every 8 weeks (± 7 days)						X
Tumor tissue	X[g]						X[h]		
Niraparib dispensed/ Accountability		X				X	X		
Adverse Event Monitoring [i]		X ---------- X							
Survival assessment									X [j]
Follow-up for MDS/AML									X
Bone marrow aspirate and biopsy for cytogenetic analysis				If clinically indicated X [k]					

a. Treatment cycles are 28 days long, with visits on Day 1 of each cycle unless otherwise specified. Visits (other than Cycle 1) continue every 28 days until study treatment discontinuation. All visits have a window of ± 3 days (calculated in reference to Cycle 1/Day 1).
b. If history, PE, ECOG-PS and screening laboratory tests are performed within 7 days prior to first dose (Cycle 1, Day 1), repeat testing is not required. Only blood pressure and heart rate will be monitored weekly for the first 2 cycles then at the start of each new cycle and periodically thereafter during treatment with niraparib. Respiratory rate, temperature, and weight are not required weekly for the first two cycles, only on Day 1 of each cycle.
c. Weekly blood draws will be performed for the first cycle (28 days), monthly for the next 11 months of treatment, and periodically thereafter. If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC will be also required for an additional 4

weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume.

d. Consisting of albumin, alkaline phosphatase, BUN, calcium, carbon dioxide (CO2), chloride, creatinine, glucose, potassium, AST, ALT, sodium, total bilirubin, total protein.
e. Female subjects of childbearing potential as defined in the eligibility criteria must have a serum or urine beta-hCG pregnancy test within ≤ 72 hours prior to initiating protocol therapy, approximately every month at End of Treatment and until 180 days after the last dose. FSH level screening may be performed to determine if it is in the postmenopausal range.
f. RANO tumor assessment via Brain-MRI or CT will be required at screening, every 8 weeks (± 7 days; but it can be evaluated in a case by case basis) from Cycle 1/Day 1 for 6 months, and then every 12 weeks until progression. If MRI schedule for the patient is changed for clinical purposes, this regimen will be altered to avoid duplicate scans, but ensure one is taken at least every 3 months.
g. Tumor tissues should be collected at screening (either archival tissue or fresh biopsy if recent surgery has been performed is also permitted).
h. Tumor tissue collection at EOT will be optional (obtained if part of standard of care)
i. AEs should be monitored for at least 30 days post last dose or until the AE / SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died. If an Investigator becomes aware of an SAE after the specified follow up period and considers the SAE related to the study drug, the Investigator should report the SAE to the Sponsor and GSK according to timelines for reporting SAEs. SAE and AESI (adverse event of special interest) reporting is outlined in Section 9.0.
j. For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, and for survival every 6 months for 2 years, for a maximum of four years from the date of registration to assess for MDS/AML and overall survival. All patients must also be followed through completion of all protocol therapy.
k. For any patient diagnosed with MDS/AML while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to GSK. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria) and other sample testing results related to MDS/AML.
l. Post end of treatment visit (in-person, virtual, or televisit) will be conducted at 30 days (+/- 7 days) post last date of treatment, and follow-up exams will be conducted every 3 months for 1 year, and every 6 months for the remainder of the time for a maximum of 4 years from the date of registration.

6.2.3 Biological Sample Collection for Correlative Studies

Archival tumor tissue or fresh biopsy of recurrent or persistent tumor obtained via recent surgery will be used for molecular profile, HRD, & other correlative studies. The patients will be requested to provide the results of *any* prior genetic testing they may have undergone within 6 months of screening.

Tumor samples will be evaluated by central testing to identify those with homologous-recombination deficiency (using myChoice test, Myriad Genetics). Homologous-recombination deficiency will be defined as the presence of a *BRCA* deleterious mutation, a score of at least 42 on the myChoice test or other relevant genetic analyses.

For patients with recurrence or tumor progression after treatment with niraparib, if a tumor resection or a new biopsy is performed for clinical standard of care, then we will request that the tissue be sent for repeat genetic testing with myChoice test.
The genetic testing results will be used for comparison of treatment response to HRD status [via LOH (Loss of Heterozygosity), TAI (telomeric-allelic imbalances), and LST (large-scale state transitions) results] and in a multivariant analysis to discover any genetic profiles influencing treatment response.
For additional details, see lab manual.

6.2.4 Follow up Parameter

Follow-up is required as outlined in Table 4. In brief, patients will be seen every 28 days (prior to each cycle of therapy) while receiving study treatment. MRI / CT scans to assess response will be performed every eight weeks for six months, and then every 12 weeks until progression. Patients will also be seen 30 days (+/- 7 days) after last study medication is issued. Required study procedures are based on the presence or absence of study treatment related toxicities. Additionally, birth control must continue for six months after discontinuation of niraparib.

For participants who are thought to be lost to follow-up, at least three documented attempts, including one via certified mail, should be made to contact the participant before the participant is deemed lost to follow-up.

A patient is considered off study therapy when the patient has progressed or died prior to completion of study therapy, a non-protocol drug or therapy (directed at the disease) is initiated or all study therapy is totally discontinued. Survival and progression data will continue to be collected for at least two years after the patient is off study.

7.0 STUDY MEDICATION

7.1 Niraparib

7.1.1 Formulation

Niraparib ([3S]-3-[4-(7-(aminocarbonyl)-2H-indazol-2-yl) phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP1 and PARP2 inhibitor. The excipients for niraparib are lactose monohydrate and magnesium stearate. Niraparib will be supplied as 100-mg capsules.

7.1.2 Storage

Niraparib 100-mg capsules will be packed in high-density polyethylene bottles with child resistant closures that contain 72 or 93 capsules per bottle. Niraparib supplies must be stored at room temperature. Until dispensed or administered to the patients, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.

7.1.3 Administration

Niraparib will be supplied as 100-mg capsules and will be administered orally once daily (QD) continuously starting on Cycle 1/Day 1. The daily dose to be administered each day will be 300 mg as 3 × 100 mg capsules, unless specified otherwise based on Table 1 or dosage alteration following the safety review. Patients will be instructed to take their dose at the same time each

day, preferably in the morning. Bedtime administration may be a potent method for managing nausea. Niraparib may be taken with or without food. Patients must swallow whole and not chew capsules.
Niraparib capsules will be dispensed to patients on Cycle 1 Day 1, and on Day 1 of every cycle (28-day cycles) thereafter until the patient discontinues study treatment. On Day 1 of each cycle, a niraparib dose will be administered at the clinic upon completion of the safety assessment and drug accountabilities. Patient has an option to administer medication at bedtime in the case of nausea post dose. To ensure no study medication is wasted, patients will be provided 1 cycle worth of drug at each dispensing and patients will be provided with a pill diary to keep track of their medication. Patients are to return unused medications to clinic site to be destroyed per institutional standard.
If the patient missed a dose > 12 hours from the normal dosing time, skip the dose until the next regularly scheduled dosing time. If patient vomits post dose, skip the dose until the next regularly scheduled dosing time.

7.1.4 Clinically Reported Adverse Reactions

The following adverse reactions (all CTCAE grades) have been reported in ≥20% of patients who received niraparib: anemia, thrombocytopenia, nausea, constipation, vomiting, fatigue, platelet count decreased, decreased appetite, headache, and insomnia. The median exposure to niraparib in these patients was 250 days.

The following adverse reactions and laboratory abnormalities have been identified in ≥10% to <20% of the 367 patients receiving niraparib: neutropenia, palpitations, asthenia, neutrophil count decreased, dizziness, dysgeusia, dyspnea, cough and hypertension.

The following adverse reactions and laboratory abnormalities have been identified in ≥1% to <10% of the 367 patients receiving niraparib: tachycardia, dry mouth, mucosal inflammation, white blood cell count decreased, aspartate aminotransferase increased, alanine aminotransferase increased and photosensitivity reaction.

8.0 EVALUATION CRITERIA

8.1 Parameters of Outcome – RANO Criteria or Macdonald Criteria

The primary measure of response will be by serial measures of the product of the two largest cross-sectional diameters using Response Assessment in Neuro-Oncology (RANO), which is summarized in Appendix B [31]. The older Macdonald Criteria is available in Appendix C [32]. Time interval to progression will be measured from registration until deterioration is documented by the investigator using these guides. The patient should consistently be followed with the same diagnostic imaging study (CT or MRI). NOTE: CT option ONLY for patients unable to undergo MR imaging because of non-compatible devices.

8.1.1 Definition of Measurable Lesions

Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 10 mm x 10 mm

(perpendicular measurements) on 5 mm slices on MRI when measured by conventional techniques, including MRI and CT.

8.1.2 Baseline documentation of "Target" and "Non-Target" lesions

All measurable lesions should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (see above) and their suitability for accurate repetitive measurements by one consistent method of assessment (either by imaging techniques or clinically). A sum of the products of the diameters will be reported for all target lesions at baseline.

All other lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and each of these lesions should be followed (the persistence of a non-target lesion), complete response (the disappearance of a non-target lesion) or progressive disease (the unequivocal progression of a non-target lesion).

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than 4 weeks before the beginning of treatment.

Measurement of the sum of the products of the diameters (RANO) for target lesion size is required for follow-up. Change in the sum of these dimensions affords some estimate of change in tumor size and hence therapeutic efficacy. All disease must be assessed using the same technique as baseline.

8.1.3 Response Criteria

Complete Response (CR): complete disappearance of the measurable enhancing lesion sustained for at least 4 weeks; no new lesions; and no corticosteroids.

Partial Response (PR): ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of the measurable enhancing lesion sustained for at least 4 weeks; no new lesions; and stable or reduced corticosteroid dose.

Stable Disease (SD): does not qualify for complete response, partial response, or progression and is receiving stable or decreasing doses of steroids. This will not require a confirmatory scan.

Progression (P): Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions provided that the patient has not had his/her dose of steroids decreased since the last evaluation period; and any new lesions. This will not require a confirmatory scan. A concomitant decrease in steroid dose will rule out a progression designation during the initial 12 weeks after completion of RT.

If true progression is determined by subsequent imaging, then the date of progression returns to the earlier date with increasing mass.

8.1.4 RANO Response Criteria

Efficacy determinations using RANO response criteria (Appendix B) will be obtained.

Criteria for Response Assessment Incorporating MRI and Clinical Factors

Complete Response**:** Requires all of the following:

- Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks.
- No new lesions.

- Stable or improved non-enhancing (T2/FLAIR) lesions.
- Patients must be off corticosteroids (or on physiologic replacement doses only).
- Stable or improved clinically.

Note: Patients with non-measurable disease only cannot have a complete response. The best response possible is stable disease.

Partial Response: Requires all of the following:

- Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks.
- No progression of non-measurable disease.
- No new lesions.
- Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
- The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
- Stable or improved clinically.

Note: Patients with non-measurable disease only cannot have a partial response. The best response possible is stable disease.

Stable Disease**:** Requires all of the following:

- Does not qualify for complete response, partial response, or progression.
- Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
- Stable or improved clinically.

Progression: Defined by any of the following:

- Greater than > 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*.
- Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy*, not due to co-morbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).
- Any new lesion.

- Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose.
- Failure to return for evaluation due to death or deteriorating condition.
- Clear progression of non-measurable disease.

*Stable doses of corticosteroids include patients not on corticosteroids

8.1.5 ***Overall Survival*** is the observed length of life from the date of study entry to death or the date of last contact.

8.1.6 ***Progression-Free Survival (PFS)*** is defined as the time in months from date of study entry to the first documented date of progression (based on RANO) or date of death, whichever comes first. For patients who did not die and did not have progression, the PFS is censored at the last documented tumor assessment. .

8.1.7 ***Special Considerations***: If the patient was previously treated with bevacizumab or other anti-angiogenic medication, the MRI changes must be taken into consideration as the cessation of such drugs can artificially increase the contrast enhancement of the tumor and surrounding area without indicating tumor progression. These MRI's will be specifically reviewed with the PI and radiology to determine if the changes are due to anti-angiogenic drug withdrawal or true tumor progression. MRI perfusion scans are recommended to improve assessment of such lesions changes. In addition, a repeat MRI in 4 weeks (+/- 7 days) is allowed to determine the stability of the lesion and thereby determine if the changes are related to tumor progression or to medication changes. During the time waiting for a new scan, the patient may continue to treat with niraparib at the same dose level.

8.2 Subjective Parameters:

The ECOG performance status is summarized in Appendix D. The specific symptoms, and side effects are graded according to the CTCAE v 5.0.

9.0 Safety Monitoring and Reporting Procedures

The safety plan for patients in this study is based on clinical experience with niraparib in completed and ongoing studies. The anticipated important safety risks are outlined in sections 1.4.3 and 5.4.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. After initiation of study treatment, all nonserious adverse events will be reported until 30 days after the last dose of study or until 90 days after cessation of study treatment for SAEs and AESIs (unless otherwise specified, see section 9.1.2). Guidelines for managing anticipated

adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in section 5.4.
Safety assessments will consist of monitoring and reporting adverse events and serious adverse events per protocol. This includes all events of death and any study-specific issue of concern.

9.1 Adverse Event Monitoring and Management

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to appropriate IRB(s), and GSK.

9.1.1 Definitions (per 21 CFR 312.32(a)):

Adverse event: "Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."
This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with study treatment that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as tumor biopsy).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Life-threatening adverse event or life-threatening suspected adverse reaction: "An adverse event or suspected adverse reaction is considered "life threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death."

Serious adverse event or serious suspected adverse reaction: "An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or

- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse."

Suspected adverse reaction: "Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug."

Unexpected adverse event or unexpected suspected adverse reaction: "An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation."

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

<u>Events or Outcomes Not Qualifying as Serious Adverse Events</u>

The following are not considered SAEs and therefore do not need to be reported as such:

- Pre-planned or elective hospitalization including social and/ or convenience situations
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward)
- Overdose of study treatment or concomitant medication unless the event meets SAE criteria (eg, hospitalization). See bullet 5, definition of an Adverse Event.
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. If the event has a fatal outcome within the safety

reporting period, then the event of Progression of Disease must be recorded as an AE and as a SAE with CTCAE Grade 5 (fatal outcome) indicated.

9.1.2 Definition of an Adverse Events of Special Interest

AESIs (serious or non-serious) are defined as AEs of scientific and medical concern specific to a product or program, for which ongoing monitoring and rapid communication can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Sponsor to other parties (eg, regulators) might also be warranted.

9.1.2.1 Adverse Events of Special Interest for Niraparib

AESIs for this trial are defined as:

- Myelodysplastic Syndromes (MDS)
- Acute Myeloid Leukemia (AML)
- Secondary cancers defined as any new cancers that are identified after the initiation of protocol therapy. Exceptions include:
    - adequately treated nonmelanoma skin cancer, curatively treated in-situ cancer of the cervix, ductal carcinoma in-situ (DCIS) of the breast, Stage I Grade 1 endometrial carcinoma
    - Other solid tumors and lymphomas (without bone marrow involvement) diagnosed ≥5 years prior to study participation and treated with no evidence of disease recurrence and for whom no more than 1 line of chemotherapy was applied.

AESIs meeting the definition of an SAE must be reported within 24 hours of awareness of the event to the Sponsor Institution and to GSK regardless of causality assessment to study drug and regardless of the timeframe since the last dose. A targeted follow-up questionnaire (TFUQ) is available for MDS/AML (see section 9.1.5).

9.1.3 Pregnancy

The Sponsor Institution has the responsibility to monitor the outcome of all pregnancies reported during the Investigator Sponsored Trial.
The Sponsor Institution must report all pregnancies associated with GSK product including follow up outcomes to GSK within 24 hours of awareness.
Each pregnancy must be reported on a Pregnancy Notification Form (Appendix E) within 24 hours of becoming aware of the pregnancy. Pregnancy is not an AE, and therefore does not need to be reported as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.
An elective abortion without complications should not be regarded as an AE, however, it should be reported as the outcome to the pregnancy on the Pregnancy Follow-Up Form (Appendix F).
Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported on the Pregnancy Follow-Up Form and as an AE.
Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.
Any SAE that occurs during pregnancy must be recorded on the Pregnancy Follow-Up Form, reported as an SAE on the SAE Report Form (e.g., maternal serious complications, therapeutic

abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the Sponsor Institution and GSK within 24 hours. SAE Report form is listed in Appendix G. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.
The Pregnancy Notification form, the Pregnancy Follow-Up Form, and any related SAE forms must be reported to the Sponsor as outlined for SAEs.

9.1.4 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination. After this period, investigators should only report SAEs that are attributed to study treatment and serious AESIs.

9.1.5 Documenting Adverse Events

All AE information must be documented on the case report forms. Additional follow-up information (e.g., test results, autopsy, and discharge summary) may be obtained to supplement AE reports.. A copy of all initial and follow-up SAE reports will be included with the patient's study files.

9.1.5.1 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

Diagnosis versus Signs and Symptoms: If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Deaths: All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

Preexisting Medical Conditions: A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Hospitalizations for Medical or Surgical Procedures: Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is

hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.
Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

9.1.6 Causality Assessment of Adverse Events

The relationship between an AE and the study drug will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions.
An AE will be considered associated with the use of study drug if there is a reasonable possibility that the AE may have been caused by the study drug.
The Investigator must provide a causality assessment regarding the relationship of the event with the study drug and/or study procedure for all AEs.

One of the following categories should be selected based on medical judgment, considering all contributing factors:

- **Related**: A causal relationship between the medicinal product (and/or study procedures) and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be explained by pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, or the timing or seriousness of the AE, etc. Positive rechallenge/dechallenge is supportive.
- **Not Related**: A causal relationship between the medicinal product (and/or study procedures) and AE is not a reasonable possibility: there is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable.

In addition, the following definitions may be applied to those AEs that are considered definitely, probably, and possibly related to the use of the study drug:

Definitely Related: An AE that follows a temporal sequence from administration of the study drug; follows a known response pattern to the study drug; improves after stopping the study drug (positive dechallenge) and reappears after repeat exposure (positive rechallenge); and cannot be reasonably explained by known characteristics of the patient's clinical state or by other therapies

Probably Related: An AE that follows a reasonable temporal sequence from administration of the study drug; follows a known response pattern to the study drug; improves after dechallenge; and cannot be reasonably explained by the known characteristics of the patient's clinical state or by other therapies.

Possibly Related: An AE that follows a reasonable temporal sequence from administration of the study drug and follows a known response pattern to the study drug but could have been produced by the patient's clinical state or by other therapies An AE may be considered not associated with the use of study drug if there is not a reasonable possibility that the AE may have been caused by the study drug. This definition applies to those AEs that are considered unlikely or not related to the use of the study drug:
Unlikely to be Related: An AE assessed as unlikely to be related to study drug is defined as an AE for which sufficient information exists to indicate a high improbability that the event is related to the study drug.

If the AE falls under any of the above four categories, it will be listed as "Related to the drug" on the CRFs.

Not Related: An AE assessed as not related to study drug is defined as an AE for which sufficient information exists to indicate that the etiology is unrelated to the study drug. Two or more of the following variables apply:

- The AE does not follow a reasonable temporal sequence after administration of the study drug.
- The AE is readily explained by the patient's clinical state or other therapies.
- Negative dechallenge—the AE does not abate upon dose reduction or cessation of therapy (assuming that it is reasonable to expect abatement of the AE within the observed interval).

If the AE falls under the above category, it will be listed as "Not related to the drug" on the CRFs.

9.1.7 Severity Assessment of Adverse Events

Severity of AEs will be graded according to the CTCAE Version 5.0.
Adverse events not included in the CTCAE, Version 5.0 must be graded as follows: Mild, Moderate, Severe, Life-threatening, and Fatal according to the following definitions:

- Mild: The AE is noticeable to the patient but does not interfere with routine activity.
- Moderate: The AE interferes with routine activity but responds to symptomatic therapy or rest.
- Severe: The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.
- Life-threatening: The AE places the patient at risk of death at the time of the event.
- Fatal: The AE results in the death of the patient.

9.1.8 SAE Reporting

The Investigator must report all SAEs, and all follow up information to the Sponsor and GSK on the GSK SAE Report Form or MedWatch 3500A form within 24 hours of becoming aware of the initial event or follow-up information. SAEs must be entered on the study REDCap database within 24 hours of becoming aware of the initial event or follow-up information, with the MedWatch 3500A form.

The Investigator must provide a causality assessment and must sign and date all SAE Report Forms.
If supporting documentation is included in the SAE submission to GSK (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), please redact any patient identifiers (including Medical Record number).

GSK SAE, Serious AESI, Pregnancy Reporting Information
GSK Email: OAX37649@gsk.com and Sponsor Notification: Study REDCap database

Suspected Unexpected Serious Adverse Reactions (SUSARs)

Per regulatory requirements, if an event is assessed by the Sponsor Institution as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor Institution to submit the SUSAR to Regulatory Authorities according to applicable regulations. GSK should receive a copy of the submission documents.

In addition, the SUSAR will be distributed to the Investigators/sites utilizing a Council for International Organizations of Medical Sciences (CIOMS) report form, or the MedWatch 3500A form).

Reporting Product Quality Complaints for Niraparib
Any written, electronic or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, labeling, packaging, or shipping, must be reported by the investigator or qualified designee to GSK at gsk-rd.complaints@gsk.com within 1 working day of first becoming aware of the possible defect. The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

Reporting to Sponsor
All SAEs and UPs (unanticipated problems) must be reported to the Sponsor via the the REDCap database within 24 hours of becoming aware of the initial event or follow-up information for Sponsor reporting to Regulatory agencies.

9.2 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/medwatch/getforms.html

Follow-up Information:
Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

9.3 Study Monitoring

All aspects of the study will be carefully monitored at periodic intervals throughout the study per FDA/ICH "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance" dated April 1996. All Case Report Forms (CRFs) will be up to 100% source verified against corresponding source documentation (e.g., office and clinical laboratory records) for each patient. The monitoring visits provide the PI with the opportunity to evaluate the progress of the study, to verify appropriate consent form procedures, review drug accountability and to verify the accuracy and completeness of CRFs, to resolve any inconsistencies in the study records and to assure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.
Furthermore, this study will fall under the purview of the Sponsor's study-specific monitoring plan.

9.4 Data Disclosure and Patient Confidentiality

Patient medical information obtained as a result of this study is considered confidential. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to patients in this study will identify each patient only by their initials and number. Medical information resulting from a patient's participation in this study may be given to the patient's personal physician or to the appropriate medical personnel responsible for the patient's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency inspectors, the clinical trial office auditors and monitors, University of Oklahoma Office of Compliance, and the Institutional Review Board (IRB)).
All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by a coded number to maintain patient confidentiality. All study records will be kept in

a locked file cabinet or other secured area. All computer entry and networking programs will be identifiable only by coded numbers. Patient personal medical information may be reviewed by representatives of the Sponsor, of the IRB, or of regulatory authorities in the course of monitoring the progress of the clinical trial. Every reasonable effort will be made to maintain such information as confidential.

10.0 STATISTICAL ANALYSIS PLAN

Consideration for sample size

This phase II study consists of a safety lead-in and a dose-expansion phase. In the safety lead-in phase, three or six patients will be enrolled depending on the safety profile. See Section 6.1 for more details. A total of 45 evaluable patients (including those from the safety lead-in phase), evenly distributed among 3 gliomas including GBM, Astrocytoma, and Oligodendroglioma, will be enrolled into dose-expansion phase. Conservatively allowing for up to 10% dropout, we will enroll up to 48 patients for an evaluable 45 patients. In the sample size calculation, the DCR (disease control rate) for the historical control and for Niraparib are assumed to be 31% and 52%, respectively. A sample size of 45 evaluable patients will provide 80% power to show statistical significance for a two-sided .05 level Z-test.

10.1 Analysis Populations

The safety lead-in and dose-expansion phases will be statistically analyzed separately. The safety lead-in phase analysis population will include all patients who have received at least one dose of niraparib.

The analysis populations in the dose-expansion phase are defined as below.

- Safety population: All patients who receive at least one dose of niraparib will be included in the analyses of compliance and safety.
- Biomarker population: For biomarker analysis, the biomarker population will comprise all patients who have sufficient baseline measurements.
- Efficacy Evaluable population: For tumor response analysis, the evaluable population will comprise all patients who have sufficient baseline and on-study measurements of tumor response parameters.

10.2 Data Analysis

10.2.1 Patient Disposition

Patient disposition will be summarized and include the number dosed, the number in each patient population for analysis, the number who withdrew prior to completing the study and reason(s) for withdrawal.

10.2.2 Demographic and Baseline Characteristics

Patient demographic and characteristics at study entry will be summarized with frequency tables for categorical variables, and with descriptive statistics such as the mean, standard deviation, median, and range as appropriate, for quantitative variables.

10.2.3 Medical History and Cancer History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v20.1. The count and percentage of subjects under each history term, coded by system organ class (SOC) and preferred term (PT), will be summarized.
Cancer history data will also be summarized, including the primary site of cancer, the stage and grade of cancer at study entry, time from initial diagnosis of cancer to Day 1 of the study in days, duration of metastatic disease in days (first dose date – date of diagnosis of metastatic disease + 1), the extent of metastatic disease, and the histology.

10.2.4 Study Drug Administration and Compliance

Study drug administration will be summarized in terms of the actual doses administered and the proportion of drug actually taken relative to the amount that should have been taken; these data will be summarized in frequency distributions by cycle and dose level. The total number of cycles administered; the median (range) of cycles administered; dose modifications, dose delays, and dose omissions; and reasons for deviations from planned therapy will be summarized by dose level.

10.2.5 Safety Analyses

10.2.5.1 Adverse Events

Adverse events will be tabulated using MedDRA v23.1. The severity of the AE will be graded by the Investigator using the NCI CTCAE, version 5.0. The frequency of patients experiencing a specific AE will be tabulated by dose level, cycle, system organ class, preferred term, seriousness, worst severity, timing of occurrence, outcome, and relationship to study drug. In addition, the number and percentage of patients experiencing a specific AE will be tabulated similarly.

10.2.5.2 Laboratory Abnormalities

The severity of laboratory abnormalities will be graded using the NCI CTCAE, version 5.0, whenever possible. The frequency of patients experiencing a specific laboratory abnormality will be tabulated by dose level, cycle, worst severity, and timing of occurrence. In addition, the number and percentage of patients experiencing a specific laboratory abnormality will be summarized similarly.

10.2.5.3 Other Safety Assessments

The results of vital sign measurements, body weight assessments, ECOG performance status determinations and physical examinations will be summarized by cycle and dose level, using appropriate descriptive statistics.

10.2.6 Biomarkers

Data of molecular profile from myChoice test will be collected. The tumor biomarkers from tumor biopsies, such as HRD, IDH1 /IDH2 mutation and PARP in tumor, will be summarized for each patient.

10.2.7 Antitumor Evaluation

The statistical analysis for the dose-expansion phase will be performed by the types of gliomas. The disease control rate (complete and partial response, and stable disease) will

be summarized as the proportion (and 95% exact Clopper-Pearson CI) of patients with disease control. The duration of disease control (DDC) will be calculated as time from date of first response [complete response (CR), partial response (PR), pathological complete response (pCR), or stable disease (SD)] to the first date of non-response post treatment on the study (first documentation of disease progression or death, whichever comes first) Duration of disease control will be summarized using the Kaplan-Meier method. Median duration of disease control with 95% CI will be computed. Results will be presented in tabular and graphic form, as appropriate. The response rate will be compared between biomarker status using the chi-squared test and/or Fisher's Exact Test, where applicable.

Progression-Free Survival (PFS) is defined as the time in months from study entry to the first documented date of progression or date of death, whichever comes first. For patients who did not die and did not have progression, the PFS is censored at the last documented tumor assessment. Survival curve for PFS will be generated using the Kaplan-Meier method. Median PFS with 95% CI will be computed. Six-month PFS rate is defined as the percentage of patients who are alive and progression-free at 6-month from the start of study treatment; with tumor response including CR (or pathological CR), PR and SD (estimated by the Kaplan-Meier method). PFS will be compared between biomarker status using the log-rank test.

Overall survival (OS) time is defined as the length of time from date of study entry to death or the date of last contact. Patients who are still alive at EOS are censored on the date they were last known to be alive. An exploratory analysis to determine 6 months or 9 months OS rate will be estimated by the Kaplan-Meier method. Median OS with 95% CI will be computed. OS will be compared between biomarker status using the log-rank test.

The raw data may be reviewed and evaluated by the PI, biostatistics team, and sponsor at any given point for the purposes of updating the study team, presentation at conferences, development of new protocols, grant applications, or other functions once discussed with the study management team at GSK.

10.3 Accrual and Study Duration

This is a single arm, phase II, multi-center study. Forty-five evaluable patients will be enrolled at two medical centers including the Stephenson Cancer Center. Based on our prior experience with similar patient population, we anticipate enrollment of 20-25 patients in two years at both study sites.

Up to six patients will be enrolled in the safety lead-in phase as outlined in Section 6.1. These patients will be included in the dose expansion phase total patient analysis in which a total of 45 evaluable patients will be enrolled. Conservatively allowing for up to 10% dropout, we will enroll up to 48 patients for an evaluable 45 patients. It is anticipated that this study will require approximately 24-36 months of accrual assuming a uniform accrual rate of ~10 patients per year at each site. It is estimated that 12 months of post accrual follow-up will be necessary to observe the minimum number completed cycles.

11.0 DATA MANAGEMENT PLAN

11.1 Data Quality Assurance

Stephenson Cancer Center (SCC) will be responsible for clinical monitoring of all data for this study.

11.2 Electronic Case Report Forms

The Principal Investigator will develop electronic case report forms for study data entry. All study data will be stored in a 21 CFR 11 compliant database. Only Investigator and assigned research staff will have access to study data. The electronic case report forms will be available to the sponsor, IRB and regulatory authorities in event of an audit.

11.3 Data and Safety Monitoring Committee

Safety oversight will be performed by Stephenson Cancer Center's (SCC) internal Data and Safety Monitoring Committee (DSMC). The DSMC is composed of individuals with the appropriate expertise in adult and pediatric hematology and medical oncology, radiation oncology, translational and correlative science, pharmacy, nursing and biostatistics. The DSMC operates under the rules of an approved data safety monitoring plan which complies with the National Cancer Institute (NCI) guidelines published as *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by NCI* as of January 2005 and the "*NIH Policy for Data and Safety Monitoring*," *NIH Guide for Grants and Contracts*, http://grants.nih.gov/grants/guide/notice-files/not98-084.html.

The Data Safety Monitoring Committee is charged with oversight of participant safety, study conduct and the validity and integrity of data for clinical trials at SCC. While the focus of the DSMC is to monitor interventional investigator initiated trials (IITs) that are not subject to external monitoring, it has the authority to monitor any SCC protocol when potential concerns are identified. The DSMC also has the authority to suspend or close a study until the principal investigator addresses any issues that may cause harm or increase risks to subjects. The DSMC reports all findings to the Institutional Review Board (IRB).

Under the direction of the DSMC chair, a full board meeting is convened on a quarterly basis to review the accumulated safety data, accrual information, and additional information as stated in the DSMC plan.

11.4 DSMC Auditing

In addition to monitoring, the DSMC oversees an internal auditing process to ensure subject safety and data quality. All cancer-related clinical trials active at the SCC are eligible for audit; however, priority is placed on those clinical trials that are not monitored or audited by an outside entity. If an external entity conducts an audit of a clinical trial at the SCC, then the findings of that audit are reported to the DSMC, either through the formal audit report provided by the external auditing entity, if available, or from the PI, who will report any findings communicated during the audit process.

11.5 Record Retention

Investigator will retain all research documents and case report forms at study site per institutional standards.

12.0 PUBLICATION PLAN

The study drugs to be used in this protocol will be supplied by GSK Inc. under a Collaborative Agreement (CTA) between GSK Inc. and the University Oklahoma Stephenson Cancer Center (OUSCC).

The following obligations/guidelines apply to the use of the Agent in this study:

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of GSK Inc. the Funding Collaborator. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement.

2. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), OUSCC and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

3. Any data provided to the Collaborator(s) for this study must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

4. Potential manuscripts may be submitted to Neuro-Oncology, J. Neuro-Oncology, or JCO for publication. Any manuscripts reporting the results of this clinical trial must be provided to GSK by the principal investigator for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to GSK Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to GSK prior to release.

No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

13.0 ETHICAL AND REGULATORY CONSIDERATIONS

Before initiation of the study, the Investigators must provide the Sponsor with a completed Form FDA 1572. Study medication may be administered only under the supervision of the Investigators listed on this form. Curriculum vitae must be provided to the Sponsor for the site Principal Investigator and made available upon request for the sub-Investigators.

13.1 Ethical Conduct of the Study

The study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki in addition to the requirements of the ICH E2A guidelines. This study will also comply with U.S. FDA regulations in addition to local, state, and federal laws.

13.2 Informed Consent

The informed consent document will be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent document used in this study, and any changes made during the course of the study, will be prospectively approved by the IRB. The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The study site will retain the original of each patient’s signed consent document. A signed copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

13.3 Institutional Review Board or Ethics Committee

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator’s Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere.

13.4 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will

require written IRB approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients.
When immediate deviation from the protocol is required to eliminate an immediate hazard to patients, the Investigator will contact the Sponsor or its designee if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation.

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15.0 APPENDIX

Appendix A. Substrates for CYP1A2

Data from https://www.fda.gov/drugs/

	Sensitive substrates	Moderate sensitive substrates
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon	clozapine, pirfenidone, ramosetron, theophylline

Additional substrates for CYP1A2: Data from https://drug-interactions.medicine.iu.edu

Acetaminophen, amitriptyline, clomipramine, cyclobenzaprine, doxepin, duloxetine, estradiol, fluvoxamine, haloperidol, imipramine n-deme, mexiletine, nabumetone, napqi, naproxen, olanzapine, ondansetron, phenacetin, propranolol, riluzole, ropivacaine, rcaparib, tacrine, tizanidine, triamterene, varpamil, warfarin, zileuton, zolmitriptan.

Appendix B. Summary of RANO Response Criteria [31]

Criterion	CR	PR	SD	PD#
T1-Gd +	None	≥ 50%↓	< 50%↓ - < 25%↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA**
Clinical Status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	all	All	Any*

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; FLAIR, fluid-attenuated inversion recovery; ↓= decrease; ↑**=** increase
Progression occurs when any of the criteria with * is present.
NA**: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Appendix C. Macdonald Criteria for Repsonse Assessment Incorporating MRI and Clinical Factors

Current Response Criteria for Malignant Gliomas (Macdonald Criteria)

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; no corticosteroids; and stable or improved clinically
Partial response	Requires all of the following: ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no new lesions; stable or reduced corticosteroid dose; and stable or improved clinically
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; and stable clinically
Progression	Defined by any of the following: ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions; any new lesion; or clinical deterioration

Source: Macdonald et al., 1990

Appendix D. ECOG Performance Status*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982; 5:649-655.

Appendix E. GSK Pregnancy Notification Form

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Protocol Identifier	Subject Identifier	Centre Number	

PREGNANCY NOTIFICATION FORM (Continued)

FATHER'S RELEVANT MEDICAL/FAMILY HISTORY

Only recorded if required by the protocol and Informed Consent of the father has been obtained.

(Include habitual exposures such as alcohol/substance abuse, chronic illnesses, familial birth defects/genetic/ chromosomal disorders and medication use)

_____

_____

DRUG EXPOSURES

In the following table, list all medications (including study medications) the subject received during the study period (e.g. prescription, OTC, vaccines, recreational, alcohol, etc.). ***Enter the investigational product details on the first line*** *(if the investigational product is blinded, enter 'Investigational Product' on this line). If there are extensive concomitant medications, attach a copy of the Concomitant Medications CRF page.*

Drug Name *(Trade Name preferred)*	Route of Admin. or For-mulation	Total Daily Dose	Units	Started Pre-Study Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Med-ication Y=Yes N=No	Reason for Medication

Was the subject withdrawn from the study as a result of this pregnancy? ☐ Yes ☐ No

REPORTING INVESTIGATOR INFORMATION *(Forward to a more appropriate physician if needed)*

Name _____ Title __ Speciality _____

Address _____

City or State/Province _____

Country _____

Post or Zip Code _____

Telephone No _____

Fax No _____

Investigator's signature _____ Date ☐☐ ☐☐☐ ☐☐
Day Month Year
(confirming that the data on these pages are accurate and complete)

Investigator's name (print) _____

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Protocol Identifier	Subject Identifier	Centre Number	

PREGNANCY NOTIFICATION FORM (Continued)

FATHER'S RELEVANT MEDICAL/FAMILY HISTORY

Only recorded if required by the protocol and Informed Consent of the father has been obtained.

(Include habitual exposures such as alcohol/substance abuse, chronic illnesses, familial birth defects/genetic/ chromosomal disorders and medication use)

_____

_____

DRUG EXPOSURES

*In the following table, list all medications (including study medications) the subject received during the study period (e.g. prescription, OTC, vaccines, recreational, alcohol, etc.). **Enter the investigational product details on the first line** (if the investigational product is blinded, enter 'Investigational Product' on this line). If there are extensive concomitant medications, attach a copy of the Concomitant Medications CRF page.*

Drug Name *(Trade Name preferred)*	Route of Admin. or For-mulation	Total Daily Dose	Units	Started Pre-Study Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Med-ication Y=Yes N=No	Reason for Medication

Was the subject withdrawn from the study as a result of this pregnancy? ☐ Yes ☐ No

***REPORTING INVESTIGATOR INFORMATION** (Forward to a more appropriate physician if needed)*

Name _____ Title __ Speciality _____

Address _____

City or State/Province _____

Country _____

Post or Zip Code _____

Telephone No _____

Fax No _____

Investigator's signature _____ Date ☐☐ ☐☐☐ ☐☐
(confirming that the data on these pages are accurate and complete) Day Month Year

Investigator's name (print) _____

Appendix F. GSK Pregnancy Follow-up Form

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Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number

PREGNANCY FOLLOW-UP FORM - CURRENT PREGNANCY INFORMATION

One form should be completed per foetus (e.g., if a subject is carrying twins a form should be completed for each twin).

Who is this form being completed for, ✓ *one:* ☐ Subject ☐ Subject's partner

PREGNANCY STATUS

While pregnancy itself is not an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. A spontaneous abortion is always considered to be an SAE and will be reported as described in the protocol. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the investigational product by the Investigator will be reported to GSK per the protocol. Whilst the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

☐ Stillbirth
☐ Foetal death
☐ Method used for delivery, *specify* _____

Early termination, ✓ *if applicable:*
☐ Spontaneous abortion
☐ Elective abortion
☐ Other, *specify* _____

InForm studies:

- *If a female subject is pregnant and the outcomes/associated events fulfill the criteria of an SAE, complete the information in the eCRF SAE form and on this paper Pregnancy Follow-up form.*
- *If male subject's partner is pregnant and the outcomes/associated events fulfill the criteria of an SAE, then complete the information in the paper SAE form and send together with this paper Pregnancy Follow-up form.*

Paper studies: If any of the outcomes/associated events fulfil the criteria of an SAE, complete the SAE section in the CRF.

FOETAL/NEONATAL STATUS

☐ Normal
☐ Birth defect (i.e., structural/chromosomal disorder) *Complete Serious Adverse Event pages*
☐ Other disorder (e.g., non-structural, premature birth, intrauterine death/stillbirth)

If birth defects are diagnosed, is the origin of the defect known? ☐ Yes ☐ No

If Yes, specify _____

INFANT INFORMATION

Date of birth/miscarriage/termination ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Gestational weeks at birth/miscarriage/termination ☐☐ Weeks

Infant's sex ☐ Male ☐ Female ☐ Unknown

Length ☐☐.☐ cm Weight ☐☐☐☐.☐☐ g

Apgar score (0 - 10) ☐☐ First assessment ☐☐ Second assessment

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Protocol Identifier	Subject Identifier	Centre Number	

PREGNANCY FOLLOW-UP FORM - CURRENT INFORMATION (Continued)

ADDITIONAL DETAILS (Provide additional details on current labour/delivery/discharge notes etc.)

_____

_____

_____

_____

DRUG EXPOSURES DURING PREGNANCY

Complete drug section for all drugs (including OTC/vaccines) taken by the mother during pregnancy. Do not include drugs that have already been included on the Pregnancy Notification Form.

Drug Name *(Trade Name preferred)*	**Route of Admin. or For-mulation**	**Total Daily Dose**	**Units**	**Started Pre-Study** Y=Yes N=No	**Start Date** Day Month Year	**Stop Date** Day Month Year	**Ongoing Med-ication** Y=Yes N=No	**Reason for Medication**

REPORTING INVESTIGATOR INFORMATION (Forward to a more appropriate physician if needed)

Name _____ Title ___ Speciality _____

Address _____

City or State/Province _____

Country _____

Post or Zip Code _____

Telephone No _____

Fax No _____

Investigator's signature _____ Date ☐☐ Day ☐☐☐ Month ☐☐ Year
(confirming that the data on these pages are accurate and complete)

Investigator's name (print) _____

Appendix G. GSK SAE Report Form

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SERIOUS ADVERSE EVENTS (SAE) (Page 1 of 6)
DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

A serious adverse event is any untoward medical occurrence that, at any dose:

a) results in death.

b) is life-threatening.

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) requires hospitalisation or prolongation of existing hospitalisation.

Note: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is 'serious'.

When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered 'serious'. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity, or

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) is a congenital anomaly/birth defect.

f) other.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

g) possible drug-induced liver injury

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SERIOUS ADVERSE EVENTS (SAE) (Page 2 of 6)
MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'no' box at the top of the page has been completed.
- Start dates must be provided for the reporting of serious adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that **no** medical or investigational procedures are captured on Serious Adverse Events pages.
- **Death** should not be recorded as an SAE but should be recorded as the outcome of an SAE. The condition that resulted in the death should be recorded as the SAE.
- Confirm that any SAEs marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject was withdrawn from the study due to an SAE, confirm that the following variables are consistent for the SAE which resulted in withdrawal:
  - If study treatment was permanently withdrawn due to an adverse event ...
    - 'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'
  - If the subject was withdrawn from the study for an adverse event ...
    - 'Withdrawal' on the SAE page is recorded as 'Yes'.
    - 'Most Clinically Significant Action Taken with Study Treatment(s) as a Result of the SAE' on the SAE page is recorded as 'Study Treatment Withdrawn'.

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THE INVESTIGATOR MUST INFORM GSK OF SERIOUS ADVERSE EVENTS BY FAX OR TELEPHONE (FAX PREFERRED) WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT. ALL OF THE HEADER INFORMATION MUST BE COMPLETED BEFORE SENDING BACK TO GSK.
(The original pages must remain in the Case Report Form/Study File).

SERIOUS ADVERSE EVENTS (SAE) (Page 3 of 6)
INVESTIGATOR INSTRUCTIONS

Diagnosis	Record one SAE diagnosis per line, or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered and the sign/symptom crossed out, initialled and dated by the investigator. A separate form should be used for each SAE. However, if multiple SAEs which are temporally or clinically related are apparent at the time of initial reporting then these may be reported on the same page. If this was recorded previously as a non-serious event but has progressed to serious, put a line through the Non-Serious AE record and transcribe the details onto the SAE form.
Start Date Start Time	Record the start date and time of the first occurrence of the event or signs/symptoms of the serious event, not the date and time the event became serious.
Outcome	All SAEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. If the SAE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as 'Not recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the SAE was ongoing at the time of death, but was not the cause of death, enter fatal for the SAE which was the direct cause of death.
End Date End Time	Record the end date. This is the date the SAE Recovered/Resolved, or if the outcome was fatal, record the date the subject died. If the event Recovered/ Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the SAE is 'Not recovered/Not resolved' or 'Recovering/Resolving'. Record the end time of the SAE.
Maximum Intensity	Record the maximum intensity that occurred over the duration of the event. Amend the intensity if it increases. Mild = An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. Moderate = An event that is sufficiently discomforting to interfere with everyday activities. Severe = An event that prevents normal everyday activities. Not applicable = Those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).
Most Clinically Significant Action Taken with Study Treatment(s) as a Result of the SAE	Indicate the response to the adverse event, whether it be from the investigator, local physician not in the study, or the subject. Study treatment(s) withdrawn = Administration of study treatment(s) was permanently discontinued. Dose reduced = Dose is reduced for one or more study treatment(s). Dose increased = Dose increased for one or more study treatment(s). Dose not changed = Study treatment(s) continues even though an adverse event has occurred. Dose interrupted/Delayed = Administration of one or more study treatment(s) was stopped/interrupted temporarily but then restarted. Not applicable = Subject was not receiving study treatment(s) when the event occurred (e.g., pre-or post-dosing) or the subject died and there was no prior decision to discontinue Study Treatment(s).

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SERIOUS ADVERSE EVENTS (SAE) (Page 4 of 6)
INVESTIGATOR INSTRUCTIONS

Did the subject withdraw from the study as a result of this SAE	Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal from the study, otherwise indicate 'No'.
Date/Time site was made aware of the SAE	Record Date/Time site was made aware of the SAE.
Relationship to Study Treatment(s)	It is a regulatory requirement for investigators to assess relationship to study treatment(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

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Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number	

SERIOUS ADVERSE EVENT (SAE)

Did the subject experience a serious adverse event during the study? [Y] ☐ Yes [N] ☐ No *If Yes, record details below.*

SECTION 1

Event	Start Date	Start Time	Outcome	End date	End Time	Maximum Intensity	Most Clinically Significant Action Taken with Study Treatment(s) as a Result of the SAE	With-drawal	Date site was made aware of the SAE	Time site was made aware of the SAE	Relationship to Study Treatment(s)
Diagnosis Only (*if known*) Otherwise Sign/Symptom	Day Month Year	Hr : Min 00:00-23:59	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae 5=Fatal	*If fatal, record date of death.* Day Month Year	Hr : Min 00:00-23:59	1=Mild 2=Moderate 3=Severe X=Not applicable	1=Study Treatment(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted/ Delayed X=Not applicable	Did the subject withdraw from study as a result of this SAE? Y=Yes[1] N=No	Day Month Year	Hr : Min 00:00-23:59	Is there a reasonable possibility the SAE may have been caused by the study treatment? Y=Yes N=No
e.g., Anaphylaxis	*25 JAN 18*	*13:25*	*1*	*27 JAN 18*	*10:20*	*1*	*4*	*Y*	*30 JAN 18*	*13:25*	*Y*
		:			:					:	
		:			:					:	

[1] *Complete Study Conclusion page and ✓ Adverse event as reason for withdrawal.*

SECTION 2 Seriousness *(specify reason(s) for considering this a SAE, ✓ all that apply:*

[A] ☐ Results in death
[B] ☐ Is life-threatening
[C] ☐ Requires hospitalisation or prolongation of existing hospitalisation
[D] ☐ Results in disability/incapacity
[E] ☐ Congenital anomaly/birth defect
[F] ☐ Other, *specify* _____ (*see definition of SAE*)
[G] ☐ Possible drug-induced liver injury (see definition in SAE section of the protocol)

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SERIOUS ADVERSE EVENTS (SAE) (Page 5 of 6)

INVESTIGATOR INSTRUCTIONS

SECTION 4 **If Study Treatment was Stopped, Did the Reported Event(s) Recur After Further Study Treatment(s) Were Administered?**	If deliberate or inadvertent administration of further dose(s) of study treatment(s) to the subject occurred, did the reported adverse event recur?

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Protocol Identifier	Subject Identifier	

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 3 Demography Data	*For GSK use only* *Enter the subject's year of birth.*	
Year of birth ____ Year	Imputed date of birth 30 JUN ____ Day Month Year	Sex ☐ Male ☐ Female Weight ____.__ kg Height ____ cm

SECTION 4 If Study Treatment(s) was Stopped, Did the Reported Event(s) Recur After Further Study Treatment(s) were Administered?

☐ Yes ☐ No ☐ Unknown at this time ☐ Not applicable

SECTION 5 Possible Causes of SAE Other Than Study Treatment(s), ✓ *all that apply:*

☐ Disease under study
☐ Medical condition(s) *specify* _____
☐ Lack of efficacy
☐ Withdrawal of study treatment(s)
☐ Concomitant medication(s) *specify* _____
☐ Activity related to study participation *(e.g., procedures)*
☐ Other, *specify* _____

SECTION 6 RELEVANT Medical Conditions

Specify any RELEVANT past or current medical disorders, allergies, surgeries that can help explain the SAE. Ensure each medical condition recorded in this section is also recorded in the appropriate Medical Conditions form.	**Date of Onset** Day Month Year	**Condition Present at Time of the SAE?** Y=Yes N=No	***If No, Date of Last Occurrence*** Day Month Year

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SERIOUS ADVERSE EVENTS (SAE) (Page 6 of 6)
INVESTIGATOR INSTRUCTIONS

SECTION 9 **Details of Study Treatment(s)**	Complete this section using the information in the Study Treatment page. Details of all study treatment(s) taken until the time of the SAE should be included. Provide specific details in Section 11 Narrative Remarks if the subject has taken an overdose of study treatment(s), including whether it was accidental or intentional.

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Protocol Identifier	Subject Identifier	

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 7 Other RELEVANT Risk Factors *Provide any family history or social history (e.g., smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the SAE). Ensure each risk factor recorded in this section is also recorded in the appropriate Medical Conditions form.*

SECTION 8 RELEVANT Concomitant Medications *Include details of any concomitant medication(s) that may help explain the SAE, may have caused the SAE or was used to treat the SAE. Ensure each concomitant medication recorded in this section is also recorded in the Concomitant Medication form.*

Drug Name (Trade Name preferred)	Dose	Unit	Frequency	Route	Taken Prior to Study? Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Medication? Y=Yes N=No	Reason for Medication
e.g., Zantac	*150*	*mg*	*BID*	*PO*	*N*	*25 JAN 18*	*27 JAN 18*	*N*	*Gastric ulcer*

SECTION 9 Details of Study Treatment(s)

Was treatment blind broken at investigational site? ☐ Yes ☐ No ☐ Not applicable

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GlaxoSmithKline

CONFIDENTIAL

Protocol Identifier	Subject Identifier	

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 10 Details of RELEVANT Assessments *Provide details of any tests or procedures carried out to diagnose or confirm the SAE (e.g., laboratory data with units and normal range) if data for this SAE have not been previously entered, and the CRF includes a page for the test, ensure the data is also entered on the page.*

SECTION 11 Narrative Remarks *(provide a brief narrative description of the SAE and details of treatment given)*

Investigator's signature _____
(confirming that the data on the SAE pages are accurate and complete)

Date ☐☐ ☐☐☐ ☐☐ (Day / Month / Year)

Investigator's name (print) _____

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